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EDITORIAL OFFICE
Xiu-Xia Song, Director
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Baishideng Publishing Group Inc
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Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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THERAPEUTICS ADVANCES

Best practices in supervising cognitive behavioral therapy with youth

Robert D Friedberg

Robert D Friedberg, Center for the Study and Treatment of Anxious Youth, Palo Alto University, Palo Alto, CA 94304, United States

ORCID number: Robert D Friedberg (0000-0001-8821-1723).

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Correspondence to: Robert D Friedberg, PhD, ABPP, ACT Professor, Director, Center for the Study and Treatment of Anxious Youth, Palo Alto University, 1791 Arastradero Rd, Palo Alto, CA 94304, United States. rfriedberg@paloaltou.edu
Telephone: +1-408-7754904

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Abstract

Clinical supervision of cognitive behavioral therapy (CBT) with youth ensures better patient care and fosters trainees' professional development. However, often insufficient attention is directed toward disseminating best practices in supervision of CBT with youth. This Therapeutic Advances contribution aims to communicate the core content of supervision. Additionally, the key supervisory practices associated with CBT with youth are described. Supervisory outcomes are summarized and recommendations for supervisory practices are made.

Key words: Cognitive behavioral therapy; Pediatric populations; Supervision

Core tip: There are several core tips in this therapeutic advances article. First, the pivotal content of supervision of cognitive behavioral therapy with youth include training in case conceptualization, ethics/laws, collaborative empiricism, guided discovery, session structure, embracing immediacy, measurement-based care, and cognitive-behavioral technique. Enactive supervision characterized by behavioral rehearsal is essential. Further, tracking trainee progress *via* objective rating scales and providing frequent, constructive feedback is indispensable.

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INTRODUCTION

Fortunately, the state of the science of cognitive behavioral therapy (CBT) with youth is strong[1-3]. CBT shows good results with patients diagnosed with multiple disorders including depression[4], anxiety[5] obsessive-compulsive disorder[6], trauma[7], and disruptive behavior

disorders[8,9].

Equipping supervisees with state-of-the-practice cognitive behavioral therapy skills for youth is an important yet very challenging training imperative. Didactic training acquired in classes and workshops is not a powerful way to change professional practices[10,11]. Ongoing consultation potentiates didactic training. More specifically, "consultation likely provides therapists with a venue for clarification and practice of concepts, learning concepts over time, case consultation, and using problem solving to overcome implementation barriers"[10].

Clinical supervision of CBT with youth is a multipronged professional activity that targets various foci[12,13]. Of course, assuring the emotional and psychological well-being of young patients is the pre-eminent goal. Additionally, building trainees skills, knowledge and attitudes is a second pivotal task. Finally, assisting supervisees with difficult patients and igniting their professional development are important undertakings. Achieving these meritorious goals is both a rewarding and challenging endeavor.

This therapeutic advances article highlights several issues. The paper begins with a discussion about the importance of supervision. Second, the common content of supervision is explicated. Next, core supervisory practices are explained. A consideration of supervisory outcomes follows. The article concludes with recommendations for proper supervision of CBT with youth.

IMPORTANCE OF SUPERVISION

In the United States, there is a growing call for evidence-based approaches for treating psychiatric disorders in youth[14]. Lack of access to good supervision is commonly seen as an obstacle to effective implementation in community contexts[15]. Many clinicians label themselves as cognitive behavioral therapists, but this self-identification does not reflect the actual behaviors demonstrated in sessions[14]. In particular, a recent study found that 71% of clinicians who self-labeled as CBT therapists failed to display evidence of CBT competence[14]. Further, there were equivalent levels of non-competence between those clinicians who did and did not identify themselves as CBT clinicians. Additionally, over 50% of community clinicians trained in CBT reported departing from the approach suggesting that CBT is not being implemented with sufficient fidelity[16]. Truth in labeling is imperative. If clinicians inaccurately claim a CBT orientation, the treatment dose is diluted and the delivery method is compromised. Competent supervision enables essential quality control. Without this quality control, clinicians are free to go rogue and suffer sizeable theoretical/technical drift.

CONTENT OF SUPERVISION

CBT clinicians are made not born. There is much to learn when becoming a cognitive behavioral therapist with youth[17]. Good CBT with youth involves numerous competencies[17-21]. Appreciating the state of the science supporting CBT and the theoretical foundations which underlie the approach is imperative. Fashioning flexible and robust case formulations is also expected. Employing guided discovery and collaborative empiricism throughout the clinical work is another vital component. Adhering to the prototypical cognitive therapy session structure is *de rigeur*. Of course, mastery of the variety of CBT procedures and processes such as Socratic questioning, self-instruction, problem solving, imagery, behavioral activation, social skills training, behavioral experiments, and exposure/response prevention is fundamental.

Supervision is portrayed as the "pedagogical engine" of clinical training in CBT[22]. Attention to core content areas and allocating sufficient time for training are vital. Research has indicated that in community based clinics, there is little discussion of evidence based procedures in supervision[23]. Insufficient training times are associated with trainees' overestimation of their competence[24]. Indeed, there is much heavy lifting to do in CBT training. Therefore, supervisors must promote high level didactic, procedural, and self-reflective learning experiences in an efficient manner. Fortunately, CBT supervision is described as goal-directed, structured, time limited, and personalized to the trainee[25,26].

Supervisors and trainees are wise to remember that "cognitive therapy is work not magic"[27]. This section details the core elements embedded in good supervision of CBT with youth including training in case conceptualization, ethical and legal alertness, multicultural responsiveness, employing collaborative empiricism and guided discovery, measurement based care, technical proficiency, as well as addressing trainees' beliefs about the clinical work.

Case conceptualization[13,17-21,28-32] is an indispensable task. In fact, case conceptualization is seen as the nucleus of good CBT practice[19]. Case formulation obviates an eclectic approach and bag of tricks mentality. Authors[33] recently argued, "We have no data to suggest that an 'a la carte' approach to CBT produces positive patient outcomes". The selection, timing, and targets of various interventions are launched by case conceptualization. However, the ability to formulate cases is an acquired skill set[20,34]. Case conceptualization involves several component bits of knowledge[19,20]. More specifically, fluency in operant, classical, and social learning theory paradigms is essential. Additionally, full comprehension of theoretical tenets such as the hierarchical organizational model[35,36] and the content-specificity hypothesis[37-41] is necessary. Appreciation of socio-cultural variables and developmental vicissitudes is also pivotal. Required reading lists are encouraged to bulk up trainees' knowledge bases. Fortunately, several excellent teaching and training resources exist[42-46]. Additionally, completing written case formulations and receiving supervisory feedback on them is also recommended[30].

Instruction in ethics and legal regulations is also

necessary when supervising CBT with youth[13,17,47]. Attention to issues of confidentiality are especially important when working with young patients. Clinicians need to be ever mindful regarding WHO is their patient. Additionally, alertness to child abuse and maltreatment is a priority. Training supervisees in identifying and managing common hazardous issues such as self-injurious, suicidal, homicidal, risky sexual and substance abusing behaviors is also pivotal.

Training in collaborative empiricism[32,48] is an indispensable pedagogical task. Collaboration is especially valuable since it promotes trust and fosters experimentation with techniques[32]. The empiricism part of the equation refers to the transparent data based nature of CBT with youth. Moreover, the reliance on data coming directly from young patients and their families is linked to CBT's phenomenological roots[49]. In particular, collaboration is a difficult practice to develop especially for supervisees who are more comfortable with either overly prescriptive or non-directive approaches.

Teaching trainees the rudiments of guided discovery is important yet quite challenging[48]. Many supervisees perceive guided discovery as a common pitfall in clinical practice[33]. Simply stated, guided discovery involves helping young patients form more adaptive conclusions and flexible attitudes based on their personal data base. Similar to collaborative empiricism, guided discovery is rooted in a hypothesis testing stance[50]. Simply stated, guided discovery facilitates the art of the possible[45]. Empathic listening, Socratic dialogues homework assignments and behavioral experiments are components of guided discovery.

Teaching trainees' to implement the trademark session structure is another crucial task. Mood check-ins, agenda setting, processing session content, assigning homework, and eliciting feedback are the requisite components[51]. Applying a regular format to sessions is typically foreign to most beginning trainees. It is also helpful to teach them that these elements are both procedures and processes so they are less likely to apply a mechanical, stereotyped approach to session structure.

Embracing immediacy in CBT with is another core skill[52-54]. Immediacy involves addressing emotionally evocative moments in the here and now. A contemporary article contended immediacy occurs when "psychotherapeutic moments are charged with the urgency and genuineness of emotional experience in present tense and real time[53]." Immediacy in session avoids an intellectualized, emotionally sterile, and mechanical approach to CBT with young people.

Measurement based care (MBC) is another vital content element. MBC ensures accountability and collaborative monitoring of treatment progress. Simply, MBC involves regular periodic examination of patients' functioning through a combination of symptom scales, indices of functional improvement, and patient satisfaction measures[55].

Instruction in the theory, empirical support and practice of traditional cognitive behavioral techniques is standard fare in CBT supervision with youth[56-67]. Teaching psychoeducational, behavioral tasks, cognitive restructuring techniques, and exposure procedures typically involves reading assignments, verbal discussion, modeling, and opportunities for trainees to rehearse the intervention. Of course, practice is accompanied by supervisory feedback.

Supervisees' experience various thoughts and feelings regarding clinical work with young patients. Accordingly, processing trainees' thoughts, feelings and actions[13,21,25-27,30,45-47,57,67-69] is an integral supervisory responsibility. Trainees hold various dysfunctional beliefs about their competence and adhere to unrelenting performance standards. Moreover, trainees may be impatient and intolerant of ambiguity. Some supervisees may be reluctant to address patients' heightened negative affectivity. Others may fear their young patients' anger. Trainees may also worry about risking their supervisees' disapproval. It is not uncommon for students' to resent getting direction from their supervisors. Regardless of the particular beliefs about their clinical work that go through supervisees' minds, supervisors apply cognitive behavioral practices and processes such as collaboration, guided discovery, and socratic dialogues to straighten out crooked thinking during training.

SUPERVISORY PROCEDURES AND PROCESSES

Supervisees' skills are sharpened *via* audio/video taped review didactic instruction, Socratic methods, modeling, behavioral rehearsal, and feedback[12,13]. The procedures and processes utilized in supervision of CBT for youth are embedded within a productive learning environment. This section discusses the deployment of audiotaped/review, enactive supervision, and structured rating scales during training.

Trainees appear to learn best from supervisory relationships that are characterized by supportiveness, authenticity, and are clinically relevant[70]. Moreover, supervisors who are respectful, knowledgeable, and collaborative appear most effective[62]. Supervisees appreciate sessions that address clinical practice[70]. In short, supervisors are well advised to cultivate a productive learning environment[30].

Audio and/or video-taped review of trainees sessions with young patients is widely recommended[12,13,18,22,23,59,60,62,63,70,71]. However, the actual use in community settings is disappointing[23,71-74]. Several studies in the United Kingdom found reviews of tapes to occur inn 6%[74] and 20% of cases[72]. Further, only 18% of supervisors studied in the United Kingdom reported reviewing tapes[72]. These low incidences also characterize supervision in the United States. Only 12% of supervisors studied employed video-tape review and 8% used audiotape[23].

Enactive supervision is recommended a best training strategy[12,13,20,30,31,69]. Behavioral rehearsal is a powerful

training tool[26,63,75-78]. In a recent study[78], the procedure was defined as "a simulated interaction between a trainee and another individual". Essentially, behavioral rehearsal facilitates learning through repeated practice. Authors[63] have argued that "providing an opportunity for trainees to experiment with nascent skills promotes greater self-efficacy and better conceptual understanding".

Supervisors are advised to keep several guidelines for role-playing in mind[20,78]. Role-plays need to be explicitly and systematically processed. The lessons learned through the role-play need to be reviewed with the supervisee. Second, role-plays need to be emotionally similar to real life clinical scenarios in order to facilitate transfer of learning. More specifically, "if role plays are too emotionally sanitized and dissimilar to genuine therapist-patient interactions they are merely abstract intellectualized activities rather than experiential learning exercises"[20].

There is some evidence that BR is anxiety producing for trainees[79]. For instance, in one study, fewer trainees were willing to participation in a study involving performance evaluations based on BR and there was a high attrition rate. There appears to be a dose effect for BR with a 2:1 passive to active learning ratio suggested[70]. Supervisors should strike a balance between exhausting trainees with too much BR and electing to do too little practice. Additionally, behavioral rehearsal is shown to be most effective with supervisees who are most engaged in the learning process[77].

Providing positive and negative feedback to supervisees is another critical task[12,13,29,61,80]. More specifically, trainees who engaged in behavioral rehearsal tended to overestimate their performance following the role-play[81]. Further, supervisors tend to be overly complimentary perhaps in a desire to please their trainees[26]. When constructive feedback is given, the criticisms are generally vague and unstructured[26]. Feedback is important so supervisees can identify and address their smart spots, dumb spots and blind spots[20]. In particular, smart spots are strengths, dumb spots refer to gaps in knowledge, and blind spots are errors caused by lack of awareness and/or obliviousness to the patient[20].

Recording trainee progress on rating scales is an essential practice for providing feedback[12,13,21,22,57,80]. Various instruments for measuring trainee progress were recently summarized[22]. Most of the available measurement methods are based on work with trainees treating adults. The instruments emphasize application of procedural knowledge. The Cognitive Therapy Rating Scale (CTRS)[56] is a widely used gold standard. It includes 11 items evaluated on a 6 point Likert scale. The items include understanding, interpersonal effectiveness, pacing, agenda setting, feedback, homework, focus on key cognitions, strategy for change, collaboration, guided discovery, and proficiency in cognitive behavioral procedures.

The Cognitive Behavioural Therapy Scale for Children and Young People (CBTS-CYP)[64] assesses supervisees' performance on across various competency areas. These domains include general skills, investigating, partnership, empathy, cognitive techniques, behavioral techniques, emotional techniques, formulation, and discovery experiments. Initial data indicates very sound psychometric properties.

The Cognitive Therapy Rating Scale for Children and Adolescents[65,81,82] is a promising new measure that is based on the original CTRS but is modified to fit the needs of clinicians working with young patients. It retains items addressing pacing, interpersonal effectiveness/empathy, agenda setting, feedback, homework, strategy for change, focus on key cognitions, guided discovery, collaboration, and technical proficiency. However, the CTRS-CA adds extra items evaluated clinicians' playfulness, informality, and credibility. Initial reports indicate supervisors' high levels of satisfaction with the instrument[83].

The Self-evaluation learning form (SELF)[83] was originally developed for supervision with psychiatric residents, but it is also applicable to work with trainees from other disciplines. The SELF tracks patient metrics and supervisees' progress as well as summarizing content from each supervisory session. The worksheet also serves as a reminder for any homework tasks assigned to the supervisee.

Training professionals to become supervisors is an area gaining increased attention. Most recently, meta-supervision is being employed as a training procedure. Meta-supervision is defined as the circumstance where "a highly experienced clinician serves as a consultant to a clinical supervisor[84]." Essentially, this is supervision of supervision. Meta-supervision works to improve supervision skills, operationalize progress through performance ratings, and offers case management tips[84].

A useful rubric and accompanying rating scale for meta-supervision is recently available[25]. The rating scale addresses the supervisory context, aims, session structure, use of educational principles, CBT competencies, feedback, theoretical faithfulness, intervention methods, supervisory relationship issues as well as pacing and timing. The items are scored on a 1 (incompetent)-6 (expert) scale with higher scores indicating greater skillfulness. Further, the Cognitive Therapy Supervision Checklist[85] is a checklist for supervisors to rate trainees' competence. The scale evaluates clinical proficiency on various CBT procedures and processes. It explicitly addresses competencies set for by the American Association of Directors of Psychiatric Residency Training (AADPRT).

SUPERVISION OUTCOMES

While clinical supervision is the primary way trainees learn to do psychotherapy, there is minimal literature evaluating its effectiveness[23]. Effectiveness may be studied in a variety of ways. Outcomes could be operationalized as positive changes in supervisory performance or young patients' clinical presentations. For instance,

effectiveness could be measured as increases in young people's adaptive functioning or improved symptom scores. Alternatively, good supervisory outcomes could be evaluated in terms of trainees' acquisition/application of skills, fidelity to a treatment approach, and/or self-reflection.

Clinical effectiveness or improved treatment outcome is defined as the "acid test" of good supervision[86-88]. In a recent study, supervision was found to have a significant moderate effect on clinical outcomes[88]. More specifically, supervision accounted for 18% of the variance in patient outcomes. This effect is approximately two times the effect size owned by the common factors research[88]. In general, there is wide agreement that good CBT training on is associated with improved supervisee performance[74,89,90]. Effective training improves staff performance and technical proficiency[15].

There is a growing body of research examining the effectiveness of supervision emphasizing self-practice and self-reflection[90-94]. Self-reflection and self-practice increased trainees understanding of the cognitive model[91-93]. Additionally, this model of supervision enhanced supervisees' technical proficiency[90-92]. Finally, supervisees' flexibility was improved *via* this practice[91].

LIMITATIONS

The majority of work on supervision of cognitive behavioral therapy is characterized by anecdotal reports, case studies, surveys, and quasi-experimental designs rendering the results vulnerable to various threats to internal and external validity. Factors such differential history, maturity, selection bias, and attrition compromise scientific conclusions. Finally, there is significant ambiguity regarding the selection of proper outcome variables or measures. Some investigators propose patient improvement as the gold-standard or acid-test whereas others employ indices reflecting improved skills, knowledge, and attitudes. The unclarity of outcome measures truncates generalizability of results.

RECOMMENDATIONS

Delivering and receiving good clinical supervision in CBT with youth are necessary steps toward improving the care of young patients. Achieving these lofty goals requires deliberate action. Based on the literature reviewed, several recommendations for advancing the science and practice of CBT supervision follows.

Competent supervision for CBT with youth requires that trainers are skillful in both clinical practice with young patients and training inexperienced colleagues. Consequently, supervisors need to be properly credentialed in the approach. Fortunately, credentialing bodies exist (American Board of Professional Psychology, Academy of Cognitive Therapy, British Association of Behavioral and Cognitive Psychotherapy, Oxford University, *etc.*). In short, supervisees are well-advised to seek supervision from documented experts.

Focused attention should be directed to the core content in supervision of CBT with youth. Acquiring and applying didactic and procedural knowledge is essential for trainees. Enactive supervision is highly recommended. Consequently, the opportunity to engage in behavioral rehearsal is key. In an action-oriented approach, practicing procedures is a priority. Behavioral rehearsal seems especially important when training supervisees in exposure techniques. Gaining greater self-efficacy in this crucial intervention may increase more application in clinical settings.

In order to do their job well, supervisors need first-hand knowledge of their students' work and young patients' functioning. Audiotape, videotape, or direct observation of sessions is a preferred pedagogical strategy. Reviewing tapes is commonly anxiety producing to supervisees. Additionally, tape review is time-consuming for supervisors. Finally, taping requires the proper electronic equipment which translates to increased cost to agencies. Perhaps, these are some the reasons that tape reviews are relatively rare in treatment-as-usual settings.

Hiring competent supervisors and creating a training infra-structure that supports best practices in supervision are costly endeavors. Good training efforts should be scalable and reach as many practitioners as possible. In an environment where lean budgets are pervasive, scalability of training is clearly linked with economic considerations.

Administrators, clinical supervisors, and front-line staff should be on the same page regarding the value of good supervision. However, often these multiple stakeholders are at odds with each other. Administrators worry about the loss of revenue when staff are engaged in activities that do not involve reimbursable clinical encounters. Staff then become concerned about their ability to meet productivity benchmarks if they take time away for supervision. Advocates for better supervision and training must persuade stakeholders that these educational activities are good returns on their investment of time and money. The studies listed in the supervisory outcome section offers a nice launching pad for arguments regarding returns on investment.

This therapeutic advances article made the case for providing competent supervision to clinicians conducting CBT with youth. The value of supervision was delineated. The core elements of supervision of CBT with youth were outlined and the fundamental supervisory processes were discussed. Finally, a sample of supervisory outcome studies were summarized. Ideally, this contribution in therapeutic advances spurs academicians, clinicians, and behavioral health care administrators to fully invest in competent supervision of clinicians who provide CBT to young patients.

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REVIEW

Behavioural and emotional disorders in childhood: A brief overview for paediatricians

Michael O Ogundele

Michael O Ogundele, Department of Community Paediatrics, NHS Fife, Glenwood Health Centre, Glenrothes KY6 1HK, United Kingdom

ORCID number: Michael O Ogundele (0000-0003-0744-1434).

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Correspondence to: Dr. Michael O Ogundele, MBBS, MRCP, MSc, Consultant Paediatrician, Department of Community Paediatrics, NHS Fife, Glenwood Health Centre, Napier Road, Glenrothes KY6 1HK, United Kingdom. m.ogundele@nhs.net
Telephone: +44-1592-765096
Fax: +44-1592-765096

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Abstract

Mental health problems in children and adolescents include several types of emotional and behavioural disorders, including disruptive, depression, anxiety and pervasive developmental (autism) disorders, characterized as either internalizing or externalizing problems. Disruptive behavioural problems such as temper tantrums, attention deficit hyperactivity disorder, oppositional, defiant or conduct disorders are the commonest behavioural problems in preschool and school age children. The routine Paediatric clinic or Family Medicine/General Practitioner surgery presents with several desirable characteristics that makes them ideal for providing effective mental health services to children and adolescents. DSM-5 and ICD-10 are the universally accepted standard criteria for the classification of mental and behaviour disorders in childhood and adults. The age and gender prevalence estimation of various childhood behavioural disorders are variable and difficult to compare worldwide. A review of relevant published literature was conducted, including published meta-analyses and national guidelines. We searched for articles indexed by Ovid, PubMed, PubMed Medical Central, CINAHL, EMBASE, Database of Abstracts and Reviews, and the Cochrane Database of Systematic reviews and other online sources. The searches were conducted using a combination of search expressions including "childhood", "behaviour", "disorders" or "problems". Childhood behaviour and emotional problems with their related disorders have significant negative impacts on the individual, the family and the society. They are commonly associated with poor academic, occupational, and psychosocial functioning. It is important for all healthcare professionals, especially the Paediatricians to be aware of the range of presentation, prevention and management of the common mental health problems in children and adolescents.

Key words: Childhood behavioural disorders; Disruptive behaviour disorder; Conduct disorder; Challenging behaviour; Emotional disorder; Anxiety; Depression; Autism; Pervasive developmental disorders

Core tip: Mental health problems in children and young people (CYP) include several types of emotional and behavioural disorders, including disruptive, depression, anxiety and pervasive developmental (autism) disorders, characterized as either "internalizing" or "externalizing". The routine Paediatric or General Practitioner clinic present with several desirable characteristics that makes them ideal for providing effective mental health services to CYP. Childhood mental health disorders have significant negative impacts on the individual, the family and the society. It is particularly important for all Paediatricians to be aware of the range of presentation, prevention and management of the common mental health problems in CYP.

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INTRODUCTION

Mental health disorders (MHD) are very common in childhood and they include emotional-obsessive-compulsive disorder (OCD), anxiety, depression, disruptive (oppositional defiance disorder (ODD), conduct disorder (CD), attention deficit hyperactive disorder (ADHD) or developmental (speech/language delay, intellectual disability) disorders or pervasive (autistic spectrum) disorders[1]. Emotional and behavioural problems (EBP) or disorders (EBD) can also be classified as either "internalizing" (emotional disorders such as depression and anxiety) or "externalizing" (disruptive behaviours such as ADHD and CD). The terminologies of "problems" and "disorders" are interchangeably used throughout this article.

While low-intensity naughty, defiant and impulsive behaviour from time to time, losing one's temper, destruction of property, and deceitfulness/stealing in the preschool children are regarded as normal, extremely difficult and challenging behaviours outside the norm for the age and level of development, such as unpredictable, prolonged, and/or destructive tantrums and severe outbursts of temper loss are recognized as behaviour disorders. Community studies have identified that more than 80% of pre-schoolers have mild tantrums sometimes but a smaller proportion, less than 10% will have daily tantrums, regarded as normative misbehaviours at this age[2,3]. Challenging behaviours and emotional difficulties are more likely to be recognized as "problems" rather than "disorders" during the first 2 years of life[4].

Emotional problems, such as anxiety, depression and post-traumatic stress disorder (PTSD) tend to occur in later childhood. They are often difficult to be recognised early by the parents or other carers as many children have not developed appropriate vocabulary and comprehension to express their emotions intelligibly[5]. Many clinicians and carers also find it difficult to distinguish between developmentally normal emotions (*e.g.*, fears, crying) from the severe and prolonged emotional distresses that should be regarded as disorders[6]. Emotional problems including disordered eating behaviour and low self-image are often associated with chronic medical disorders such as atopic dermatitis, obesity, diabetes and asthma, which lead to poor quality of life[7-9].

Identification and management of mental health problems in primary care settings such as routine Paediatric clinic or Family Medicine/General Practitioner surgery are cost-effective because of their several desirable characteristics that makes it acceptable to children and young people (CYP) (*e.g.*, no stigma, in local setting, and familiar providers). Several models to improve the delivery of mental health services in the Paediatric/Primary care settings have been recommended and evaluated recently, including coordination with external specialists, joint consultations, improved Mental Health training and more integrated on-site intervention with specialist collaboration[10,11].

A review of relevant published literature was conducted, including published meta-analyses and national guidelines. We searched for articles indexed by Ovid, PubMed, PubMed Medical Central, CINAHL, the Cochrane Database of Systematic reviews and other online sources. The searches were conducted using a combination of search expressions including "childhood", "behaviour", "disorders" or "problems".

CLINICAL PRESENTATIONS OF CHILDHOOD BEHAVIOURAL AND EMOTIONAL DISORDERS

Various definitions for a wide range of childhood behavioural disorders are being used. The DSM-5[12] offers the commonest universally accepted standard criteria for the classification of mental and behaviour disorders. The ICD-10 is the alternative classification standard[13].

Challenging behaviours

Any abnormal pattern of behaviour which is above the expected norm for age and level of development can be described as "challenging behaviour". It has been defined as: "Culturally abnormal behaviour (s) of such an intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy or behaviour which is likely to seriously limit or deny access to and use of ordinary community facilities"[14]. They can include self-injury, physical or verbal aggression, non-compliance, disruption of the environment, inappropriate vocalizations, and various stereotypies. These behaviours can impede

Table 1 Subtypes of attention deficit hyperactivity disorder (based on DSM-5)

Subtypes	Predominantly inattentive (ADD)	Predominantly hyperactivity/ impulsivity	Combined ADHD
Criteria	6 of 9 inattentive symptoms	6 of 9 hyperactivity/ impulsivity symptoms	Both criteria for (1) and (2)
Details	Fails to pay close attention to details or makes careless mistakes	Squirms and fidgets	
	Has difficulty sustaining attention	Can't stay seated	
	Does not appear to listen	Runs/climbs excessively	
	Struggles to follow through on instructions	Can't play/work quietly	
	Has difficulty with organization	"On the go"/"driven by a motor"	
	Avoids or dislikes tasks requiring a lot of thinking	Blurts out answers	
	Loses things	Is unable to wait for his turn	
	Is easily distracted	Intrudes/interrupts others	
		Talks excessively	
Other criteria	Onset before age of 12, lasting more than 6 mo, symptoms pervasive in 2 or more settings, causing significant impairment of daily functioning o development		

ADHD: Attention deficit hyperactivity disorder.

learning, restrict access to normal activities and social opportunities, and require a considerable amount of both manpower and financial resources to manage effectively.

Many instances of challenging behaviour can be interpreted as ineffective coping strategies for a young person, with or without learning disability (LD) or impaired social and communication skills, trying to control what is going on around them. Young people with various disabilities, including LD, Autism, and other acquired neuro-behavioural disorders such as brain damage and post-infectious phenomena, may also use challenging behaviour for specific purposes, for example, for sensory stimulation, gaining attention of carers, avoiding demands or to express their limited communication skills[15]. People who have a diverse range of neurodevelopmental disorders are more likely to develop challenging behaviours[16].

Some environmental factors have been identified which are likely to increase the risk of challenging behaviour, including places offering limited opportunities for making choices, social interaction or meaningful occupation. Other adverse environments are characterized by limited sensory input or excessive noise, unresponsive or unpredictable carers, predisposition to neglect and abuse, and where physical health needs and pain are not promptly identified. For example, the rates of challenging behaviour in teenagers and people in their early 20 s is 30%-40% in hospital settings, compared to 5% to 15% among children attending schools for those with severe LD[15].

Aggression is a common, yet complex, challenging behaviour, and a frequent indication for referral to child and adolescent Psychiatrists. It commonly begins in childhood, with more than 58% of preschool children demonstrating some aggressive behaviour[17]. Aggression has been linked to several risk factors, including individual temperaments; the effects of disturbed family dynamics; poor parenting practices; exposure to violence and the influence of attachment disorders. No single factor is sufficient to explain the development of aggressive behaviour[18]. Aggression is commonly diagnosed in association with other mental health problems including ADHD, CD, ODD, depression, head injury, mental retardation, autism, bipolar disorder, PTSD, or dyslexia[19].

Disruptive behaviour problems

Disruptive behaviour problems (DBP) include attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and conduct disorder (CD). They constitute the commonest EBPs among CYP. Recent evidence suggests that DBPs should be regarded as a multidimensional phenotype rather than comprising distinct subgroups[20].

ADHD is the commonest neuro-behavioural disorder in children and adolescents, with prevalence ranging between 5% and 12% in the developed countries[21]. ADHD is characterized by levels of hyperactivity, impulsivity and inattention that are disproportionately excessive for the child's age and development[12]. The ICD-10[13] does not use the term "ADHD" but "hyperkinetic disorder", which is equivalent to severe ADHD. DSM-5 distinguishes between three subtypes of the disorder: predominantly hyperactive/impulsive, predominantly inattentive and combined types (Table 1).

CD refers to severe behaviour problems (Table 2), characterized by repetitive and persistent manifestations of serious aggressive or non-aggressive behaviours against people, animals or property such as being defiant, belligerent, destructive, threatening, physically cruel, deceitful, disobedient or dishonest, excessive fighting or bullying, fire-setting, stealing, repeated lying, intentional injury, forced sexual activity and frequent school truancy[13,22]. Children with CD often have trouble understanding how other people think, sometimes described as being callous-unemotional. They may falsely misinterpret the intentions of other people as being mean. They may have immature language skills, lack the appropriate social skills to establish and maintain friendships, which aggravates their feelings of sadness, frustration and anger[12].

CD is the commonest reason for CYP referral for psychological and psychiatric treatment. Roughly 50% of all CYP with a MHD have a CD[23]. About 30%-75% of children with CD also have ADHD and 50% of them will also meet criteria for at least one other disorder including

Table 2 DSM-5 definition of conduct disorder and oppositional defiant disorder

Oppositional defiant disorder	Conduct disorder
A pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness lasting at least 6 mo as evidenced by at least four out of 8 symptoms from any of the following categories, and exhibited during interaction with at least one individual who is not a sibling Angry/irritable mood: (1) Often loses temper; (2) Is often touchy or easily annoyed; (3) Is often angry and resentful Argumentative/defiant behavior: (4) Often argues with authority figures or, for children and adolescents, with adults; (5) Often actively defies or refuses to comply with requests from authority figures or with rules; (6) Often deliberately annoys others; (7) Often blames others for his or her mistakes or misbehavior Vindictiveness: (8) Has been spiteful or vindictive at least twice within the past 6 mo Note: The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic and the behavior should occur at least once per week for at least 6 mo The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (*e.g.*, family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder Specify current severity: Mild; moderate or severe based on number of settings with symptoms shown	A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of at least three of the following 15 criteria in the past 12 mo from any of the categories below, with at least one criterion present in the past 6 mo Aggression to people and animals: (1) Often bullies, threatens, or intimidates others; (2) Often initiates physical fights; (3) Has used a weapon that can cause serious physical harm to others (*e.g.*, a bat, brick, broken bottle, knife, gun); (4) Has been physically cruel to people; (5) Has been physically cruel to animals; (6) Has stolen while confronting a victim (*e.g.*, mugging, purse snatching, extortion, armed robbery); (7) Has forced someone into sexual activity Destruction of property: (8) Has deliberately engaged in fire setting with the intention of causing serious damage; (9) Has deliberately destroyed others' property (other than by fire setting) Deceitfulness or theft: (10) Has broken into someone else's house, building, or car; (11) Often lies to obtain goods or favors or to avoid obligations (*i.e.*, "cons" others); (12) Has stolen items of nontrivial value without confronting a victim (*e.g.*, shoplifting, but without breaking and entering; forgery) Serious violations of rules: (13) Often stays out at night despite parental prohibitions, beginning before age 13 yr; (14) Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period; (15) Is often truant from school, beginning before age 13 yr The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning If the individual is age 18 yr or older, criteria are not met for antisocial personality disorder Specify whether: Childhood-onset type (prior to age 10 yr); Adolescent-onset type or Unspecified onset Specify if: With limited prosocial emotions: Lack of remorse or guilt; Callous-lack of empathy; Unconcerned about performance or Shallow or deficient affect Specify current severity: Mild; Moderate or Severe ICD-10 It also requires the presence of three symptoms from the list of 15 (above), and duration of at least 6 mo. There are four divisions of conduct disorder: Socialised conduct disorder, unsocialised conduct disorder, conduct disorders confined to the family context and oppositional defiant disorder

Mood, Anxiety, PTSD, Substance abuse, ADHD, learning problems, or thought disorders[24,25]. Majority of boys have an onset of CD before the age of 10 years, while girls tend to present mainly between 14 and 16 years of age[26]. Most CYP with CD grow out of this disorder, but a minority become more dissocial or aggressive and develop antisocial personality disorder as adults.

ODD is considered to be the mildest and commonest of the DBPs, with prevalence estimates of 6%-9% for pre-schoolers and boys outnumbering girls by at least two to one[27]. CYP with ODD are typically openly hostile, negativistic, defiant, uncooperative, and irritable. They lose their tempers easily and are mean and spiteful towards others (Table 2). They are mostly defiant towards authority figures, but they may also be hostile to their siblings or peers. This pattern of adversarial behaviour significantly negatively impact on their lives at home, school, and wider society, and seriously impairs all their relationships[28].

Emotional problems

Emotional problems in later childhood include panic disorder, generalized anxiety disorder (GAD), separation anxiety, social phobia, specific phobias, OCD and depression. Mild to moderate anxiety is a normal emotional response to many stressful life situations. Anxiety is regarded as a disorder when it is disproportionately excessive in severity in comparison to the gravity of the triggering circumstances, leading to abnormal disruption of daily routines. Panic disorder is characterized by panic attacks untriggered by external stimuli. GAD is characterized by generalized worry across multiple life domains. Separation anxiety disorder is characterized by fear related to actual or anticipated separation from a caregiver. Social anxiety disorder (also called social phobia), is characterized by fear of social situations where peers may negatively evaluate the person[12].

Common manifestations of Anxiety disorders include physical symptoms such as increased heart rate, shortness of breath, sweating, trembling, shaking, chest pain, abdominal discomfort and nausea[29]. Other symptoms include worries about things before they happen, constant concerns about family, school, friends, or activities, repetitive, unwanted thoughts (obsessions) or actions (compulsions), fears of embarrassment or making mistakes, low self-esteem and lack of self-confidence[30].

Depression often occurs in children under stress, experiencing loss, or having attentional, learning, conduct or anxiety disorders and other chronic physical ailments. It also tends to run in families[7-9,31]. Symptoms of depression are diverse and protean, often mimicking other physical and neurodevelopmental problems,

Table 3 DSM-5 criteria for autism spectrum disorders

Persistent deficits in social communication and social interaction across multiple contexts, as manifested by 3 out 3 of the following, currently or by history
Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions
Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication
Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers
Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two out of 4 of the following, currently or by history
Stereotyped or repetitive motor movements, use of objects, or speech (*e.g.*, simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases)
Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (*e.g.*, extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day)
Highly restricted, fixated interests that are abnormal in intensity or focus (*e.g.*, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest)
Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (*e.g.*, apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement)
Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life)
Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
Specify if
With or without accompanying intellectual impairment
With or without accompanying language impairment
Associated with a known medical or genetic condition or environmental factor
Specify current severity based on social communication impairments and restricted, repetitive patterns of behavior

including low mood, frequent sadness, tearfulness, crying, decreased interest or pleasure in almost all activities; or inability to enjoy previously favourite activities, hopelessness, persistent boredom; low energy, social isolation, poor communication, low self-esteem and guilt, feelings of worthlessness, extreme sensitivity to rejection or failure, increased irritability, agitation, anger, or hostility, difficulty with relationships, frequent complaints of physical illnesses such as headaches and stomach aches, frequent absences from school or poor performance in school, poor concentration, a major change in eating and/or sleeping patterns, weight loss or gain when not dieting, talk of or efforts to run away from home, thoughts or expressions of suicide or self-destructive behaviour[31].

Disruptive mood dysregulation disorder (DMDD) is a childhood disorder characterized by a pervasively irritable or angry mood recently added to DSM-5. The symptoms include frequent episodes of severe temper tantrums or aggression (more than three episodes a week) in combination with persistently negative mood between episodes, lasting for more than 12 mo in multiple settings, beginning after 6 years of age but before the child is 10 years old[32].

Autistic spectrum and pervasive development disorder

The definition of Autism has evolved over the years and has been broadened over time. DSM-IV-TR[33] and the ICD-10[13] defined the diagnostic category of pervasive developmental disorders (PDD) as the umbrella terminology used for a group of five disorders characterized by pervasive "qualitative abnormalities in reciprocal social interactions and in patterns of communication, and by a restricted, stereotyped, repetitive repertoire of interests and activities" affecting "the individual's functioning in all situations". These included autism, asperger syndrome, childhood disintegrative disorder (CDD), pervasive developmental disorder not otherwise specified (PDD-NOS) and Rett syndrome.

Autism and Asperger Syndrome are the most widely recognised and clinically diagnosed among this group of disorders. CDD is a term used to describe children who have had a period of normal development for the first 2-3 years before a relatively acute onset of regression and emergence of autistic symptoms. PDD-NOS was used, particularly in the United States, to describe individuals who have autistic symptoms, but do not meet the full criteria for Autism or Asperger's Syndrome, denote a milder version of Autism, or to describe atypical autism symptoms emerging after 30 mo of age, and autistic individuals with other co-morbid disorders[34].

The category of PDD has been removed from DSM-5[12] and replaced with Autism Spectrum disorders (ASD). ASD (Table 3) is diagnosed primarily from clinical judgment usually by a multidisciplinary team, with minimal support from diagnostic instruments. Most individuals who received diagnosis based on the DSM-IV should still maintain their diagnosis under DSM-5, with some studies confirming that 91% to 100% of children with PDD diagnoses from the DSM-IV retained their diagnosis under the ASD category using the new DSM-5[35,36], while a systematic review has found a slight decrease in the rate of ASD with DSM-5[37].

There are many intervention approaches and strategies, used alone or in combination, for supporting individuals with ASD. These interventions need to

Table 4 Summary of common social communication enhancement strategies

Method	Description	Ref.
Augmentative and alternative communication	Supplements/replaces natural speech and/or writing with aided [*e.g.*, Picture Exchange Communication System, line drawings, Blissymbols, speech generating devices, and tangible objects] and/or unaided (*e.g.*, manual signs, gestures, and finger spelling) symbols Effective in decreasing maladaptive or challenging behaviour such as aggression, self-injury and tantrums, promotes cognitive development and improves social communication	[39,129-131]
Activity schedules/visual supports	Using photographs, drawings, or written words that act as cues or prompts to help individuals complete a sequence of tasks/activities or behave appropriately in various settings Scripts are often used to promote social interaction, initiate or sustain interaction	[132]
Computer-/video-based instruction	Use of computer technology or video recordings for teaching language skills, social skills, social understanding, and social problem solving	[40]

Table 5 Summary of common behavioural modification strategies for management of childhood emotional and behavioural disorder

Method	Description	Ref.
ABA	Uses principles of learning theory to bring about meaningful and positive change in behaviour, to help individuals build a variety of skills (*e.g.*, communication, social skills, self-control, and self-monitoring) and help generalize these skills to other situations	[122,123]
Discrete trial training	A one-to-one instructional approach based on ABA to teach skills in small, incremental steps in a systematic, controlled fashion, documenting stepwise clearly identified antecedent and consequence (*e.g.*, reinforcement in the form of praise or tangible rewards) for desired behaviours	[40]
Functional communication training	Combines ABA procedures with communicative functions of maladaptive behaviour to teach alternative responses and eliminate problem behaviours	[124]
Pivotal response treatment	A play-based, child-initiated behavioural treatment, designed to teach language, decrease disruptive behaviours, and increase social, communication and academic skills, building on a child's initiative and interests	[125]
Positive behaviour support	Uses ABA principles with person-centred values to foster skills that replace challenging behaviours with positive reinforcement of appropriate words and actions. PBS can be used to support children and adults with autism and problem behaviours	[126]
Self-management	Uses interventions to help individuals learn to independently regulate, monitor and record their behaviours in a variety of contexts, and reward themselves for using appropriate behaviours. It's been found effective for ADHD and ASD children	[127]
Time delay	It gradually decreases the use of prompts during instruction over time. It can be used with individuals regardless of cognitive level or expressive communication abilities	[40]
Incidental teaching	Utilizes naturally occurring teaching opportunities to reinforce desirable communication behaviour	[128]
Anger management	Various strategies can be used to teach children how to recognise the signs of their growing frustration and learn a range of coping skills designed to defuse their anger and aggressive behaviour, teach them alternate ways to express anger, including relaxation techniques and stress management skills	

ABA: Applied behaviour analysis; ADHD: Attention deficit hyperactivity disorder; ASD: Autistic spectrum disorder.

individualized and be closely tailored to the level of social and linguistic abilities, cultural background, family resources, learning style and degree of communication skills[38].

Various communication enhancement strategies have been designed to manage ASD[39], including augmentative and alternative communication (AAC), Facilitated Communication, computer-based instruction and video-based instruction (Table 4). Several behavioural and psychological interventions (Table 5) have also been used successfully in managing ASD children, including applied behaviour analysis (ABA) and functional communication training (FCT)[40].

Social (pragmatic) communication disorder

Social (pragmatic) communication disorder (SCD) is a new diagnosis included under Communication Disorders in the Neurodevelopmental Disorders section of the DSM-5[12]. It is characterized by persistent difficulties with using verbal and nonverbal communication for social purposes, which can interfere with interpersonal relationships, academic achievement and occupational performance, in the absence of restricted and repetitive interests and behaviours (Table 6). Some authors consider that CYP with SCD present with similar but less severe restricted and repetitive interests and behaviours (RRIBs) characteristic of children on the autistic spectrum[41]. SCD is thought to occur more frequently in family members of individuals with autism[42].

The term "pragmatic" has been used previously to describe the communication skills that are needed in normal social intercourse and the rules that govern routine interpersonal interactions, including ability to pay at least some attention to the other person in a conversation, take turns, not interrupting the other speaker unless there is a very good reason, match language and volume to the situation and the listener, *etc*[43]. Social and pragmatic deficit are known to also occur in

Table 6 DSM-5 criteria for social (pragmatic) communication disorder

Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following
Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for social context
Impairment in the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on a playground, talking differently to a child than to an adult, and avoiding use of overly formal language
Difficulties following rules for conversation and storytelling, such as taking turns in conversation, rephrasing when misunderstood, and knowing how to use verbal and nonverbal signals to regulate interaction
Difficulties understanding what is not explicitly stated (*e.g.*, making inferences) and nonliteral or ambiguous meaning of language (*e.g.*, idioms, humor, metaphors, multiple meanings that depend on the context for interpretation)
The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement, or occupational performance, individually or in combination
The onset of the symptoms is in the early developmental period (but deficits may not become fully manifest until social communication demands exceed limited capacities)
The symptoms are not attributable to another medical or neurological condition or to low abilities in the domains of word structure and grammar, and are not better explained by autism spectrum disorder, intellectual disability (intellectual developmental disorder), global developmental delay, or another mental disorder

diverse clinical populations, including ADHD, William's syndrome, CD, closed head injury and spina bifida/hydrocephalus[44].

Treatment modalities that have been used for supporting children with SCD are similar to those that have been used for several years in children with ASD (Tables 4 and 5). The first randomized controlled trial of social communication interventions designed primarily for children with SCD was reported in 2012[45]. The Social Communication Intervention Project (http://www.psych-sci.manchester.ac.uk/scip/) targets development in social understanding and interaction, verbal and nonverbal pragmatic skills and language processing among children with SCD.

Pathological demand avoidance or Newson's syndrome

Pathological demand avoidance (PDA) or Newson's Syndrome is increasingly being accepted as part of the autism spectrum. PDA was first used in 2003[46] for describing some CYP with autistic symptoms who showed some challenging behaviours. It is characterized by exceptional levels of demand avoidance requested by others, due to high anxiety levels when the individuals feel that they are losing control. Avoidance strategies can range from simple refusal, distraction, giving excuses, delaying, arguing, suggesting alternatives and withdrawing into fantasy, to becoming physically incapacitated (with an explanation such as "my legs don't work") or selectively mute in many situations. If they feel threatened to comply, they may become verbally or physically aggressive, best described as a "panic attack", apparently intended to shock[46]. They tend to resort to "socially manipulative" behaviours. The outrageous acts and lack of concern for their behaviour appears to draw parallels with conduct problems (CP) and callous-unemotional traits (CUT), but reward-based techniques, effective with CP and CUT, seem not to work in people with PDA[47]. PDA is currently neither part of the DSM-5[12] nor the ICD-10[13].

Though demand avoidance is a common characteristic of CYP with ASD, it becomes pathological when the levels are disproportionately excessive, and normal daily activities and relationships are negatively impaired. Unlike typically autistic children, people with PDA tend to have much better social communication and interaction skills, and are consequently able to use these abilities to their advantage. They often have highly developed social mimicry and role play, sometimes becoming different characters or personas. The people with PDA appear to retain a keen awareness of how to "push people's buttons", suggesting a level of social insight when compared to CYP with Autism. On the other hand, children with PDA exhibit higher levels of emotional symptoms compared to those with ASD or CD. They also often experience excessive mood swings and impulsivity. While the prevalence of ASD in boys is more than four times higher compared to that of girls, the risk of developing PDA appears to be the same for both boys and girls[47].

O'Nions *et al*[48] have recently reported on the development and preliminary validation of the "Extreme Demand Avoidance Questionnaire" (EDA-Q), designed to quantify PDA traits based on parent-reported information, with good sensitivity (0.80) and specificity (0.85). EDA-Q is available online (https://www.pdasociety.org.uk/resources/extreme-demand-avoidance-questionnaire).

PREVALENCE OF BEHAVIOURAL AND EMOTIONAL DISORDERS IN CHILDHOOD

Accurate estimation of various childhood EBPs is difficult due to the problems of research methodologies relying on subjective assessments and varying definitions used. According to most studies, between 10% and 20% of CYP are affected annually by MHDs, and the rates are very similar across different racial and ethnic groups after controlling for income, resident status, education, and neighbourhood support. However, poverty and low socioeconomic status are risk factors that appear to increase the rate of MHDs across populations[49]. A 2001 WHO report [50] indicated the 6-mo prevalence rate for any MHD in CYP, up to age 17 years, to be 20.9%, with disruptive behaviour disorders (DBD) at 10.3%, second

only to Anxiety disorders at 13%. About 5% of CYP in the general population suffer from Depression at any given point in time, which is more prevalent among girls (54%)[31,51].

A previous British Child and Adolescent Mental Health (CAMH) survey carried out by the office of National Statistics (ONS) in 1999 and 2004, comprising 7977 interviews from parents, children and teachers, found the prevalence of MHD among CYP (aged 5-16 years) to be 6% for conduct problems, 4% for emotional problems (Depression or Anxiety) and 1.5% for Hyperkinetic disorders[51]. A similar survey in the United States between 2005 and 2011, the National survey of children's health (NSCH) involving 78042 households, indicated that 4.6% of CYP aged 3-17 years had a history DBD, with prevalence twice as high among boys as among girls (6.2% *vs* 3.0%), Anxiety (4.7%), Depression (3.9%), and ASD (1.1%)[24]. Reported prevalence rates for DMDD range from 0.8% to 3.3% with the highest rate in preschool children[52].

AETIOLOGY AND RISK FACTORS FOR CHILDREN'S BEHAVIOURAL AND EMOTIONAL DISORDERS

The exact causes of various childhood EBPs are unknown. Several studies have identified various combinations of genetic predisposition and adverse environmental factors that increase the risk of developing any of these disorders. These include perinatal, maternal, family, parenting, socio-economic and personal risk factors[53]. Table 7 summarizes the evidence for various risk factors associated with development of childhood EBPs.

There is ample evidence supporting the genetic inheritability of many EBDs in CYP from their parents. From a prospective study of 209 parents along with their 331 biological offsprings, moderate inheritability ($r = 0.23$, $P < 0.001$) between parental and offspring CD was found[74]. Anxiety seems to be transmissible from mothers to their preschool children, through both genetic factors and also through behaviour modelling and an anxious style of parenting[6].

A developmental taxonomy theory has been proposed by Patterson *et al*[75] to help understand the mechanisms underlying early onset and course of CPs. They described the vicious cycle of non-contingent parental responses to both prosocial and antisocial child behaviour leading to the inadvertent reinforcement of child behaviour problems. Parents' engagement in "coercive cycles" lead to children learning the functional value of their aversive behaviours (*e.g.*, physical aggression) for escape and avoidance from unwanted interactions, ultimately leading to the use of heightened aversive behaviours from both the child and parents to obtain social goals. This adverse child behavioural training combined with social rejection often lead to deviant peer affiliation and delinquency in adolescence[76].

NEUROBIOLOGY OF CHILDHOOD BEHAVIOURAL AND EMOTIONAL DISORDERS

Conflicting findings have been reported in the brain structural variations among CYP with EBPs using magnetic resonance imaging (MRI) studies. The most consistently reported structural abnormalities associated with the DBD include reduced grey matter volume (GMV) in the amygdala, frontal cortex, temporal lobes, and the anterior insula, which is involved in part of a network related to empathic concern for others. Reduced GMV along the superior temporal sulcus has also been found, particularly in girls[77]. A decreased overall mean cortical thickness, thinning of the cingulate and prefrontal cortices; and decreased grey matter density in different brain regions have been reported[78].

Subtle neurobiological changes in different parts of the brain of CYP with EBPs have been reported from many research studies of functional scans. Peculiar brain changes have been found in the hypothalamus, inferior and superior parietal lobes, right amygdala and anterior insula[79]. Functional MRI studies have demonstrated less activation in the temporal cortex in violent adult offenders[80] and in antisocial and psychopathic individuals[81] compared to non-aggressive offenders.

Reduced basal Hypothalamic-Pituitary-Adrenal (HPA) axis activity has been reported in relation to childhood DBDs and to exposure to abuse and neglect[82]. It has been hypothesized that high levels of prenatal testosterone exposure appears to be part of the complex aetiology of EBDs, providing possible explanation for the higher prevalence in males for DBDs, by increasing susceptibility to toxic perinatal environments such as exposure to maternal nicotine and alcohol in pregnancy[83].

COMPLICATIONS OF CHILDHOOD BEHAVIOURAL AND EMOTIONAL DISORDERS

EBDs in childhood, if left untreated, may have negative short-term and long-term effects on an individual's personal, educational, family and later professional life. CD has been linked to failure to complete schooling, attaining poor school achievement, poor interpersonal relationships, particularly family breakup and divorce, and experience of long-term unemployment. DBPs in parents have been linked to the abuse of their offspring, thereby increasing their risk of developing CD[84,85]. Children presenting with hyperactivity-inattention behaviours are more likely to have a more favourable educational outcome compared with those with aggression or oppositional behaviours[86,87].

A high prevalence of sleep disturbances is associated with various childhood EBPs. Sleep problems in early childhood is associated with increased prevalence of

Table 7 Summary of common risk factors for development of childhood emotional and behavioural disorder

Domain	Characteristic examples	Ref.
Maternal psychopathology (mental health status)	Low maternal education, one or both parents with depression, antisocial behaviour, smoking, psychological distress, major depression or alcohol problems, an antisocial personality, substance misuse or criminal activities, teenage parental age, marital conflict, disruption or violence, previous abuse as a child and single (unmarried status)	[4,54]
Adverse perinatal factors	Maternal gestational moderate alcohol drinking, smoking and drug use, early labour onset, difficult pregnancies, premature birth, low birth weight, and infant breathing problems at birth	[55,56]
Poor child-parent relationships	Poor parental supervision, erratic harsh discipline, parental disharmony, rejection of the child, and low parental involvement in the child's activities, lack of parental limit setting	[57,58]
Adverse family life	Dysfunctional families where domestic violence, poor parenting skills or substance abuse are a problem, lead to compromised psychological parental functioning, increased parental conflict, greater harsh, physical, and inconsistent discipline, less responsiveness to children's needs, and less supportive and involved parenting	[59]
Household tobacco exposure	Several studies have shown a strong exposure–response association between second-hand smoke exposure and poor childhood mental health	[60,61]
Poverty and adverse socio-economic environment	Personal and community poverty signs including homelessness, low socio-economic status, overcrowding and social isolation, and exposure to toxic air, lead, and/or pesticides or early childhood malnutrition often lead to poor mental health development Chronic stressors associated with poverty such as single-parenthood, life stress, financial worries, and ever-present challenges cumulatively compromise parental psychological functioning, leading to higher levels of distress, anxiety, anger, depressive symptoms and substance use in disadvantaged parents. Chronic stressors in children also lead to abnormal behaviour pattern of 'reactive responding' characterized by chronic vigilance, emotional reacting and sense of powerlessness	[62-66]
Early age of onset	Early starters are likely to experience more persistent and chronic trajectory of antisocial behaviours Physically aggressive behaviour rarely starts after age 5	[67-69]
Child's temperament	Children with difficult to manage temperaments or show aggressive behaviour from an early age are more likely to develop disruptive behavioural disorders later in life Chronic irritability, temperament and anxiety symptoms before the age of 3 yr are predictive of later childhood anxiety, depression, oppositional defiant disorder and functional impairment	[70-72]
Developmental delay and Intellectual disabilities	Up to 70% of preschool children with DBD are more than 4 times at risk of developmental delay in at least one domain than the general population Children with intellectual disabilities are twice as likely to have behavioural disorders as normally developing children Rate of challenging behaviour is 5% to 15% in schools for children with severe learning disabilities but is negligible in normal schools	[15,73]
Child's gender	Boys are much more likely than girls to suffer from several DBD while depression tends to predominately affect more girls than boys Unlike the male dominance in childhood ADHD and ASD, PDA tends to affect boys and girls equally	[24,25,27,47,51]

ADHD: Attention deficit hyperactivity disorder; ASD: Autistic spectrum disorder; DBD: Disruptive behaviour disorder; PDA: Pathological demand avoidance.

later Anxiety disorders and ODD[88,89].

Several studies have confirmed a strong relationship between early childhood EBPs and poor future long-term physical and mental health outcomes. Chronic irritability in preschool children, CD and ODD in older children each may be predictive of any current and lifetime Anxiety, Depression and DBDs in later childhood, Mania, Schizophrenia, OCD, major depressive disorder and panic disorder[84,90-92]. Individuals on the adolescent-onset CP path often consume more tobacco and illegal drugs and engage more often in risky sexual behaviour, self-harm, and PTSD, than individuals without childhood conduct problems. They also frequently experience parenting difficulties, including over-reactivity, lax and inconsistent discipline, child physical punishment and lower levels of parental warmth and sensitivity[74,84,93,94]. Approximately 40%-50% of CYP with CD are at the risk of developing antisocial personality disorder in adulthood[84]. Other potential complications include adverse mental and physical health outcomes, social justice system involvement including incarceration, substance use and abuse, alcoholism, homelessness, poverty and domestic abuse[95,96].

An analysis of several Scandinavian studies up to the 1980s has shown higher rates of violent death, estimated to be almost five times higher than expected among young people with previous MHD, with common associated predictive factors including behavioural problems, school problems, and co-morbid alcohol or drug abuse and criminality[97].

ASSESSMENT AND DIAGNOSIS OF CHILDHOOD BEHAVIOURAL AND EMOTIONAL DISORDERS

Assessment through detailed history taking as well as observation of a child's behaviour are indispensable sources of information required for clinical diagnosis of EBPs[1]. This should include general medical, developmental, family, social, educational and emotional history. Physical and neurological examination should include assessment of vision, hearing, dysmorphic features, neuro-cutaneous stigmata, motor skills and cognitive assessment. Condition-specific and generic observer feedback on screening rating scales and questionnaires can be used to complement direct clinical observations.

There is no single gold-standard diagnostic tool available for the diagnosis of EBDs, which largely depends on the clinical skills of an integrated collaboration of multi-professional experts. Diagnosis relies on interpretation of subjective multi-source feedback from parents or carers, teachers, peers, professional or other observers provided through a number of psychometric questionnaires or screening tools[98]. Significant discrepancies between various respondents are quite common and clinical diagnosis cannot rely on the psychometric tools alone. There is evidence from the literature suggesting that parents have a tendency to over-report symptoms of ODD and CD in children compared to the teachers[99].

There are several screening tools that are used for assessing the risk of MHD among CYP. The tools help to identify which individuals would require more in-depth clinical interventions[100]. Supplement material shows a list of common Mental Health screening and assessment tools, summarizing their psychometric testing properties, cultural considerations and costs. The commonest behaviour screening tools include the Behavioral and Emotional Screening System (BESS; ages 3-18 years), the Behavior Assessment System for Children-2nd edition, Pediatric Symptom Checklist (PSC), the Ages and Stages Questionnaire-Social Emotional (ASQ-SE, Ages 0 to 5 years) and the Achenbach System of Empirically Based Assessment (ASEBA), for children aged 1.5 years through adulthood.

MANAGEMENT OF BEHAVIOURAL AND EMOTIONAL DISORDERS IN CHILDREN

Identification of appropriate treatment strategies depend on careful assessment of the prevailing symptoms, the family and caregiver's influences, wider socio-economic environment, the child's developmental level and physical health. It requires multi-level and multi-disciplinarian approaches that include professionals such as Psychologists, Psychiatrists, Behavioural Analysts, Nurses, Social care staff, Speech and language Therapists, Educational staff, Occupational Therapists, Physiotherapists, Paediatricians and Pharmacists. Use of pharmacotherapy is usually considered only in combination with psychological and other environmental interventions[15].

Holistic management strategies will include various combinations of several interventions such as child- and family-focused psychological strategies including Cognitive Behavioural Therapy (CBT), behavioural modification and social communication enhancement techniques, parenting skills training and psychopharmacology play significant roles in the management of children with a wide range of emotional, behavioural and social communication disorders. Effective alternative educational procedures also need to be implemented for the school age children and adolescents.

In early childhood, similar parenting strategies have been found useful to manage several apparently dissimilar EBPs (*e.g.*, infant feeding or sleeping problems, preschool tantrums, disruptive and various emotional problems). This may suggest there is a common maintaining mechanism, which is probably related to poor self-regulation skills, involving the ability to control impulses and expressions of emotion[101].

Several studies have confirmed the effectiveness of various psychological and pharmacologic therapies in the management of childhood EBDs. A meta-analysis of thirty-six controlled trials, involving 3042 children (mean sample age, 4.7 years), evaluating the effect of psychosocial treatments including parenting programmes on early DBPs, demonstrated large and sustained effects (Hedges'g = 0.82), with the largest effects for general externalizing symptoms and problems of oppositionality and non-compliance, and were weakest, relatively speaking, for problems of impulsivity and hyperactivity[102].

The treatment of CD among CYP with callous-unemotional traits is still at early stages of research. The mainstay of management for CDs includes individual behavioural or cognitive therapy, psychotherapy, family therapy and medications[103].

Parental skills training

Any challenging behaviour from CYP is likely to elicit persistent negative reactions from many parents, using ineffective controlling strategies and a decrease in positive responses[104]. There is evidence from published research that social-learning and behaviourally based parent training is capable of producing lasting improvement in children with callous-unemotional traits or CD, reducing externalizing problems for children with DBDs, leading to significant parent satisfaction, particularly when delivered early in childhood[84,105-107]. These interventions are typically delivered in a group format, one 2-h session per week for 4-18 wk, by trained leaders, with the focus on improving parenting skills to manage child behaviour, where parents typically learn to identify, define and observe problem behaviours in new ways, as well as learn strategies to prevent and respond to oppositional behaviour[108,109].

Pooled estimates from a review of 37 randomised controlled studies identified a statistically significant

improvement on several rating scales among children with CD up to the age of 18 years[23]. A previous meta-analysis of 24 studies confirmed that Parent-Child Interaction Therapy (PCIT) demonstrated significantly larger effect sizes for reducing negative parent behaviours, negative child behaviours, and caregiver reports of child behaviour problems than did most or all forms of Positive Parenting Programme (Triple P)[110]. A recent Cochrane review of 13 studies confirmed the efficacy and cost-effectiveness of group-based parenting interventions for alleviating child conduct problems, enhancing parental mental health and parenting skills, at least in the short term[111].

Differentiated educational strategies

Research has focused on identifying alternative educational strategies that can be used to improve learning opportunities for children presenting with challenging behaviours from various causes. Supportive school strategies for children with EBDs have traditionally focused on classroom management, social skills and anger management, but many researchers have more recently argued that academically-focused interventions may be most effective[112]. Traditional school policies of suspending or expelling children with EBD can be harmful to them. Researchers have developed "step-by-step" guidelines for teachers to guide them in the selection and implementation of evidence-based strategies that have been identified as effective in increasing levels of engagement and achievement by children with EBD, including peer-assisted learning procedures, class-wide peer tutoring, self-management interventions and tiered intervention systems - most notably Response to Intervention (RtI) and Positive Behavioural Interventions and Supports (PBIS)[113,114].

There is increasing evidence to confirm that school-based interventions to address emerging DBPs produce significant reductions in both parent-, self- and teacher-reported internalizing and externalizing symptoms[114,115].

Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) is an educational system designed for the management of children with Autism and related communication disorders[116,117]. There is some evidence that TEACCH programmes also lead to some improvements in motor skills and cognitive measures[117].

Best practice management strategies for children with PDA are known to differ from those with Autism. Specific guidelines for children with PDA[118] have been published by the British institute for Learning Disabilities. Educational support for CYP with PDA relies on highly individualized strategies that allows them to feel in control. They would respond much better to a more indirect and negotiative approaches. For example, "I wonder how we might…" is likely to be more effective than "Now let's get on with your work"[118].

Child-focused psychological interventions

Cognitive behavioural therapy (CBT) is one of the most widely used non-pharmacologic treatments for individuals with emotional disorders, especially depression, and with individuals with behavioural problems including ASD[119]. CBT integrates a combination of both cognitive and behavioural learning principles to encourage desirable behaviour patterns. Research evidence from several trials[120] provide strong support for the effectiveness of cognitive–behavioural interventions among CYP with Anxiety and Depression. A recent study of child-focused CBT programme introduced at schools has shown that it produces significant improvement in disruptive behaviours among children[121].

Self-esteem building strategies can help many children with EBDs, who often experience repeated failures at school and in their interactions with others. These children could be encouraged to identify and excel in their particular talents (such as sports) to help build their self-esteem.

Behavioural modification and social communication enhancement strategies

Behavioural interventions and techniques are designed to reduce problem behaviours and teach functional alternative strategies using the basic principles of behaviour change. Most interventions are based on the principles of Applied Behaviour Analysis (ABA) which is grounded on behavioural learning theory. Table 5 summarizes the common behavioural modification strategies for management of childhood EBDs.

Several strategies have been designed to help children acquire important social skills, such as how to have a conversation or play cooperatively with others, using social group settings and other platforms to teach peer interaction skills and promote socially appropriate behaviours and communication. There is ongoing research in the development of social communication treatment approaches[45]. Table 4 summarizes common social communication enhancement strategies.

PSYCHOPHARMACOLOGY OF CHILDHOOD BEHAVIOURAL AND EMOTIONAL DISORDERS

Medications are often prescribed as part of a comprehensive plan for the management of childhood EBDs that includes other therapies. The greatest level of evidence for pharmacotherapy of childhood EBDs is available for their use in the management of childhood and adolescent ADHD. There is less evidence of any efficacy for medications in the management of other DBPs including ODD and CD. Table 8 lists the common classes of medications used in the management of childhood EBD.

Psychostimulants (including different formulations of Methylphenidate and Dexamphetamines) remain the primary medication of choice for management of ADHD in CYP for more than 60 years. About 75% to 80% of children with ADHD will benefit from the

Table 8 Major classes of medications used in management of childhood emotional and behavioural disorders

	Common examples	Indications for use	Common Side-effects	Follow up monitoring
Traditional antipsychotics	Haloperidol, Chlorpromazine, Thiotixene, Perphenazine, Trifluoperazine	Schizophrenia, Bipolar disorder, Schizoaffective, Disorder, Obsessive-compulsive disorder,	Tremors, Muscle spasms, Abnormal movements, Stiffness, Blurred vision, Constipation	Frequent blood tests (Clozapine), Blood pressure checks, Cholesterol testing, Heart Rate checks, Blood Sugar testing,
Atypical antipsychotics	Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone	Depression, Aggression, Mood instability, Irritability in ASD	Low white blood cell count (Agranulocytosis - with Clozapine), Diabetes, Lipid abnormalities, Weight gain, Other medication-specific side effects	Electrocardiogram, Height, Weight and blood chemistry tests
Tricyclic antidepressants	Amytriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline	Depression, Anxiety, Seasonal Affective, Disorder, OCD, Posttraumatic Stress Disorder,	Dry mouth, Constipation, Blurry vision, Urinary retention, Dizziness, Drowsiness	Watch for worsening of depression and thoughts about suicide, Watch for unusual bruises, bleeding from the gums when brushing teeth, especially if taking other medications, Blood tests and Blood pressure checks may be needed
Selective Serotonin Reuptake Inhibitors	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Sertraline	Social Anxiety, Bed-wetting and pre-menstrual syndrome	Headache, Nervousness, Nausea Insomnia, Weight Loss	
Serotonin-norepinephrine reuptake inhibitor	Venlafaxine, Levomilnacipran, Duloxetine, Desvenlafaxine			
Other antidepressants	Bupropion, Mirtazepine, Trazodone			
Stimulants	Methylphenidate Immediate Release and Modified Release (*e.g.*, Concerta XL, Equasym XL), Dexamfetamines Immediate Release and Modified Release (*e.g.*, Lisdexamfetamine)	ADHD	Decreased appetite/ weight loss, Sleep problems, Jitteriness, restless, Headaches, Dry mouth, Dysphoria, feeling sad, Anxiety, Increased heart rate, Dizziness	Blood pressure and heart rate will be checked before treatment and periodically during treatment. Child's height and weight are monitored
Non-stimulants	Atomoxetine			
Alpha-2 agonists	Clonidine, Guanfacine		Drowsiness, Dizziness, Sleepiness	
Benzodiazepines	Lorazepam, Clonazepam, Diazepam, Alprazolam, Oxazepam, Chlordiazepoxide	Anxiety, Panic disorder, Alcohol withdrawal, PTSD, OCD	Drowsiness, Dizziness, Sleepiness, Confusion, Memory loss, Blurry vision, Balance problems, Worsening behaviour	Do not stop these medications suddenly without slowly reducing (tapering) the dose as directed by the clinician. While taking buspirone, avoid grapefruit juice,
Antihistamines	Hydroxyzine HCl, Hydroxyzine, Pamoate, Alimemazine		Sleepiness, Drowsiness, Dizziness, Dry mouth, Confusion, Blurred Vision, Balance problems, Heartburn	Avoid alcohol, Blood tests may be needed prior to the start of treatment and during treatment
Other anxiolytics	Buspirone		Dizziness, Nausea, Headache, Lightheadedness, Nervousness	
Sleep-enhancement	Zolpidem, Zaleplon, Diphenhydramine, Trazodone	Insomnia (short-term)	Headache, Dizziness, Weakness, Nausea, Memory loss, Daytime sleepiness, Hallucinations, Dry mouth, Confusion, Blurred Vision, Balance problems, Heartburn	Blood tests may be needed before the start of treatment. Avoid alcohol

Modified from "Medications used for behavioral and emotional disorders. A guide for parents, foster parents, families, youth, caregivers, guardians, and social workers." May 2010. Available Online: URL: http://www.ct.gov/dcf/lib/dcf/ccmu/pdf/cmcu_-_educational_booklet_5-7-2010.pdf. ADHD: Attention deficit hyperactivity disorder; ASD: Autistic spectrum disorder; PTSD: Post traumatic stress disorder; OCD: Obsessive-compulsive disorder.

use of psychostimulants. Non-stimulant therapy with Atomoxetine or alpha 2-adrenergic agonists (Clonidine and Guanfacine) are also effective second-line alternative options[133]. A recent analysis of 16 randomized trials

and one meta-analysis, involving 2668 participants with ADHD, showed that both stimulant and non-stimulant medications led to clinically significant reductions in core symptoms with consistently high effect sizes. The psychosocial treatments alone combining behavioural, cognitive behavioural and skills training techniques demonstrated small- to medium-sized improvements for parent-rated ADHD symptoms, co-occurring emotional or behavioural symptoms and interpersonal functioning[134].

The use of pharmacological treatments for symptoms of ASD is common but challenging, as there are no medications that directly treat the social and language impairments present in individuals with ASD. The medications used most frequently include antipsychotics (*e.g.*, Risperidone) and Selective Serotonin Reuptake Inhibitors (SSRI) to treat mood and repetitive behaviour problems, and stimulants and other medications used to treat ADHD-related symptoms. The evidence base is good for using atypical antipsychotics to treat challenging and repetitive behaviours, but they also have significant side effects[119,135]. Naltrexone is an opioid antagonist that has been shown from a systematic review (involving 155 children from 10 studies) to significantly improve symptoms of self-injury, irritability, restlessness and hyperactivity in autistic children, with minimal side effects and generally good tolerance, although long-term data are lacking[136].

Medication use in preschool children for control of ASD and ADHD symptoms is still largely controversial. Stimulant medications for treatment of ADHD are not uniformly licensed for pre-schoolers as there is limited available research evidence to confirm efficacy and safety. Moreover, the effectiveness of parenting interventions in this age group are comparable to the effects of using stimulant drugs among the older CYP[137,138].

Research evidence from two systematic reviews and 20 randomized controlled trials has recently documented the efficacy of psychopharmacology in the management of childhood DBP. Psychostimulants have have been shown to have a moderate-to-large effect on oppositional behaviour, conduct problems, and aggression in youths with ADHD, with and without ODD or CD, while Atomoxetine has only a small effect. There is very-low-quality evidence that Clonidine and Guanfacine have a small-to-moderate effect on oppositional behaviour and conduct problems in youths with ADHD[139].

Other behavioural disorders in children could also be successfully treated by medications. Traditional and the newer atypical antipsychotics can be used for OCD, Depression, aggression and mood instability[140].

The commonest antidepressants in used in children are the SSRI and Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) medications as they work well and usually have fewer side effects compared to the older Tricyclic Antidepressants. Antidepressants can be used in the management of Major Depression, Anxiety, Seasonal Affective Disorder (SAD), OCD, PTSD and Social Anxiety. They may also be used to treat enuresis and pre-menstrual syndrome[141].

CONCLUSION

Childhood EBDs have significant negative impacts on the society, in the form of direct behavioural consequences and costs, and on the individual, in the form of poor academic, occupational and psychosocial functioning and on the family. The costs to society include the trauma, disruption and psychological problems caused to the victims of crime or aggression in homes, schools and communities, together with the financial costs of services to treat the affected individuals, including youth justice services, courts, prison services, social services, foster homes, psychiatric services, accident and emergency services, alcohol and drug misuse services, in addition to unemployment and other required state benefits[23].

Prevention and management of EBD is not easy and it requires an integrated multidisciplinary effort by healthcare providers at different levels to be involved in the assessment, prevention and management of affected individuals, and also to provide social, economic and psycho-emotional support to the affected families.

There is increasing evidence base for several psychosocial interventions but less so for pharmacological treatment apart from the use of stimulants for ADHD. Preventive measures that have been researched for controlling the risk of childhood emotional and behaviour problems include breastfeeding[142], avoiding second-hand smoke exposure in non-smoker youths [143] and intensive parenting interventions.

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REVIEW

Controversies in diagnosis and management of Kawasaki disease

Rakesh Kumar Pilania, Dharmagat Bhattarai, Surjit Singh

Rakesh Kumar Pilania, Dharmagat Bhattarai, Surjit Singh, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh 160012, India

ORCID number: Rakesh Kumar Pilania (0000-0002-9015-1704); Dharmagat Bhattarai (0000-0003-4838-5037); Surjit Singh (000-0002-8738-4582).

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Correspondence to: Surjit Singh, FRCP (C), MBBS, MD, FAMS, Professor, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research (PGIMER), Sector 12, Chandigarh 160012, India. surjitsinghpgi@rediffmail.com
Telephone: +91-987-2283832

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Abstract

Kawasaki disease (KD) is a common medium vessel systemic vasculitis that usually occurs in small children. It has a predilection for the coronary arteries, but other medium sized arteries can also be involved. The etiology of this disorder remains a mystery. Though typical presentation of KD is quite characteristic, it may also present as incomplete or atypical disease in which case the diagnosis can be very challenging. As both incomplete and atypical forms of KD can be associated with serious coronary artery complications, the pediatrician can ill afford to miss these diagnoses. The American Heart Association has enunciated consensus guidelines to facilitate the clinical diagnosis and treatment of this condition. However, there are still several issues that remain controversial. Intravenous immunoglobulin remains the cornerstone of management but several other treatment modalities, especially glucocorticoids, are increasingly finding favour. We review here some of the contemporary issues, and the controversies thereon, pertaining to management of KD.

Key words: Kawasaki disease; Diagnosis; Intravenous immunoglobulin; Treatment; Controversies

Core tip: The diagnosis of Kawasaki disease poses several challenges for the treating pediatricians as it is based on a set of criteria that are entirely clinical. To further complicate matters, several children present with incomplete and atypical forms of the disease. It is known that children with incomplete and atypical Kawasaki disease do not have milder form of the disease, rather the rate of coronary and non-coronary complications may even be higher in these subgroups as the diagnosis often gets delayed. While intravenous immunoglobulin

remains the cornerstone of management, several children require additional form of therapy thereby further challenging the clinical skills and judgment of the pediatricians.

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WHAT IS KAWASAKI DISEASE?

Kawasaki disease (KD) is the most common medium vessel vasculitis and usually affects young children. It has a special predilection for coronary arteries[1,2]. KD is now the leading cause of pediatric acquired heart disease in developed countries like Japan, Korea and Taiwan as also in countries in North America and Europe. In several resource poor countries (*e.g.*, India, China) as well, KD is now being increasingly reported[3]. However, anecdotal evidence suggests that many children still remain undiagnosed and untreated in such settings[4]. The etiology of KD remains an enigma[5,6].

This disease was first recognized in 1961 by Dr. Tomisaku Kawasaki based on a constellation of clinical signs and symptoms and he reported it in 1967 as "muco-cutaneous lymph node syndrome"[7]. Since then it has been reported from all continents. Even though the initial description of KD was given more than 50 years ago, the diagnosis still remains clinical and there is no laboratory test that can confirm a clinical diagnosis of KD[8].

DIAGNOSIS OF KD

Diagnosis of KD is essentially based on a constellation of clinical signs and symptoms and supported by laboratory investigations[8-12]. It cannot be overemphasized that there is no pathognomonic laboratory test for diagnosis of KD. A careful and meticulous history from parents, or documented clinical findings by a physician who has seen the child previously, may be useful in facilitating a diagnosis of KD[13].

The diagnostic criteria for KD have been modified from time to time. There are two sets of diagnostic criteria that have been used most frequently for diagnosis of KD. These included the Kawasaki Disease Research Committee guidelines [Japanese Ministry of Health (JMH) guidelines], 2002[14] and the American Heart Association (AHA) guidelines[1,13]. AHA guidelines were published in 2004 and have been widely used since then[1]. Mccrindle *et al*[13] have recently published the AHA 2017 revised guidelines for diagnosis and management of KD. These criteria are based on clinical findings and do not differ significantly from the original descriptions of cases of KD given by Dr. Kawasaki himself in 1967[7].

Complete KD

The AHA 2017 have proposed a set of diagnostic criteria for complete KD (Table 1)[13]. Fever is the most common presenting clinical manifestation and is seen in nearly all patients. While fever is essential for the diagnosis of KD as per AHA criteria but according to the Japanese criteria, fever need not be present in all patients (Table 2)[14]. The duration of fever in KD is variable and is usually less than 2 wk but may persist for much longer periods of time. Clinical manifestations of KD evolve over days and many signs and symptoms may have disappeared by the time the patient seeks medical attention. This issue has been clearly highlighted in the recent AHA 2017 guidelines (Table 3)[13].

Incomplete KD and atypical KD

The diagnosis of KD can test the clinical acumen of even an astute physician. The signs and symptoms of KD are nonspecific and may overlap with those of infectious diseases seen in young children[2]. Adding to this challenge are patients with KD who do not fulfill the diagnostic criteria. A diagnosis of incomplete KD is usually made when there is ongoing fever but less than four clinical features[13]. In such cases the attending pediatrician has to do a thorough clinical assessment and look at supportive laboratory investigations. Incomplete KD is common in infants (especially in babies below 6 mo) and young children. On the other hand, atypical KD is said to be present when there are atypical manifestations, as for instance nephritis[15,16], pneumonia,[17] arthritis[18], myositis[19,20], uveitis[21], retinal vasculitis[22,23] and CNS involvement[24,25]. Incomplete or atypical forms of KD should by no means be considered as mild KD because the risk of coronary abnormalities in these patients is comparable with, if not higher than, classic KD. This fact cannot be overemphasized[26-29].

Important clinical signs not included in the diagnostic criteria

There are several manifestations that are not included in the diagnostic criteria but may provide important clues towards diagnosis of KD. Perineal desquamation is one such clinical sign. It usually appears a few days prior to the appearance of periungual desquamation and may provide the initial clinical clue[30-32]. Similarly, reactivation of the Bacillus Calmette-Guérin (BCG) injection site is a pathognomonic clinical sign of KD and is almost exclusively observed in infants[33-36]. However, this has not been given enough consideration in the diagnostic criteria. Reason for this may be that many developed countries are not using BCG vaccine as a routine. Sterile pyuria[37,38], peripheral arthritis[18] and gall bladder hydrops[39,40] are other important indicators of KD. Extreme irritability, out of proportion to the fever, is often observed in young children with KD and may be a prominent clinical finding-but this too does not find a mention in the diagnostic criteria[41,42].

Table 1 American Heart Association guidelines for diagnosis of Kawasaki disease (2017)[13]

Classic KD is diagnosed with fever persisting for least 5 d
At least four of the five principal clinical features:
Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
Changes in extremities
Acute: Erythema of palms, soles; edema of hands, feet
Subacute: Periungual peeling of fingers and toes in weeks 2 and 3
Polymorphous exanthema (diffuse maculopapular, urticarial, erythroderma, erythema-multiforme like, not vesicular or bullous)
Bilateral bulbar conjunctival injection without exudates
Cervical lymphadenopathy (> 1.5 cm diameter), usually unilateral
A careful history may reveal that ⩾ 1 principal clinical features were present during the illness but resolved by the time of presentation
Exclusion of other diseases with similar findings (*e.g.*, scarlet fever, viral infections like measles, adenovirus, enterovirus, Stevens-Johnson syndrome, toxic shock syndrome, drug hypersensitivity reactions, systemic juvenile idiopathic arthritis)

KD: Kawasaki disease.

Table 2 Kawasaki Disease Research Committee guidelines (Japanese Ministry of Health guidelines) for diagnosis of Kawasaki disease (2002)[14]

Five of the following six criteria
Fever persisting ⩾ 5 d
Bilateral conjunctival congestion
Changes of lips and oral cavity
Polymorphous exanthema
Changes of peripheral extremities
Acute non-purulent cervical lymphadenopathy

CONTROVERSIES IN DIAGNOSIS OF KD

Infections and KD

KD should be considered as a diagnostic possibility in all children with fever more than 5 d for which there is no discernable cause[13]. KD is more common in young children and 80% of patients are under 5. This is the age group wherein viral infections are also common. Some of the clinical features of KD (*e.g.*, conjunctival injection, rash and cervical lymphadenopathy) are also a common feature of viral illnesses like measles[43], rubella[32], adenoviral[44,45], and enteroviral infections[13,44]. It is, therefore, not difficult to understand why KD can be confused with a viral illness. There are, however, some clinical features that can help in this differentiation. Children with KD usually do not have rhinorrhea or conjunctival discharge, in contrast to patients with viral infections[46]. They are also often very irritable. Edema over dorsum of hands and feet and the characteristic desquamation (perianal in first few days and periungual after days 10-12) is typical of KD but these findings are not there in all patients and can be easily missed if not looked for carefully[46,47]. However, the picture gets further complicated when KD occurs concomitantly with a viral infection as is sometimes the case[13,44].

One of the closest mimics of KD is scarlet fever. However, involvement of the lips and presence of conjunctival injection are features that are seen in KD but not in scarlet fever. Further, the fever in children with scarlet fever responds briskly to antimicrobials[48].

KD in infants

Diagnosis of KD in infants is a challenging exercise for physicians and delays in diagnosis in this age group are not uncommon. KD in infants often does not fulfil the standard diagnostic criteria. KD may be incomplete in a large proportion of patients in this age group[13]. Morbidity and mortality in this age group is highest compared to any other age group[13,49]. Fever and excessively irritability may be the only clinical manifestations of KD in babies below 6 mo and such presentations can pose several difficult questions for the attending pediatrician. Delays in diagnosis are common in such situations. Young infants are said to be at highest risk of developing coronary artery abnormalities. The presence of fever and pyuria in an infant can be mistakenly attributed to a urinary tract infection. This is not uncommon in our experience. Other clinical features of KD (*e.g.*, rash, red eyes, and red lips) may then be ascribed to an adverse drug reaction to antimicrobials that are often given in such situations. Salgado *et al*[50] have reiterated these facts in their recent publication on KD in infants below 6 mo. Our experience is also similar[51]. It is easy to understand why the diagnosis (and consequently the treatment) of KD gets delayed in these circumstances. Unfortunately, such delays can have disastrous consequences in the baby.

As per the recent AHA 2017 guidelines, the diagnosis of KD in infants may be considered in the following situations[13]: (1) Infants < 6 mo old with prolonged fever and irritability; (2) infants with prolonged fever and unexplained aseptic meningitis; (3) infants or children with prolonged fever and unexplained or culture-negative shock; (4) infants or children with prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy; (5) infants or children with prolonged fever and retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy.

KD in older children and adolescents

Diagnosis in older children and adolescents is difficult because KD is rarely kept as differential diagnosis by adult physicians. As the diagnosis usually gets delayed

Table 3 Salient differences between American Heart Association 2004 and 2017 criteria[1,13]

Duration of fever	In the presence of ⩾ 4 principal clinical features, particularly when redness and swelling of the hands and feet are present, KD can be diagnosed even with 4 d of fever
History	Presence of one or more principal clinical manifestations of disease that can be revealed on history but have disappeared by the time of presentation, have been considered important for diagnosis
KD shock syndrome	KDSS has been given special consideration in the 2017 revised guidelines because in the presence of shock the diagnosis of KD is often not considered
KD in infants	Clinicians should have a lower threshold for diagnosis of KD in this age group
Incomplete KD	Algorithm for incomplete KD has been simplified
KD and infections	The issue of infections and KD has been detailed at length. Diagnosis of KD must not be excluded even in the presence of a documented infection when typical clinical features of KD are present
Bacterial lymphadenitis	Ultrasonography and computed tomography findings in differentiating the 2 conditions- bacterial lymphadenitis is often single and has a hypoechoic core on ultrasonography, while lymphadenopathy in KD is usually multiple and is associated with retropharyngeal edema or phlegmon
2D-echocardigraphy	The limitations of echocardiography and other diagnostic modalities have been highlighted. Z-score (by Manlihot *et al*) for severity classification of coronary artery abnormalities has been adapted

KD: Kawasaki disease; KDSS: Kawasaki disease shock syndrome.

in these children, there is higher risk of coronary artery abnormalities[52,54]. Further, echocardiographic coronary artery assessment in this group of patients is difficult because of the thick chest wall[55].

Clinical consequences of missed KD can present as coronary ischemia in early adulthood[56,57]. Due to lack of adequate awareness amongst adult cardiologists, such patients may never get recognized as having had late complications due to missed childhood KD[57].

KD shock syndrome

Myocarditis is nearly universal in acute phase of KD and, at times, it can be severe and symptomatic[58,59]. These patients are usually admitted in intensive care units with cardiovascular collapse and may be mistakenly treated for bacterial sepsis and septic shock[13,60,61]. As a result, the diagnosis of KD gets delayed and this can have serious consequences. Such patients are at high risk of developing coronary artery abnormalities, intravenous immunoglobulin (IVIg) resistance and myocardial dysfunction[62]. It is, therefore, prudent to keep a differential diagnosis of KD in all children presenting with seemingly obscure myocardial dysfunction and shock. A presumptive diagnosis of viral myocarditis / septic shock in the intensive care setting should have a differential diagnosis of KD. It is for these, and many other, reasons that KD shock syndrome (KDSS) has been given special consideration in the AHA 2017 revised guidelines[13].

Laboratory investigations may not always be corroborative

There is no single laboratory test for confirmation of diagnosis of KD. Laboratory markers rarely provide conclusive evidence for diagnosis of KD. Clinical laboratory investigation may be used to support the diagnosis of KD, especially in children with incomplete or atypical KD and to assess the intensity of inflammation. Thrombocytopenia in acute stage of KD can be a marker of macrophage activation syndrome[13,63]. Low platelet count has also been found to correlate with development of coronary aneurysms and such patients often have severe forms of the disease[62].

N terminal pro-B-type natriuretic peptide (NT-pro-BNP) is a cardiac biomarker and has been found to be significantly elevated during acute stage of KD when compared to febrile controls[64]. There are age based Pro-BNP nomograms to help the treating physician in differentiating KD from other febrile illnesses[65]. The values are higher in patients who develop coronary artery abnormalities as compared to those with normal coronaries. Thus it has both diagnostic and prognostic implications. Level of ProBNP is also correlated with myocardial dysfunction in acute stage of KD[66].

CONTROVERSIES IN IMAGING STUDIES IN KD

Role of 2D-echocardiography in KD

2D-echocardiography is an essential component of the diagnostic work-up in children with KD. It is a useful tool to assess the status of coronary arteries and other cardiac structures during acute stage as well as on follow-up[13,55,67]. It is important to bear in mind, however, that a negative echocardiographic examination does not rule out KD. However, from the perspective of a developing country, there are several issues with regard to this investigation. It cannot be overemphasized that the quality of scans obtained on echocardiography is operator dependent. This investigation has significant inter-observer variability and needs expertise and patience, especially in infants and young children[10]. Artifacts pose an important problem and these can make the examination exceptionally difficult, especially when the left circumflex or right coronary artery is being scanned[55]. In developing countries like India there is a dearth of trained pediatric cardiologists. As a result, the investigation may be carried out by an adult cardiologist, who may not have the requisite expertise to assess the coronary arteries especially in young infants. It comes as no surprise that echocardiography reports are often incomplete and inaccurate in clinical practice, especially in developing countries[10].

Table 4 Coronary artery abnormalities severity classification in different guidelines

Criteria	Description
JMH criteria[14]	Aneurysm definition < 5 yr - ID > 3 mm ⩾ 5 yr - ID > 4 mm
Updated JMH (2008)[93]	Small aneurysm (dilatation with ID < 4 mm or if child is ⩾ 5 yr of age, ID ⩽ 1.5 times that of an adjacent segment) Medium aneurysm (dilatation with ID > 4 mm but ⩽ 8 mm or if child is ⩾ 5 yr of age, ID 1.5 to 4 times that of an adjacent segment) Large aneurysm (dilatation with ID > 8 mm or if child is ⩾ 5 yr of age, ID > 4 times that of an adjacent segment)
AHA 2004 criteria[1]	Aneurysm ID z score > 2.5 (as per body surface area adjusted z scores) Small: < 5 mm Medium: 5 to 8 mm Giant aneurysm: > 8 mm based on absolute diameter
AHA 2017 criteria (Manlhiot *et al*)[13,68]	No involvement (Z score < 2) Dilation only (Z score 2 to < 2.5; or if initially < 2, a decrease in Z score during follow-up ⩾ 1 thereby suggesting that coronary artery was dilated during acute stage though diameter was within normal standards and the diameter has regressed on follow-up) Small aneurysm (Z score ⩾ 2.5 to < 5) Medium aneurysm (Z score ⩾ 5 to < 10, and absolute dimension < 8 mm) Large or giant aneurysm (⩾ 10, or absolute dimension ⩾ 8 mm)

ID: Internal diameter; AHA: American Heart Association; JMH: Japanese Ministry of Health.

The Japanese Ministry of Health has enunciated criteria for defining coronary involvement in KD on the basis of absolute dimension of internal diameter of coronary artery[14]. McCrindle *et al*[13] and Manlhiot *et al*[68] have proposed the classification scheme based on z score for severity of coronary artery abnormalities, which has been adapted and recommended by AHA 2017 guidelines (Table 4). It is mandatory that body surface area-adjusted 'Z' scores be used to grade the severity of coronary artery involvement so that objectivity can be maintained and results can be compared with other studies[13]. Echocardiography findings in KD other than coronary artery ectasia, dilatation and aneurysm, include lack of tapering of coronary arteries, myocardial dysfunction, pericardial effusion, aortic root dilatation and valvular regurgitation[13,55,59]. As myocarditis is almost universal, functional abnormalities are likely to be more in acute stage of KD[58]. An echocardiography examination should be done at diagnosis and, if normal, should be repeated on a daily basis for the next few days. Repeat echocardiography should be carried out 1-2 wk later and then at 4-6 wk. A normal echocardiography examination during the first week of illness does not rule out the development of coronary artery aneurysms later. Echocardiography should be repeated more frequently in children who have coronary artery z-scores > 2[13]. Recent literature suggests that follow-up echocardiography examination should include assessment of myocardial functions in addition to assessment of coronary arteries[69].

CT (computerized tomography) coronary angiography in KD

While 2-dimensional echocardiography remains the imaging modality of choice to identify coronary artery abnormalities, it is subject to several fallacies and is operator dependent. CT coronary angiography is rapidly emerging as a useful imaging modality for better characterization of dilatations, ectasia and aneurysms especially in the mid- and distal segments of coronary arteries. It provides precise details in terms of aneurysm size and morphology[70]. The limiting factor in more widespread use of this investigation hitherto was the high radiation exposure and therefore its application in children was rather limited. Over the last 5 years, with the advent of higher detector and dual-source CT scanners (DSCT), it is possible to delineate the coronary artery anatomy with higher temporal resolution and motion-free images at all heart rates with acceptable radiation risk[70]. CT coronary angiography can detect dilatations, ectasia and aneurysms in the mid and distal segments of coronary arteries with precise details in terms of aneurysm size and morphology. In the convalescent phase, it also can be used to delineate complications like segmental stenosis, intra-aneurysmal thrombus and mural calcifications.

MR (Magnetic resonance) coronary angiography

MR is useful in evaluation of coronary artery lesions and myocardial involvement in all stages of KD. The main advantage of MR is that there is no radiation exposure. However, young children would often need to be sedated and the procedure is time consuming. Interpretation of MR images requires a lot of expertise and skill[71,72].

CONTROVERSIES IN MANAGEMENT OF KD

Treatment of KD is yet another challenging and controversial issue. Prompt treatment of KD is absolutely

essential if one is to avoid the chances of development of CAA[11,13]. Intravenous immunoglobulin (IVIG) remains the standard of care based on objective evidence collated from prospective studies and meta-analyses[13]. However, there are still several controversies regarding management of children with KD.

Acute phase management

IVIG: For IVIG to be most effective, it should be given in the first few days of the illness[73]. However, if the child presents after day 10 of fever, IVIG should still be given if the acute inflammatory parameters are high[73]. Though there are recent meta-analyses stating similar outcomes of KD treatment at different doses of IVIg, a dose of 2 gm/kg administered intravenously is the preferred option[13,74]. It has also been suggested that administration of IVIG before day 5 of fever may inadvertently increase the need for further IVIG therapy and also increase the chances of developing a refractory state[75].

Aspirin: Though aspirin is a widely used anti-inflammatory agent in KD and is given along with IVIG, its efficacy remains questionable as there is no proof that addition of aspirin in the acute phase significantly decreases the chances of development of coronary artery abnormalities[76].

Most clinicians prefer to use aspirin in doses of 30-50 mg/kg during the acute phase of KD. Duration of aspirin therapy is another controversial issue[77,78]. Some centres prefer to continue it for 2 wk irrespective of fever status but consensus is rapidly evolving over continuing it only for febrile phase and then to change to a low dose (3 to 5 mg/kg per day) for its anti-platelet effect[79]. This low dose is then continued for 6-8 wk and is stopped if follow-up echocardiographic examination is normal. Aspirin is continued indefinitely if there is persistence of CAA[13].

Corticosteroid therapy in acute phase: Kato *et al*[80] reported that administration of steroids during the acute phase of KD resulted in increased incidence of CAA. But it is now argued that these results were due to the confounding factor of steroids having been given to children who were sicker than the other group[81]. Kobayashi *et al*[82] have recently published their study on use of steroids with IVIG and found that steroids may be useful in acute phase of KD.

Recent AHA guidelines do not support for administration of methylprednisolone pulses simultaneously with IVIG therapy but suggest possible benefit of 2-3 wk tapering steroid therapy along with IVIG and aspirin doses[13]. Upfront steroid therapy may be considered only for patients with KD who are proven to be IVIG resistant or presenting with significant CAA[10,46]. The choice of steroid is usually intravenous methylprednisolone pulse followed by tapering dose of oral prednisolone[13].

Refractory Kawasaki disease

Almost one-tenth patients with KD may be refractory to primary IVIG therapy. In such conditions, fever will continue to appear even after more than 36 to 48 h of IVIG therapy. There is no consensus on management protocols to be followed in such patients. AHA guidelines emphasize use of a repeat dose of IVIG (2 mg/kg) in this subgroup. Alternatively, the guidelines reiterate the role of 3 doses of methylprednisolone with tapering prednisolone[13]. Infliximab, given as a single dose of 5-6 mg/kg intravenously, is also very useful in treatment of refractory KD and appears to decrease the chances of developing CAA[83]. Administration of infliximab often results in prompt reduction of fever[84,85]. Tremoulet *et al*[86] have shown that addition of infliximab in the primary treatment regimen did not reduce the incidence of IVIG resistant KD. However, fever duration, inflammatory markers and reaction rate were less in the infliximab group. There are various ongoing randomized trials to assess the efficacy of anti-TNF drugs. Plasma exchange has also been found to be helpful in patients with intractable KD[87,88]. Other therapeutic options that are being considered includes interleukin-1 antagonist (*e.g.,* anakinara), cyclosporine, and tacrolimus, *etc*[89-91].

For the preventing of thrombosis, low dose aspirin remains the first choice of therapy. If the patients show evidence of rapidly expanding CAA, heparin or warfarin anticoagulation along with aspirin can be given[13]. Aspirin with another antiplatelet agent along with systemic anticoagulant agent like heparin or warfarin may be considered for patients with history of coronary thrombosis or giant aneurysm[79]. Thrombolytic treatment or coronary recanalization procedures may be required for the minority of patients who develop coronary thrombosis in the context of KD. Abciximab is also useful in such patients[13].

Management after acute phase

Risk stratification of coronary artery abnormalities is of primary importance for the long term follow-up and management of patients with KD. It is our practice to keep all children with KD on long term follow-up, because there is some concern regarding development of premature atherosclerosis even in children who do not have overt CAA during the acute phases[92,93]. Healthy lifestyle and an active physical regimen should be emphasized upon.

Patients with coronary dilatation that persists beyond 6 wk need to be kept on low dose aspirin for longer periods of time. For patients with large and giant aneurysms, frequent echocardiographic assessment should be continued. Such patients may also require CT coronary angiography at periodic (say 3-5 yearly) intervals. Statins have also been recommended in these situations. Thromboprophylaxis can be maintained with antiplatelet drugs (*e.g.,* aspirin/dipyrimadole used singly or in combination) and anticoagulants (*e.g.*, heparin/warfarin)[13].

To conclude KD is now one of the most common causes for acquired heart disease in children and all pediatricians need to be familiar with its varied clinical

presentations. With some experience it is not difficult to pick up children with classic KD. However, the diagnosis of children with incomplete and atypical KD can pose significant issues for the attending pediatrician. The recent AHA 2017 guidelines have suggested a simplified management protocol for children with KD. Therapies other than IVIG are now being increasingly used in these patients.

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MINIREVIEWS

Review of the evidence for the management of co-morbid Tics disorders in children and adolescents with attention deficit hyperactivity disorder

Michael O Ogundele, Hani F Ayyash

Michael O Ogundele, Department of Community Paediatrics, NHS Fife, Glenwood Health Centre, Glenrothes KY6 1HK, United Kingdom

Hani F Ayyash, Cambridgeshire and Peterborough NHS Foundation Trust, Peterborough Integrated Neurodevelopmental Service, University of Cambridge Health Partners, Cambridge CB21 5EF, United Kingdom

ORCID number: Michael O Ogundele (0000-0003-0744-1434); Hani F Ayyash (0000-0002-1005-1667).

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Correspondence to: Dr. Michael O Ogundele, MBBS, MRCP, MSc, Consultant Paediatrician, Department of Community Paediatrics, NHS Fife, Glenwood Health Centre, Napier Road, Glenrothes KY6 1HK, United Kingdom. m.ogundele@nhs.net
Telephone: +44-1592-765096

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Abstract

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children and adolescents, with prevalence ranging between 5% and 12% in the developed countries. Tic disorders (TD) are common co-morbidities in paediatric ADHD patients with or without pharmacotherapy treatment. There has been conflicting evidence of the role of psychostimulants in either precipitating or exacerbating TDs in ADHD patients. We carried out a literature review relating to the management of TDs in children and adolescents with ADHD through a comprehensive search of MEDLINE, EMBASE, CINAHL and Cochrane databases. No quantitative synthesis (meta-analysis) was deemed appropriate. Meta-analysis of controlled trials does not support an association between new onset or worsening of tics and normal doses of psychostimulant use. Supratherapeutic doses of dextroamphetamine have been shown to exacerbate TD. Most tics are mild or moderate and respond to psychoeducation and behavioural management. Level A evidence support the use of alpha adrenergic agonists, including Clonidine and Guanfacine, reuptake noradrenenaline inhibitors (Atomoxetine) and stimulants (Methylphenidate and Dexamphetamines) for the treatment of Tics and comorbid ADHD. Priority should be given to the management of co-morbid Tourette's syndrome (TS) or severely disabling tics in children and adolescents with ADHD. Severe TDs may require antipsychotic treatment. Antipsychotics, especially Aripiprazole, are safe and effective treatment for TS or severe Tics, but they only moderately control the co-occurring ADHD symptomatology. Short vignettes of different common clinical scenarios are presented to help determine the most appropriate treatment to consider in each patient presenting with ADHD and co-morbid TDs.

Key words: Tics disorders; Childhood; Attention deficit hyperactive disorder; Adolescence; Tourette's syndrome

Core tip: Attention deficit hyperactive disorder (ADHD) and Tic disorders (TD) are common co-morbidities in children and adolescents, with 60% of children with Tourette's syndrome having ADHD. This review covers the classification, prevalence, aetiology, diagnosis and treatment of childhood TD and co-morbid ADHD. Most tics are mild or moderate, responding to psychoeducation and behavioural management. Level A evidence supports the use of alpha adrenergic agonists, Atomoxetine and stimulants for the treatment of Tics and co-morbid ADHD. Severe TDs may require antipsychotic treatment. Short clinical vignettes are presented to help guide the selection of the most appropriate treatment in each patient presenting with ADHD and co-morbid TDs.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the commonest neurobehavioural disorder in children and adolescents, with prevalence ranging between 5% and 12% in the developed countries[1]. Up to 80% of ADHD patients have one or more co-morbid conditions which include Tic disorders (TD). There is a complex interplay between TD and ADHD in children and young people. TDs are common comorbidities in paediatric ADHD patients with or without treatment with pharmacotherapy. ADHD and other co-morbid disorders like Tics/Tourette's syndrome (TS), especially if left untreated, can have lasting impairing effects on several aspects of daily functioning.

Tics naturally wax and wane in clinical severity and are exacerbated by stress, including consequences of untreated ADHD. There has been conflicting evidence of the role of psychostimulants in either precipitating or exacerbating TDs in ADHD patients. Some anecdotal evidence also suggests that tics may improve with ADHD treatment.

SYMPTOMS AND NATURAL HISTORY OF TD

Tics have been defined as sudden, rapid, recurrent, non-rhythmic, stereotyped, involuntary movements or vocalizations. Motor tic can be either simple or complex, depending on whether one or several muscle groups are simultaneously or concurrently affected. Motor tics commonly include behaviours such as eye-blinking, lip-licking, or mouth opening. It can also involve more complex movements like facial grimacing, head movements, shoulder shrugging or combinations of these[2].

Vocal or phonic tics are involuntary sounds that include throat clearing, coughing, barking, sniffing, unnecessary belching or more complex vocalizations such as repeating parts of words or phrases[3].

TS (also known as Gilles de la Tourette's syndrome) is a complex neurodevelopmental disorder characterized by combination of motor and vocal tics. Motor tics often precede the onset of phonic tics of TS by many years. The phonic tics may commence from about the age of 3 years. Severe TS may manifest as forceful bouts of self-harming motor tics, including hitting or biting, as well as socially unacceptable utterances (coprolalia) and gestures[3].

The Tourette's Syndrome Study Group definition from 1993 requires the concurrent presence of motor and vocal tics occurring almost daily for at least one year, beginning before the 21st birthday[4]. The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) requires both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently for the diagnosis of TS. It also describes TD/TS as waxing and waning in frequency and symptoms must have lasted for more than one year since the first onset[5]. The average age of developing TS is 7 years, with a range from three to eight years. Most patients with childhood TD show remarkable symptoms improvement by the age of 19 years. Adult-onset cases of TS are usually the most severe forms of presentation[3].

Motor or phonic tics often begin with the patient experiencing some psycho-sensory phenomena known as the "premonitory urge" which may be localized to an area of the tics or a generalised inner tension. Most individuals with Tics/TS also experience feelings of momentary relief after the tic has occurred. TD are typically exacerbated by stressful life-events associated with high levels of emotional excitements and fatigue, and can include normally routine activities such as the start of school, birthdays, arrival of a new sibling, changes in the social or physical environment like moving house or going on holidays.

The symptoms of childhood TD/TS are usually mild and they are almost invariably co-morbid with other mental health and behavioural problems including ADHD, Obsessive-compulsive behaviour or disorder (OCD), learning disabilities (LD) and mood disorders. Tics/TS can significantly impair the patient's self-esteem, peer and or family relationships[3]. Although tics often improve after adolescence, recent studies suggest that comorbid OCD and ADHD often persist[6]. Other common co-morbidities in children with Tics/TS include anxiety disorders, depression, autistic spectrum disorder (ASD), conduct disorder (CD), oppositional defiant disorder (ODD), self-injurious behaviours, sleep disorders, rage attacks and personality disorders[2,7].

CLASSIFICATION OF TD

DSM-5[5] classifies TD into four categories, according to the duration and age of symptoms onset: (1) TS: Both multiple motor and one or more vocal tics (not necessarily concurrently) that have been present for more than a year; (2) Chronic TD: Presence of a single or multiple motor or vocal tics (not both), appearing before age 18, present for more than a year; (3) Transient TD: Single or multiple motor or vocal tics (not both), occurring nearly daily for at least 4 wk but not longer than 12 consecutive months; and (4) TD not otherwise specified: Tics that do not meet the conditions for definition of any other TD. This includes adult-onset tics.

PREVALENCE OF TD AND CO-MORBID CHILDHOOD ADHD

Transient TD affect between 5% and 25% of school children at any given time[8]. The reported prevalence of TD/TS is variable according to different sample sources, definitions or diagnostic methods used. It is also influenced by the age and sex of the study cohorts. A published meta-analysis including 13 studies reported that the prevalence of childhood TS varied between 0.4% and 3.8% and average 1% among school children (higher in boys, 1.06% *vs* 0.25% in girls)[9].

ADHD is the commonest neurodevelopmental comorbidity reported among in children with TS. While only seven percent of children and adolescents with ADHD are diagnosed with TS, up to 60% of patients with TS have ADHD. ADHD diagnosis is generally known to antedate the occurrence of motor or vocal tics among children with TS, but their concurrent emergence is also possible[2]. The Yale Global Tic Severity Scale (YGTSS) scores in children with ADHD are reported not to be significantly different from those without ADHD, but children with obsessive compulsive behaviours tend to have significantly higher YGTSS scores[10].

AETIOLOGY OF TD

Several genetic studies among twins and families have contributed significantly to our knowledge about the important roles of genetic risk factors in predicting vertical transmission of TS and related TD. The exact nature and mechanism of the genetic inheritance are however unknown. The genetic vulnerability of TS has been associated with some extensively studied candidate genes, including the dopamine receptors (*DRD1*, *DRD2*, *DRD4*, and *DRD5*), the dopamine transporter, some noradrenergic genes (*ADRA2a*, *ADRA2C*, and *DBH*), and serotonergic genes (*5HTT*)[3]. Abnormalities in any one or more of these genes could potentially act together with unfavourable environmental factors, to increase the risk of individuals having TD/TS.

POSSIBLE COMMON PATHOGENESIS OF CHILDHOOD TD AND ADHD

The risk for developing ADHD as well as TD is associated with early exposure to certain adverse perinatal conditions. The extensive co-occurrence of the two disorders also suggests a shared genetic background[11,12]. Prenatal maternal smoking is associated with increased risk for TS/TD as well as its comorbidity with other psychiatric conditions[13].

Abnormalities in noradrenergic and dopaminergic chemoreceptors and neurotransmission within cortico-striatal circuits have been implicated in the development of both TS/Tics and ADHD. These alterations are thought to be responsible for clinical symptoms arising from failure to inhibit intrusive thoughts, sensory input, and motor output[14]. Iron deficiency has also been commonly associated with ADHD and recently with Tics/TS[15,16].

DIAGNOSTIC CHALLENGES OF TD

The Diagnostic and Statistical Manual, 5th edition (DSM-5)[5] and the International Classification of Disease and related Health Problems, 10th revision (ICD-10)[17] are the most universally accepted diagnostic criteria for TS/TD. The clinical nature and progression of TS/TD present the clinician with some peculiar challenges. The intermittent symptoms may delay recognition in the early stages of the disorder. Assessment of childhood and adolescent TD/TS requires multi-source feedback from several familiar carers to document the frequency and severity of the symptoms, specific triggers, and ascertain the level of any functional impairment, including effect on self-esteem and the associated mental health co-morbidities.

SCREENING AND ASSESSMENT TOOLS FOR TD

At least 5 severity scales have been recommended for use in children and young people with TS/Tics, including the Yale Global Tic Severity Scale (YGTSS), Tourette Syndrome Clinical Global Impression, Tourette's Disorder Scale, Shapiro Tourette Syndrome Severity Scale, and Premonitory Urges for Tics Scale. Six others have been suggested, including the Hopkins Motor and Vocal Tic Scale, Rush Video-Based Tic Rating Scale, Parent Tic Questionnaire and Tourette Syndrome Symptom List. The YGTSS is the commonest screening tool employed worldwide for both clinical and research purposes, and it is the most favoured tool recommended by TS international guidelines[18].

A further two screening instruments in common use, have also been recommended by an International Movement Disorders Society subcommittee; Motor tic, Obsession and compulsions, Vocal tic Evaluation Survey

Table 1 Common differential diagnosis of Tics

Stereotypy (in developmental disorders such as autism spectrum disorders and stereotypic movement disorder)
Functional movement disorders in children
Neurological: Stroke, head trauma
Primary movement disorders: Dystonia
Post-infectious: PANDAS, Sydenham's chorea
Infectious: Encephalitis
Epileptic seizures
Toxic: Carbon monoxide poisoning
Chromosomal disorders: Down syndrome and Fragile X syndrome
Genetic conditions: Huntington's disease, Wilson's disease and Tuberous sclerosis
Medication-induced tics: Neuroleptics, Stimulants, Antiepileptics, Lithium

Modified from Oluwabusi *et al*[19] 2016. PANDAS: Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

(MOVES) and Autism-Tics, Attention Deficit/Hyperactivity Disorder and Other Co-morbidities Inventory (A-TAC)[18].

DIFFERENTIAL DIAGNOSIS OF TD

The diagnosis TS/TD is based on clinical history and examination, supplemented by various screening and diagnostic feedback tools. Both DSM-5[5] and ICD-10[17] preclude the presence of any direct physiologic causes such as a substance (*e.g.*, stimulants) or a general medical condition (*e.g.*, Huntington disease or post-viral encephalitis) to make a firm diagnosis of TS/TD. TS/TD need to be differentiated from any voluntary coordinated stereotyped movements or vocalisations, which may not always be easy to achieve clinically in younger children. TS/TD diagnosis must also exclude other specific dyskinetic disorders such as akathisia, tardive dyskinesia, or other hyperkinetic movement disorders (Table 1). Routine laboratory and radiological investigations may be required to exclude other organic causes of tics[19]. Tics may be differentiated from other common movement disorders by its tendency to occur in a milder form during sleep[3].

MANAGEMENT OF TICS/TOURETTE SYNDROME (ALONE OR CO-MORBID WITH ADHD)

Tics/TS are best managed in multidisciplinary teams with multifaceted expertise in Neurology, Psychiatry, Psychology, and Paediatrics, with supportive services from Education and Social welfare services. The primary choice of management strategies depends on the severity of the symptoms and their associated impairments.

Mild to moderate symptoms

First line of management for mild to moderate TD/TS involves comprehensive psychoeducation of patients and families, addressing the aetiology, triggering factors and management strategies of tics and associated behaviours, personal coping mechanisms, prognosis, and symptomatic natural progression[14]. Counselling interventions for dealing with peer rejection, academic and family problems or employment difficulties are also recommended[2].

Comprehensive Behavioural Intervention for Tics (CBiT) is a combination of several psychological support interventions including Psychoeducation, Functional analysis, Relaxation Training, Habit Reversal Therapy (HRT), social support and reward systems[20]. Exposure and Response Prevention (ERP) is another type of therapy that enables the patient to effectively overcome and deal with the premonitory urges. For example, an alternative learnt movement is carried out for a brief moment after each pre-monitory feeling. These strategies are particularly helpful in older children[2].

Growing evidence confirm effectiveness of various elements of the CBiT including self-monitoring (counting tics), relaxation techniques, and Habit reversal therapy involving awareness and competing response training[21,22]. However, these comprehensive multidisciplinary support services are not readily available in many centres, mainly due to the paucity of well-trained therapists[23]. These counselling and behavioural modification interventions may be sufficient to successfully manage many children with uncomplicated Tics/TS, who do not need Pharmacotherapy.

Moderate to severe Tics/TS symptoms

In more complicated cases causing interference with peer or family relationships, social interactions, academic or job performance, or with other functional activities, Pharmacotherapy for TD/TS may be recommended in addition to the first line counselling and behavioural interventions[2].

First line pharmacotherapy

Alpha adrenergic agonists: Clonidine or Guanfacine (as single agent or combined with ADHD stimulants/non-stimulants) are the first line recommended treatment for tics/TS. These drugs were initially developed for the management of hypertension and have sedation or tiredness as major side effects. They can also cause possible rebound hypertension if stopped abruptly. There is a need to closely monitor blood pressure in patients on Clonidine or Guanfacine.

ADHD stimulants/non-stimulants: Apparent worsening or new onset of tics during ADHD treatment is oftentimes due to the coincidental waxing and waning

natural history of tics. It is best to persevere for a few weeks with normal doses of stimulant treatment (various formulations of Methylphenidate and or Dexamphetamines) if it is effectively controlling the ADHD symptoms. In most cases the tics will gradually subside spontaneously. If stimulants have to be stopped due to emerging or worsening tics, clinicians may consider re-challenging children with psychostimulants after a watchful period when the tics seem to have subsided. An alternative approach would involve treatment of ADHD and the co-morbid TD with alpha agonists either as replacement or additional therapy to psychostimulants.

Non-stimulant Atomoxetine should be considered as alternatives if alpha agonists are not tolerated. Atomoxetine can also be effective for treatment of ADHD with comorbid anxiety, and less effectively for co-morbid Tics/TS[24].

Second line pharmacotherapy

Antipsychotics: Various generations of antipsychotics are the recommended second line management for more complicated cases of TS/Tics. Recent studies about the atypical antipsychotics such as Risperidone, and Aripiprazole, suggest that their efficacy in the control of severe TD/TS symptoms is related to their ability to selectively block dopamine D2 postsynaptic receptors. Reviews of the atypical psychotropics have shown demonstrable effective treatment for tics, but they do not affect premonitory urges, and they are only moderately effective in controlling the co-occurring ADHD symptomatology[25].

The older generation of antipsychotics, such as Haloperidol and Pimozide, which were the preferred treatment options in the past due to their greater effectiveness, are now rarely used in the treatment of childhood TD/TS because of their significant adverse effects including extrapyramidal side-effects and tardive dyskinesia for Haloperidol, and cardiotoxicity for Pimozide[26].

Adjuvant therapy

Deep brain stimulation (DBS) has recently become a viable therapeutic option for TS in refractory cases[27]. A recent study suggests that iron deficiency may be associated with more severe tics and therapeutic iron supplements leads to alleviation of symptoms. The relationship between TD and iron deficiency appears to be independent of any co-morbidities such as OCD, ADHD, or anxiety[15].

SUMMARY OF TREATMENT FOR ADHD AND CO-MORBID TD USING COMMON CLINICAL SCENARIOS

Clinical guidelines have been published for the management of TD in Europe[28], Canada[29], and the United States[30]. We shall consider recommendations for management of ADHD co-morbid with TD/TS using three common clinical scenarios.

Scenario 1

In a patient with ADHD and co-morbid mild to moderate TD: Consider giving priority to the treatment of ADHD as it will likely be having the greater impact on the child's functioning and education. Furthermore, ADHD medications are more effective and have less potential side effects[2]. Tics reduction (and not tics exacerbation) has been reported with acute immediate release Dexmethylphenidate (IR dMPH) challenge in children and adolescents with ADHD and co-morbid Tics disorder[31]. However, supra-therapeutic doses of Dextroamphetamine should be avoided, as they may worsen tics severity in some individuals[32].

Treatment of tics may be considered in these patients only if the symptoms are associated with significant functional impairments. Various clinical options for the management of the tics include temporary withdrawal of stimulant treatment, addition or replacement of the stimulants with alpha adrenergic agents (Clonidine or Guanfacine) and or non-stimulant Atomoxetine.

Scenario 2

In a patient with ADHD and co-morbid TS or severe tics: Greater benefit and satisfaction to the patient may be achieved by treating the Tourette's symptoms first[2]. The treatment of TS/severe tics will follow the standard strategies of progressing from psychological and behavioural interventions to the first and or second line Pharmacotherapy, in that order. Treating the TS first offers the added advantage of minimizing the risk of worsening tics with the introduction of psychostimulants as the most effective treatment for ADHD.

Scenario 3

In a child already diagnosed with ADHD and treated with stimulants developing significant Tics disorder: New research evidence does not contra-indicate continuing use of the stimulants. Conservative "watchful" approach may be adopted to check if the tics will abate spontaneously (following the natural course). In most cases the tics will gradually subside.

The next step would be to consider modification of treatment (add new drug or replace medication as in scenario 2). Studies have confirmed that combination of alpha 2 agonist like Clonidine with psychostimulant Methylphenidate is effective and safe for the management of ADHD and co-morbid TD[2]. An earlier meta-analysis of 9 studies involving 477 subjects has confirmed that alpha-2 agonists offer the best combined improvement in both tics and ADHD symptoms. It also showed that Methylphenidate offers the greatest and most immediate improvement of ADHD symptoms without aggravating the tic symptoms. Atomoxetine and Desipramine also offer additional evidence-based treatments of ADHD in children with comorbid TD[32].

CONCLUSION

Recent published evidence suggests that the incidence and severity of tics and TS are not increased by the use of psychostimulants, using the usual recommended dosing, except in a small number of individual cases. A more recent meta-analysis of 22 controlled trials among 2385 ADHD children has failed to demonstrate any significant relationship between treatment with stimulants and new tics or increasing severity of existing ones. Apparent symptom worsening or new tics appearing during ADHD treatment can often be attributed to the coincidental "waxing and waning" natural history of tics[33].

Most tics respond to psychoeducation and behavioural management. Level A of evidence support the use of alpha adrenergic agonists, including Clonidine and Guanfacine, reuptake noradrenenaline inhibitors (Atomoxetine) and stimulants (Methylphenidate and Dexamphetamines) for the treatment of Tics/TS and comorbid ADHD[14]. Priority should be given to the management of co-morbid TS or severely disabling tics in children and adolescents with ADHD.

Severe TD may require antipsychotic treatment (such as Aripiprazole or Risperidone). The newer atypical antipsychotics, especially Aripiprazole, are safe and effective treatment for TS or severe tics, but they only moderately control the co-occurring ADHD symptomatology. Consideration of different common clinical scenarios could help to determine the most appropriate treatment to consider in each patient presenting with ADHD and co-morbid TD.

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ORIGINAL ARTICLE

Case Control Study

Abdominal obesity adversely affects bone mass in children

Sowmya Krishnan, Michael P Anderson, David A Fields, Madhusmita Misra

Sowmya Krishnan, David A Fields, Department of Pediatrics, University of Oklahoma Health Sciences Center, Harold Hamm Diabetes Center, Oklahoma City, OK 73104, United States

Michael P Anderson, College of Public Health, University of Oklahoma Health Science Center, Oklahoma City, OK 73104, United States

Madhusmita Misra, Massachusetts General Hospital for Children and Harvard Medical School, Boston, MA 02114, United States

ORCID number: Sowmya Krishnan (0000-0001-5600-0753); Michael P Anderson (0000-0002-2319-2282); David A Fields (0000-0002-6845-1196); Madhusmita Misra (0000-0002-9405-2981).

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Correspondence to: Sowmya Krishnan, MD, Associate Professor, Department of Pediatrics, University of Oklahoma Health Sciences Center, Harold Hamm Diabetes Center, 1200, N Children's Avenue, Suite 4500, Oklahoma City, OK 73104, United States. sowmya-krishnan@ouhsc.edu
Telephone: +1-405-2718000-43091
Fax: +1-405-2713093

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Abstract

AIM

To determine the effect of childhood obesity and insulin resistance on bone health.

METHODS

We conducted a cross sectional study in pubertal adolescents and young adults 13-20 years old who were either overweight/obese or normal weight**.** Participants were Tanner 3 or above for pubertal stage, and had fasting blood work done to measure glucose, insulin, C-reactive protein and lipid levels. Homeostatic model of insulin resistance (HOMA-IR) was calculated using the formula (Fasting Blood Glucose *Insulin/405). Body composition and bone mineral density were measured using dual energy X-ray absorptiometry (DXA; Hologic QDR 4500, Waltham, MA, United Kingdom).

RESULTS

Percent trunk fat was associated inversely with whole

body bone mineral content (BMC), whereas HOMA-IR was associated positively with whole body BMC.

CONCLUSION

Our results suggest that abdominal adiposity may have an adverse effect on whole body bone parameters and that this effect is not mediated by insulin resistance.

Key words: Obesity; Bone mineral density; Insulin resistance

Core tip: Abdominal adiposity has an adverse impact on whole body bone mineral content in adolescents. This effect does not seem to be mediated by the increased insulin resistance associated with increased abdominal adiposity. Attention to body composition rather than just body weight is needed to counsel adolescents regarding optimal bone health.

Krishnan S, Anderson MP, Fields DA, Misra M. Abdominal obesity adversely affects bone mass in children. *World J Clin Pediatr* 2018; 7(1): 43-48 Available from: URL: http://www.wjgnet.com/2219-2808/full/v7/i1/43.htm DOI: http://dx.doi.org/10.5409/wjcp.v7.i1.43

INTRODUCTION

The antecedents of adult onset osteoporosis start in childhood, and while the effect of several childhood systemic diseases on bone health[1] has been recognized, the effect of childhood obesity on bone health remains unclear. Historically in adults, higher body mass index (BMI) was believed to be bone protective with increased bone mineral density (BMD) reported with higher BMI[2]. Further studies have revealed this to be proportional to total lean mass rather than total fat mass. However, the relative distribution of fat in the body may also play a role, and visceral adiposity in particular has been demonstrated to have an adverse impact on bone[3,4]. Visceral adiposity is directly associated with insulin resistance, and the link between obesity and bone health may be mediated by the underlying insulin resistance. Insulin is a bone anabolic hormone[5] and higher insulin levels may result in increased bone formation. However, a state of insulin resistance may negate the beneficial effects of insulin on bone. This in fact has been suggested in recent studies in adults[6,7]. However, data in children remain inconclusive.

Data regarding the relationship between insulin resistance, BMD and fracture risk are conflicting. While adults with long standing type 2 diabetes tend to have more fractures[8-10], their BMD has been reported to be high or normal in various studies. Potential conflicting factors include the duration of type 2 diabetes (as type 2 diabetes can go unrecognized for a long time), and degree of hyperglycemia. While obese boys tend to have more fractures than their lean counterparts[11], the pathophysiology behind this association remains to be delineated, and the effect of insulin resistance without overt type 2 diabetes on bone health in adolescents remains unclear. In this study, we examined the association of body composition and insulin resistance with whole body BMD and bone mineral content (BMC) in a group of overweight and normal weight pubertal adolescents, none of whom had type 2 diabetes. We hypothesized that overweight children with greater visceral adiposity (as assessed by percent trunk fat) would have lower BMD and BMC compared to their normal weight counterparts, which would be associated with the degree of insulin resistance.

MATERIALS AND METHODS

This was a cross-sectional study of children 13-20 years who were either normal weight or overweight. Subjects were recruited from our clinics and through recruitment fliers and campus wide e-mail notifications between 2006-2008. A total of 37 children were enrolled. Study subjects were defined as being overweight if their BMI was above the 85th percentile for age and gender (Group 1) and normal weight if their BMI was between the 3rd to 85th percentiles for age and gender (Group 2). The research protocol was approved by the Institutional Review Board at the University of Oklahoma Health Sciences Center. All subjects < 18 years old provided assent for study participation. Participants 18 years or older and parents of participants < 18 years old provided consent for study participation.

Children were excluded from the study if: (1) They had any coexisting endocrine, genetic or metabolic disease that may affect bone metabolism; or (2) if they were on any medications that may affect bone, including those that could affect substrate metabolism, psychotropic medications, weight loss medications, and oral contraceptives for female subjects. To control for the well-described increase in bone mineral acquisition during early stages of puberty, children who were prepubertal or early pubertal (Tanner 1 and 2) were excluded. Children were also excluded if they had impaired fasting glucose or diabetes based on fasting glucose values[12].

After obtaining appropriate consent and assent, each child underwent a history and physical examination by a board certified pediatrician. Height and weight were used to calculate BMI, waist and hip circumference were obtained on each subject, and the presence and degree of acanthosis nigricans noted if present. Study participants then underwent a fasting blood draw for glucose and insulin levels, lipid profile and apolipoprotein C-Ⅲ levels. Homeostatic model of insulin resistance (HOMA-IR) was calculated using the formula: (Fasting Blood Glucose *Insulin)/405. Studies have shown that HOMA-IR correlates well with insulin resistance as measured by insulin clamp studies[13]. All testing was

Table 1 Descriptive data of the overweight and normal weight groups

Covariates	Overweight n = 23 mean (SD)	Normal weight n = 14 mean (SD)	P value
Age (mo)	187 (25.4)	198 (31.1)	0.40[b]
Gender (% age females)	43.48%	57.14%	0.42
Birth weight (g)	3385 (644)	3179 (908)	0.42[b]
Weight (kg)	93.7 (19.9)	57.4 (7.51)	< 0.0001[a]
Weight %ile	95.1 (6.35)	52.5 (20.8)	< 0.0001[b]
Height (cm)	168 (9.90)	167 (6.92)	0.72[a]
Height %ile	59.3 (30.5)	60.1 (31.2)	0.88[b]
BMI kg/m^2	32.9 (5.60)	20.5 (1.51)	< 0.0001[a]
BMI %ile	96.6 (3.17)	47.3 (17.1)	< 0.0001[b]
Total activity time/d (min)	303 (125)	307 (109)	0.93
Apolipoprotein C Ⅲ (mg/dL)	6.71 (1.53)	6.56 (140)	0.75[a]
C-reactive protein	2.81 (2.85)[c]	2.61(2.41)[d]	0.86
HOMA-IR	3.23 (1.78)	2.49 (3.49)	0.02
Waist circumference (cm)	98.5 (13.7)	69.2 (5.79)	< 0.0001[a]
Hip circumference (cm)	118 (11.4)	94.8 (5.72)	< 0.0001[a]
Waist to hip ratio	0.84 (0.06)	0.73 (0.05)	< 0.0001[a]
Total lean mass (kg) (DXA)	50.58 (10.78)	55.40 (12.68)	0.23[a]
Percent trunk fat (DXA)	36.4 (9.3)	17.1 (6.49)	< 0.0001
Spine BMD (g/cm^2)	1.06 (0.14)	1.06 (0.13)	0.95[a]
BMD L-spine Z-score	1.32 (1.24)	1.36 (1.00)	0.92
Whole body BMD (g/cm^2)	1.10 (0.09)	1.06 (0.07)	0.21[a]
Whole body BMC (g)	2417 (408)	2116 (281)	0.02[a]

[a]Student's *t*-test; [b]Wilcoxon-Mann-Whitney test; [c]n = 16; [d]n = 9. SD: Standard deviation; HOMA-IR: Homeostatic model assessment-estimated insulin resistance; BMD: Bone mineral density; BMC: Bone mineral content; BMI: Body mass index.

done by an experienced nurse assigned to the study at the General Clinical Research Center at the University of Oklahoma.

Whole body (WB) BMC and BMD, lumbar spine BMD, and body composition were measured using dual energy X-ray absorptiometry (DXA; Hologic QDR 4500, Waltham, MA, United Kingdom). Percent trunk fat [(trunk fat/total fat) × 100] was used as a surrogate for visceral fat[14]. Similarly, the waist to hip ratio was used as a surrogate for visceral fat[14]. Daily physical activity was assessed using a step activity monitor (Step Watch 3, Orthocare Innovations, Oklahoma City, OK, United States)[15]. Subjects were asked to wear the step activity monitor on their right ankle during the day time when they were awake for 5 to 7 consecutive days. The monitor records the number of strides taken on a minute to minute basis. Data from the monitor is downloaded to a computer software program which calculates the activity time in a day (any minute in which a stride was taken is considered an active time) and the total amount of strides taken each day averaged over the days the monitor was worn. The accuracy of the step activity monitor exceeds 99% ± 1% in older adults[15], as well as in children[16]. Test-retest intraclass reliability coefficient for the measurement of total daily strides and total daily minutes of activity are R = 0.94 and R = 0.91, respectively[15].

Statistical analysis

Statistical analysis for this study was performed and reviewed by Michael A Anderson (co-author), a bio-statistician at Department of public health, University of Oklahoma Health Sciences Center. Descriptive statistics were computed for age, gender, smoking, birth weight, current weight, height, BMI, waist circumference, hip circumference, waist to hip ratio, BMC and BMD, trunk % fat, and HOMA-IR. All continuous variables were assessed for normality using the Shapiro-Wilk test for normality and comparisons between overweight and normal weight groups were made using the Student *t*-test or the Wilcoxon-Mann-Whitney test, as appropriate. One outlier was identified (HOMA-IR > 13) and after checking for data entry error, this subject was excluded from data analysis. Pearson's correlation coefficient was used to test the strength of the linear association. Robust regression was used to fit a multiple linear regression model to test the effect of HOMA-IR and percent trunk fat on WB-BMC and all BMD variables while controlling for gender and physical activity (total activity time % of day), which are potential confounders of the association. The effect of percent trunk fat on HOMA-IR while controlling for gender and physical activity was similarly tested.

RESULTS

Demographic data revealed no significant difference in age, gender, birth weight or current height between the two groups (Table 1). Per study design, group 1 consisting of overweight participants had a significantly higher mean body weight, BMI, waist circumference, hip circumference, waist to hip ratio and percent trunk fat (Table 1). Total activity time per day and sedentary time per day did not differ between the two groups.

WB-BMC was significantly higher in the overweight

Table 2 Robust regression with whole body bone mineral content or spine bone mineral density as the dependent variable after

Variable	Whole body BMC		Spine BMD	
	β	*P* value	β	*P* value
Gender	-704.28	< 0.0001	0.0876	0.18
Activity time % of day	-0.55	0.79	-0.0003	0.86
Waist to hip ratio	-111.619	0.86	0.4707	0.27
Percent trunk fat	-2112.67	< 0.0001	-0.3706	0.18
Total lean mass	-0.0022	0.59	0.00	0.98
HOMA IR	123.3	< 0.0001	-0.1295	0.29

Other covariates in the model include waist to hip ratio, truck to total fat ratio, total lean mass, CRP, total activity time, apo CⅢ ratio, gender, HOMA-IR. BMC: Bone mineral content; BMD: Bone mineral density; HOMA-IR: Homeostatic model assessment-estimated insulin resistance.

group as was HOMA-IR (Table 1). BMD in both lower extremities was also significantly higher in the overweight group compared to the normal weight group (Table 1). In contrast, WB BMD, and spine BMD did not differ across groups. Similarly Lumbar spine BMD Z-score and total body less head (TBLH) BMD Z-score did not significantly differ between the two groups.

Robust regression with HOMA-IR as the dependent variable revealed that waist to hip ratio [β = 12.72 (3.88); $P < 0.01$], and activity time % of day [β = -0.03 (0.04); $P = 0.05$], but not percent trunk fat, were significantly related to HOMA-IR. Robust regression with WB-BMC as the dependent variable revealed a significant inverse association with percent trunk fat [β = -2112.67 (338.13); $P < 0.01$] (Table 2), and a positive association with HOMA-IR ($P = 0.03$) (Table 2) after controlling for potential confounders, gender and physical activity. BMD variables (WB BMD, and spine BMD) had inverse associations with percent trunk fat, but did not reach statistical significance. Apolipoprotein C-Ⅲ which is considered to be a marker of insulin resistance[17] did not differ significantly between the two groups and had no significant association with any BMD/BMC variables. Insulin values did not have a significant correlation with either WB-BMC (-0.12, $P = 0.46$) or subtotal BMC (-0.16, $P = 0.36$).

DISCUSSION

In this cross sectional study of bone parameters in normal-weight and overweight adolescents in the later stages of puberty, we show that higher trunk fat is associated with lower WB-BMC, whereas higher HOMA-IR is associated with higher WB-BMC after controlling for potential confounders. Both our groups were well matched for age and gender.

As expected, overweight subjects (Group 1) had a higher waist to hip ratio, percent trunk fat and HOMA-IR than normal-weight participants (Group 2). Waist to hip ratio is a reasonable surrogate for visceral adiposity, as is percent trunk fat[14]. The positive relationship between HOMA-IR and waist to hip ratio observed in our study has been documented by others[18,19]. Similarly higher BMC in obese and overweight subjects as observed in our study has been reported by others[20,21]. However, data are lacking regarding associations of insulin resistance parameters with bone variables in adolescents. Overweight subjects had higher BMD than normal-weight subjects in the lower extremities, consistent with the impact of greater loading (from greater body size) in overweight adolescents at this weight bearing region. This has been previously shown in the Framingham study in adults[22].

In our study, WB BMC was positively associated with HOMA-IR and negatively with the percent trunk fat, a good surrogate measure of visceral fat[14]. In adults, insulin resistance has been shown to have an adverse impact on bone mass[23]. In the MIDUS 11 study by Srikanthan *et al*[6] with approximately 717 adult participants, higher HOMA-IR levels were associated with higher BMD in the femoral neck but with decreased femoral neck strength. The femoral neck is not a site recommended for measurement of BMD in adolescents as landmarks are not well defined at this age making repeat measurements difficult. While the study by Srikanthan *et al*[6] included subjects with impaired glucose tolerance and diabetes, we excluded subjects with either of these conditions. Thus a higher HOMA IR value in our study would primarily be driven by higher insulin levels. A very elegant review by Fulzele *et al*[24] details the effects of insulin on bone acquisition, acting *via* insulin receptors expressed on osteoblasts. Given the multitude of anabolic actions of insulin on bone, it is not surprising that higher insulin levels would be associated with higher bone mass, despite associated insulin resistance. Also, HOMA-IR is a very crude measure of insulin resistance, and additionally, in any particular individual, there can be differential/partial insulin resistance in different organ/tissues[25,26]. Higher bone mass associated with higher HOMA-IR in overweight adolescents may mean that their osteoblasts are still sensitive to insulin signaling and its bone anabolic effects.

In contrast, recent literature suggests that visceral adiposity affects bone health adversely[3,27]. In our study, there was no association between WB BMC and waist to hip ratio, however, there was a significant inverse association between WB BMC and percent trunk fat, a good indicator of abdominal adiposity relative to total fat mass and visceral adiposity[14], consistent with other studies[3,28]. While it is not surprising that we

observed this inverse relationship of percent trunk fat with WB BMC, the pathogenic mechanism underlying this relationship remains unclear. Our initial postulate that the adverse effect of abdominal adiposity on bone mass in overweight children may be mediated by insulin resistance secondary to higher abdominal adiposity did not hold true. Another possible pathogenic mechanism in overweight adults may be an atherogenic lipid profile[29]. An elegant review by Tintut *et al*[29] discusses the relationship of poor bone mineralization with an adverse lipid profile, which may be mediated by vascular ischemia secondary to atherosclerosis. However, this is unlikely to be the mechanism linking low bone mass and abdominal adiposity in adolescents, in whom frank atherosclerosis is unusual despite an adverse lipid profile. In addition, we found no associations of lipids including apolipoprotein C Ⅲ with bone variables. The possibility that certain adipokines secreted preferentially by visceral fat may mediate this effect needs to be further explored.

Higher cortisol and decreased growth hormone secretion is well reported in obese subjects. A higher fracture rate has been reported in obese adolescents[11], however, our sample size was not large enough to draw any conclusions regarding fracture prevalence. It is interesting that physical activity did not differ significantly between our two groups, and may reflect low levels of activity in both groups. We do not have vitamin D levels on the subjects, however, the impact of vitamin D supplementation on bone mass in subjects who are vitamin D sufficient remains controversial[30]. Finally, this is a cross sectional study and thus the results do not imply causation.

In conclusion, our data add to existing literature that suggests that abdominal adiposity has an adverse impact on WB BMC in adolescents. In addition, our study shows that this effect is not mediated by the increased insulin resistance associated with increased abdominal adiposity. Attention to body composition rather than just body weight is needed to counsel adolescents regarding optimal bone health. Further studies are needed to delineate the mechanisms by which visceral adiposity adversely affects bone health.

ARTICLE HIGHLIGHTS

Research background

Adult onset osteoporosis has its antecedent in childhood. With the rise in obesity epidemic, the effect of childhood obesity on bone health needs to be delineated. Historically in adults, higher body mass index (BMI) was believed to be bone protective with increased bone mineral density reported with higher BMI. Further studies have revealed this to be proportional to total lean mass rather than total fat mass. However, the relative distribution of fat in the body may also play a role, and visceral adiposity in particular has been demonstrated to have an adverse impact on bone. Visceral adiposity is directly associated with insulin resistance, and the link between obesity and bone health may be mediated by the underlying insulin resistance. Insulin is a bone anabolic hormone and higher insulin levels may result in increased bone formation. However, a state of insulin resistance may negate the beneficial effects of insulin on bone. This in fact has been suggested in recent studies in adults. However, data in children remain inconclusive.

Research motivation

The main motivation for this research study was to understand the effect of body composition and insulin resistance on bone health in children.

Research methods

The study showed that percent trunk fat was associated inversely with whole body bone mineral content (BMC), whereas homeostatic model of insulin resistance was associated positively with whole body BMC.

Research results

These results suggest that abdominal adiposity may have an adverse effect on whole body bone parameters and that this effect is not mediated by insulin resistance.

Research perspectives

Future research should look at other possible connection between adipose tissue and bone health.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Neither hereditary periodic fever nor periodic fever, aphthae, pharingitis, adenitis: Undifferentiated periodic fever in a tertiary pediatric center

Silvia De Pauli, Sara Lega, Serena Pastore, Domenico Leonardo Grasso, Anna Monica Rosaria Bianco, Giovanni Maria Severini, Alberto Tommasini, Andrea Taddio

Silvia De Pauli, Sara Lega, Andrea Taddio, Department of Medicine, Surgery and Health, University of Trieste, Trieste 34142, Italy

Sara Lega, Serena Pastore, Domenico Leonardo Grasso, Anna Monica Rosaria Bianco, Giovanni Maria Severini, Alberto Tommasini, Andrea Taddio, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste 34137, Italy

ORCID number: Silvia De Pauli (0000-0002-0486-0441); Sara Lega (0000-0003-4028-4194); Serena Pastore (0000-0003-4697-0777); Domenico Leonardo Grasso (0000-0002-0617-8630); Anna Monica Rosaria Bianco (0000-0001-8101-9659); Giovanni Maria Severini (0000-0002-5790-2000); Alberto Tommasini (0000-0002-6943-7927); Andrea Taddio (0000-0001-6817-4953).

Author contributions: De Pauli S wrote the manuscript and cared for patients; Lega S discussed and revised critically the manuscript; Pastore S discussed and corrected the draft; Grasso DL performed ENT evaluation and revised the manuscript; Bianco AM performed genetic analyses and revised the manuscript; Severini GM reviewed the genetic content and discussed results; Tommasini A cared for patients and discussed the work; Taddio A cared for patients and critically discussed the manuscript; De Pauli S and Lega S contributed equally to the work.

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Correspondence to: Alberto Tommasini, MD, PhD, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, *Via* dell'Istria 65/1, Trieste 34137, Italy. alberto.tommasini@burlo.trieste.it
Telephone: +39-40-3785422
Fax: +39-40-3785452

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Abstract

AIM

To describe the frequency and clinical characteristics of patients with undifferentiated periodic fever (UPF) and to investigate whether a clinical classification of UPF based on the PRINTO-Eurofever score can help predicting the response to treatment and the outcome at follow-up.

METHODS

Clinical and therapeutic information of patients with

recurrent fever who presented at a single pediatric rheumatology center from January 2006 through April 2016 were retrospectively collected. Patients with a clinical suspicion of hereditary periodic fever (HPF) syndrome and patients with clinical picture of periodic fever, aphthae, pharingitis, adenitis (PFAPA) who were refractory to tonsillectomy underwent molecular analysis of five HPF-related genes: *MEFV* (NM_000243.2), *MVK* (NM_000431.3), *TNFRSF1A* (NM_001065.3), *NLRP3* (NM_001079821.2), *NLRP12* (NM_001277126.1). All patients who had a negative genetic result were defined as UPF and further investigated. PRINTO-Eurofever score for clinical diagnosis of HPF was calculated in all cases.

RESULTS

Of the 221 patients evaluated for periodic fever, twelve subjects with a clinical picture of PFAPA who were refractory to tonsillectomy and 22 subjects with a clinical suspicion of HPF underwent genetic analysis. Twenty-three patients (10.4%) resulted negative and were classified as UPF. The median age at presentation of patients with UPF was 9.5 mo (IQR 4-24). Patients with UPF had a higher frequency of aphthae (52.2% *vs* 0%, $P = 0.0026$) and musculoskeletal pain (65.2% *vs* 18.2%, $P = 0.0255$) than patients with genetic confirmed HPF. Also, patients with UPF had a higher frequency of aphthous stomatitis (52.2% *vs* 10.7%, $P < 0.0001$), musculoskeletal pain (65.2% *vs* 8,0%, $P < 0.0001$), and abdominal pain (52.2% *vs* 4.8%, $P < 0.0001$) and a lower frequency of pharyngitis (56.6% *vs* 81.3%, $P = 0.0127$) compared with typical PFAPA in the same cohort. Twenty-one of 23 patients with UPF (91.3%) received steroids, being effective in 16; 13 (56.2%) were given colchicine, which was effective in 6. Symptoms resolution occurred in 2 patients with UPF at last follow-up. Classification according to the PRINTO-Eurofever score did not correlate with treatment response and prognosis.

CONCLUSION

UPF is not a rare diagnosis among patients with periodic fever. Clinical presentation place UPF half way on a clinical spectrum between PFAPA and HPF. The PRINTO-Eurofever score is not useful to predict clinical outcome and treatment response in these patients.

Key words: Hereditary periodic fever syndromes; Therapy; Genetics; Autoinflammatory diseases; Undifferentiated periodic fever

Core tip: Children with non-infectious recurrent fever more often fall into two diagnostic categories. The first and most common is periodic fever, aphthae, pharingitis, adenitis (PFAPA), the second, far more rare, are hereditary periodic fevers. Very recently a third category has been increasingly recognized, and is that of undifferentiated periodic fevers or undifferentiated periodic fever (UPF). UPF include patients who do not meet the diagnostic criteria for PFAFA or for a monogenic disease. The clinical presentation and management of patients with UPF are poorly defined. In this study, the authors describe a cohort of patients with UPF showing that: (1) The clinical manifestations are on a half way of clinical spectrum between PFAPA and hereditary periodic fever; (2) PRINTO-Eurofever score is not useful to guide treatment choices and does not predict disease course; and (3) Both steroids and colchicine are useful to control symptoms in most cases. The authors conclude that further studies are needed to better define UPF and guide their management in clinical practice.

De Pauli S, Lega S, Pastore S, Grasso DL, Bianco AMR, Severini GM, Tommasini A, Taddio A. Neither hereditary periodic fever nor periodic fever, aphthae, pharingitis, adenitis: Undifferentiated periodic fever in a tertiary pediatric center. *World J Clin Pediatr* 2018; 7(1): 49-55 Available from: URL: http://www.wjgnet.com/2219-2808/full/v7/i1/49.htm DOI: http://dx.doi.org/10.5409/wjcp.v7.i1.49

INTRODUCTION

Periodic fever is defined as recurrences of seemingly unprovoked episodes of fever that last from a few days to a few weeks, separated by symptom-free intervals of variable duration[1].

The most common cause of periodic fever syndrome in children is PFAPA (periodic fever, aphthae, pharingitis, adenitis), an autoinflammatory condition[2] characterized by recurrence of fever associated with aphthous stomatitis, pharyngitis, and/or cervical adenopathy. The diagnosis of PFAPA is based on Thomas criteria: recurring fevers that begin before age 5 and are accompanied by at least one of the clinical signs aphthous stomatitis, pharyngitis or adenitis, without upper respiratory infection[3]. The pathogenesis of PFAPA is likely multifactorial, but evidence of familial recurrence of this syndrome may support a genetic predisposition. Patient with PFAPA respond to steroids[2] and heal spontaneously, usually in few years, or after tonsillectomy without sequelae[4,5]. Lack of response to tonsillectomy in PFAPA is uncommon and should raise the suspicion of a monogenic condition[6,7].

Other rarer periodic fever syndromes are due to definite monogenic defects involving mechanisms of inflammation (hereditary periodic fevers - HPF). The first described was familial mediterranean fever (FMF) which has been linked to *MEFV* gene in late nighties. Afterwards, a number of HPF syndromes have been described, and their genetic bases has been provided. This is the case for example of: tumor necrosis factor receptor-associated periodic syndrome (TRAPS), associated with *TNFRSF1A* gene defects, hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), related to *MVK* gene, and cryopyrin-associated periodic syndromes (CAPS) for which defects on either *NLRP3* or *NLRP12* have been

identified[8,9].

Timely diagnosis of HPF is essential since effective therapies are now available, and complications, such as amyloidosis and sensor neural impairment, can be avoided[10].

The term undifferentiated periodic fever (UPF) has been increasingly used to define those patients presenting with a complaint of periodic fever in whom the diagnostic criteria for PFAPA are not satisfied and genetic work-up for periodic fever gives a negative result.

On a practical ground, subjects with PFAPA who are refractory to tonsillectomy and/or to steroids may be as well included in the group of UPF.

Even though patients with UPF are increasingly recognized in clinical practice, the only epidemiologic data available comes from the Eurofever Registry were, in 2014, patients with an "undefined periodic fever" accounted for almost 9% of cases[11].

The management of such patients is challenging, as clinical manifestations are poorly described and the prognosis and response to treatment are unknown. Federici *et al*[12] recently validated a score for clinical classification of patients with periodic fever into the main four phenotypes of HPF (PRINTO-Eurofever score), and proposed that it could be used to classify patients with periodic fever in daily practice. The score considers age at disease onset, ethnicity and the presence or absence of specific clinical symptoms.

With the present study, we aimed to describe the frequency and clinical characteristics of patients with a diagnosis of UPF. Moreover, we calculated the PRINTO-Eurofever score in subjects with UPF to investigate if a clinical classification in HPF-like phenotypes (clinical score of HPF in the absence of genetic confirmation) could help predicting the response to treatment and prognosis.

MATERIALS AND METHODS

Patients

This was a retrospective cohort study conducted at a single Rheumatology Center caring for pediatric patients with rheumatologic and autoinflammatory conditions. The Study was approved by the local Ethics Committee. Clinical charts of patients who received a diagnosis of periodic fever during a ten-year period, from January 2006 through April 2016, were reviewed. Patients older than 18 years at the time of data collection were not included as they were no more referred to our Institute.

Criteria

All the patients with periodic fever were included in the study. Subjects with a clinical suspicion of HPF and subjects with a suspicion of PFAPA (Thomas's criteria) who didn't respond to steroid treatment or had a recurrence of symptoms after tonsillectomy underwent genetic analysis for five genes mostly involved in HPF, namely: *MEFV* (NM_000243.2) for familial mediterranean fever (FMF), *MVK* (NM_000431.3) for mevalonate kinase deficiency (MKD), *TNFRSF1A* (NM_001065.3) for TNFα receptor associated periodic syndrome (TRAPS), *NLRP3* (NM_001079821.2) and *NLRP12* (NM_001277126.1) for familial cold urticaria syndrome. Patients with known causative mutation were diagnosed with the corresponding disorder.

Subjects with negative results or polymorphisms of unknown significance were considered as UPF[13], irrespective of whether they came from the group of PFAPA who were refractory to tonsillectomy or patients suspected with HPF. This choice was based on the consideration that both subjects with a clinical suspicion of HPF and subjects with a suspicion of PFAPA, refractory to tonsillectomy or to steroids, share the same problems as concerns the lack of a definite prognosis and of a therapeutic approach.

Thus, three groups of subjects were finally identified based on clinical and genetical features: Typical PFAPA, genetically confirmed HPF, UPF.

Data collection

Data collected included information on: gender, family history, ethnicity, duration of fever episodes, presence of pharyngitis, adenitis or aphthae, presence of musculoskeletal, chest or abdominal pain, diarrhea, vomiting, skin rash, conjunctivitis, and sensory neural hearing loss. Data were collected at disease onset and during follow-up. PRINTO-Eurofever score was calculated retrospectively at last follow-up[12]. Based on PRINTO-Eurofever score, patients who scored positive were assigned to a specific HPF phenotype according to the same scoring system. A possible relationship between the clinical diagnosis based on PRINTO-Eurofever criteria and response to treatment at follow up was assessed.

Statistical analysis

Statistical analysis were made using GraphPad Prism 5 software. Categorical variables were summarized as frequency and percentage and were compared across independent groups by the Fisher's exact test (two tailed, confidence interval 95%). Numerical variables with asymmetrical distribution were summarized by median and interquartile range (IQR) and were compared by the Kruskal-Wallis test. A P value < 0.05 was considered for significance.

RESULTS

During a ten-year period, 221 patients were evaluated for periodic fever. Twenty-two patients had a suspicion of HPF and a definite diagnosis could be genetically confirmed in 11 of them (5 MKD, 3 TRAPS, 2 FMF, 1 FCU). The other 11 subjects resulted negative and were considered as UPF.

PFAPA was suspected in 199 subjects, 12 of whom did not respond to steroids or persisted after tonsillectomy and underwent genetic analysis. None of these

Table 1 Baseline characteristics and symptoms distribution of patients with periodic fever in our cohort

	Undifferentiated periodic fever (*n* = 23)	PFAPA (*n* = 187)	HPF (*n* = 11)
Females, *n* (%)	18 (70%)	74 (38%)	7 (63%)
Ethnicity, *n*			
EU	20	183	11
Arabian	2	2	0
Mix	1	2	0
Median age at onset, mo (IQR)	9.5 (4-24)	12.5 (2.5-96)	9 (1-174)
Median age at first visit, mo (IQR)	51 (33-113)	42.15 (8-120)	48 (12-216)
Symptoms, *n* (%)			
Pharyngitis	13 (56.6%)	152 (81.3%)	4 (36.3%)
Aphtae	12 (52.2%)	20 (10.7%)	0 (0%)
Chest pain	0 (0%)	0 (0%)	1 (9%)
Abdominal pain	12 (52.2%)	9 (4.8%)	6 (54.5%)
Musculoskeletal pain	15 (65.2%)	15 (8.0 %)	2 (18.2%)

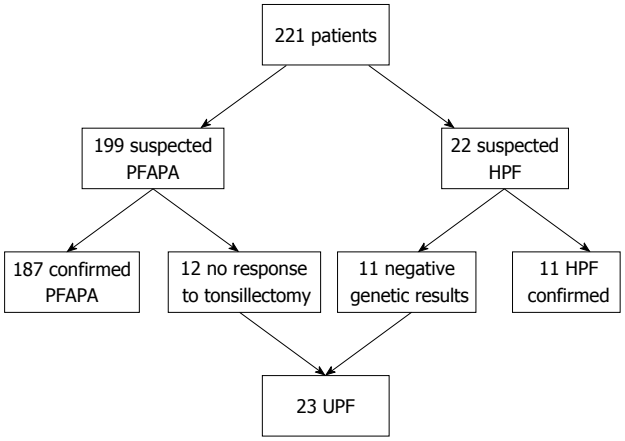

Figure 1 Selection of undifferentiated periodic fever cohort. PFAPA: Periodic fever, aphthae, pharingitis, adenitis; HPF: Hereditary periodic fever; UPF: Undifferentiated periodic fever.

subjects had causative mutations of HPF genes. In 6 patients, variants of unknown significance were found. Four patients had heterozygous mutations of which two were in the *MEFV* gene (P369S-R408Q and V726A), one in the *MVK* gene (V377I) and one in *NLRP12* (variation H304Y). Two patients had a homozygous R202Q variant in *MEFV*. Thus, all 12 subjects were considered as UPF.

Overall, a total of 23 patients (10%) met the diagnosis of UPF and where thus included in the analysis. UPF Cohort selection is reported in Figure 1.

Baseline characteristics of patients with UPF and comparison with HPF and PFAPA

Baseline demographic and clinical characteristics of patients are described in Table 1.

The most frequent complaints at first visit in UPF were exudative pharyngitis (13 patients, 56.6%), musculoskeletal pain (15 pt, 65.2%), aphthous stomatitis (12 pt, 52.2%) and abdominal pain (12 pt, 52.2%). No patient suffered from chest pain. Abdominal pain in the UPF group was reported as mild to moderate and never led to an evaluation for acute abdomen.

Median duration of disease at last follow-up was 6.3 years (IQR 0.9-17.8 year). Median follow-up since inclusion in the study was 3.3 years (IQR 0.3-9.4 year).

Subjects with UPF had a similar age at disease onset compared with HPH (P = 0.9), while they had an earlier onset compared with PFAPA (P = 0.008).

Compared with HPF, patients with UPF were more likely to have aphthae (52.2% *vs* 0%, P = 0.0026) and musculoskeletal pain (65.2% *vs* 18.2%, P = 0.0255), while compared with PFAPA they were more likely to have aphthous stomatitis (52.2% *vs* 10.7%, P < 0.0001), musculoskeletal pain (65.2% *vs* 8.0%, P < 0.0001), abdominal pain (52.2% *vs* 4.8%, P < 0.0001) but were less likely to have pharyngitis (56.6% *vs* 81.3%, P = 0.0127).

Therapeutic strategies received at any time and response to therapy in UPF

An oral glucocorticoid (betamethasone) was the first therapeutic choice in 21/23 patients. In 16 patients (69.5%), oral administration of betamethasone determined immediate resolution of the acute episode; in 11 patients, a standard dose of 0.1 mg/kg of betamethasone was effective, in 5 higher doses of 0.2-0.3 mg/kg were required. In 8 patients, who came from the group with initial suspicion of PFAPA, acute episodes became more frequent after glucocorticoid treatment. Tonsillectomy was performed in 12 patients being ineffective in all of them.

Thirteen patients were treated with daily oral colchicine (0.5-1.5 mg/die), which reduced or abated symptoms recurrence in 6 patients (46%). All patients receiving colchicine had been previously treated with steroids. The reason for switching to colchicine was steroids being ineffective in 3 patients, and need for too high or too frequent corticosteroid doses in 10 patients.

At last follow-up, 21/23 (91%) were still receiving medical treatment for the management of acute symptoms: 10 patients received corticosteroids during acute episodes; 7 patients were on daily colchicine and 4 patients were receiving non-steroidal antinflammatory drugs (NSAID); 2 patients healed spontaneously.

Classification of patients based on PRINTO-Eurofever score at baseline and response to therapy

At baseline, 11 subjects could be classified as HPF-like: 3 patients had a positive score for FMF, 5 for MKD, 3 for

Table 2 Treatment response in undifferentiated periodic fever cohort as a whole and in undifferentiated periodic fever subgroups according to PRINTO-Eurofever classification at baseline[1]

	Undifferentiated periodic fever (*n* = 23)	Positive score (*n* = 11)	Negative score (*n* = 12)
Glucocorticoids			
Total	21	11	12
Responsive	16	9	10
Not responsive	5	2	2
Colchicine			
Total	13	6	7
Responsive	6	4	2
Not responsive	7	2	5
Tonsillectomy			
Total	12	5	7
Responsive	0	0	0
Not responsive	12	5	7

[1]Statistical significance could not be calculated, due to the small size of the sample.

TRAPS, 1 for CAPS (1 patient was positive for FMF and MKD). Twelve patients had negative scores for HPF.

We didn't observe a clear relationship between PRINTO-Eurofever score at baseline and response to treatment received at any time. In particular, no patient who responded to colchicine had a clinical score supportive of FMF. As opposite, 2 out of 7 patients who did not respond to colchicine had a positive score for FMF.

DISCUSSION

In a single pediatric rheumatology center, 10% of patients presenting with a complaint of periodic fever could be classified as UPF. Even if PFAPA was by far the most frequent diagnosis, UPF was a more common diagnosis compared to HPF.

Age at symptoms presentation patients with UPF was quite varied, ranging from 2 to 111 mo. Interestingly, the median age at disease onset ~~in~~ of UPF was closer to that of HPF than that of PFAPA, similarly to what has been reported in the literature[11], suggesting the possibility of a stronger contribution of genetic factors in UPF compared with PFAPA.

Musculoskeletal pain and recurrent pharyngitis were the most frequent complaints followed by recurrence of aphthous stomatitis and abdominal pain. The high frequency of pharyngitis and stomatitis reflects the fact that the majority of patients classified as UPF had been initially diagnosed as PFAPA. It should be noted, however, that all these patients had a more complex phenotype compared to patients with a definitive diagnosis of PFAPA, as most of them complained of musculoskeletal or abdominal pain, in addition to pharyngitis.

The frequency of abdominal pain alone was similar in UPF and HPF, and in both cases it was significantly higher than in PFAPA. Notably, chest pain was never reported in patients with UPF.

According to these observations, UPF seem to be half way on a clinical spectrum of disease severity ranging from PFAPA to HPF. Patients with UPF in fact had more frequent "extrapharingeal" symptoms, namely musculoskeletal and abdominal pain, compared to PFAPA but despite their frequency, these symptoms were never as severe as those reported in HPF.

Overall, steroids were an effective strategy to control symptoms in a high proportion of patients.

For patients who needed steroids at high doses or frequency, daily oral colchicine was a useful alternative strategy to control symptom recurrence.

Tonsillectomy did not resolve fever recurrence in UPF patients, but this observation is biased, as this was one of the criteria that we chose for patients' inclusion in the UPF group.

We evaluated if a clinical classification of our cases could have been used to predict the response to therapy. So far, the only suitable classification proposed for subjects with periodic fever syndromes is the PRINTO-Eurofever score, which was developed to help experts classifying patients with suspected autoinflammatory fever syndromes without relying on genetic analyses. The score was calculated based on clinical features selected on a multivariate analysis on a large group of patients with different periodic fevers[12].

We showed that PRINTO-Eurofever classification at baseline could not predict response to any treatment.

Thus, even though the short time to last follow up for some patients, PRINTO-Eurofever score at baseline seems not to be predictive of symptoms persistence over time.

Several limitations of the study are acknowledged. Due to its retrospective design, clinical data were not systematically collected. The sample size is small, and recruitment occurred at one Tertiary-referral Clinic thus limiting the generalizability of our observation. Moreover, the median time to follow-up was too short to estimate long-term prognosis. In fact, considering that a significant proportion of UPF showed both recurrent aphthous ulcers and abdominal or musculoskeletal pain, it is still possible that part of them will develop a Behcet disease (BD) on a longer follow-up. Indeed, Cantarini *et al*[14] recently showed that many subjects with adult BD complained of periodic fever and aphthae during

childhood. Moreover, we cannot exclude that some patient with UPF could have a different monogenic disorder, but this seem unlikely at present, given that increasing the number of candidate genes in genetic panels did not result in increased diagnoses[15].

In conclusion, according to our observation patients with UPF seem not to be rare in clinical practice. Clinical presentation places them half way on a clinical spectrum between PFAPA and HPF. Classification of patients with UPF into a specific HPF phenotype according PRINTO-Eurofever criteria is not useful to guide treatment choice and does not predict disease prognosis. Given the above-mentioned limitation, what we observed represent and initial attempt to describe a poorly defined subset of patients with periodic fever commonly encountered in clinical practice. Further studies are needed to better define patients with UPF and guide their management in clinical practice.

ARTICLE HIGHLIGHTS

Research background

Undifferentiated periodic fevers (UPF) include periodic fever not meeting the diagnostic criteria for typical PFAPA of for hereditary periodic fever syndromes. Even if UPF are increasingly recognized, there is currently no recommendation to guide the management of children with this condition.

Research motivation

Clinical criteria to classify periodic fever without the help of genetic analyses have been proposed by PRINTO Eurofever, and might be particularly useful for subjects with UPF. Thus, we studied the clinical features of our patients in relation with their scores in the PRINTO-Eurofever classification.

Research objectives

Our study aims at improving knowledge on UPF and at evaluating if the application of the PRINTO-Eurofever classification can help the clinical management of these patients.

Research methods

A data base was filled in by retrospective review of clinical records, follow-up visits and phone calls. A structured questionnaire was used to classify all the subjects with the PRINTO-Eurofever score. The response to therapies and the prognosis at follow-up was compared with the clinical diagnosis obtained with the PRINTO-Eurofever score.

Research results

The clinical manifestations are on a half way of clinical spectrum between PFAPA and hereditary periodic fever. PRINTO-Eurofever score is not useful to guide treatment choices and does not predict disease course. Both steroids and colchicine are useful to control symptoms in most cases.

Research conclusions

UPF are as common as hereditary periodic fever, however knowledge on prognosis and response to therapies in these patients is lacking.

Research perspectives

Multicenter studies and experts' agreement are needed to develop recommendations for the management of UPF.

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ORIGINAL ARTICLE

Retrospective Study

Pediatricians lack knowledge for the diagnosis and management of functional constipation in children over 6 mo of age

Ariani Widodo, Badriul Hegar, Yvan Vandenplas

Ariani Widodo, Badriul Hegar, Department of Child Health, Universitas Indonesia, Jakarta 10430, Indonesia

Yvan Vandenplas, Department of Pediatrics, UZ Brussel, Vrije Universiteit Brussel, Larbeeeklan, Brussels 1090, Belgium

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Correspondence to: Yvan Vandenplas, MD, PhD, Department of Pediatrics, UZ Brussels, Vrije Universiteit Brussel, Laarbeeklaan 101, Brussels 1090, Belgium. yvan.vandenplas@uzbrussel.be
Telephone: +32-2-4775794
Fax: +32-2-4775783

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Abstract

AIM

To assess the knowledge of general pediatricians throughout Indonesia about the diagnosis and treatment of childhood constipation.

METHODS

A comprehensive questionnaire was distributed to general pediatricians from several teaching hospitals and government hospitals all over Indonesia.

RESULTS

Data were obtained from 100 pediatricians, with a mean of 78.34 ± 18.00 mo clinical practice, from 20 cities throughout Indonesia. Suspicion of constipation in a child over 6 mo of age arises when the child presents with a decreased frequency of bowel movements (according to 87% of participants) with a mean of one bowel movement per 3.59 ± 1.0 d, hard stools (83%), blood in the stools (36%), fecal incontinence (33%), and/or difficulty in defecating (47%). Only 26 pediatricians prescribe pharmacologic treatment as first therapeutic approach, while the vast majority prefers nonpharmacologic treatment, mostly (according to 68%) The preferred nonpharmacologic treatment are high-fiber diet (96%), increased fluid intake (90%), toilet training (74%), and abdominal massage (49%). Duration of non-pharmacological treatment was limited to 1 to 2 wk. Seventy percent of the pediatricians recommending toilet training could only mention some elements of the technique, and only 15% was able to explain it fully and correctly. Lactulose is the most

frequent pharmacologic intervention used (87% of the participants), and rectal treatment with sodium citrate, sodium lauryl sulfo acetate, and sorbitol is the most frequent rectal treatment (85%). Only 51% will prescribe rectal treatment for fecal impaction. The majority of the pediatricians (69%) expect a positive response during the first week with a mean (± SD) of 4.1 (± 2.56) d. Most participants (86%) treat during one month or even less. And the majority (67%) stops treatment when the frequency and/or consistency of the stools have become normal, or if the patient had no longer complaints.

CONCLUSION

These data provide an insight on the diagnosis and management of constipation in childhood in Indonesia. Although general pediatricians are aware of some important aspects of the diagnosis and mangement of constipation, overall knowledge is limited. Efforts should be made to improve the distribution of existing guidelines. These findings highlight and confirm the difficulties in spreading existing information from guidelines to general pediatricians.

Key words: Functional constipation; Guideline lactulose; Rectal treatment; Polyethylene glycol

Core tip: Diagnosis and management of functional constipation in children by general paediatricians is sub-optimal because of a lack of knowledge of published guidelines. Our data confirm that efforts should be made to improve distribution of existing guidelines to primary health care.

Widodo A, Hegar B, Vandenplas Y. Pediatricians lack knowledge for the diagnosis and management of functional constipation in children over 6 mo of age. *World J Clin Pediatr* 2018; 7(1): 56-61 Available from: URL: http://www.wjgnet.com/2219-2808/full/v7/i1/56.htm DOI: http://dx.doi.org/10.5409/wjcp.v7.i1.56

INTRODUCTION

Constipation is worldwide a common problem in children. Three to five percent of all clinic consultations to pediatricians are due to constipation, and the number keeps increasing[1]. Primary care physicians such as pediatricians or family physicians are frequently consulted by parents because of constipation[2]. Scientific societies develop clinical practice guidelines with the goal to improve diagnosis and management and result in a better quality of care. However, these recommendatations from scientific societies are not easily picked up by primary health care level[3]. Guidelines for the diagnosis and management of constipation, both for adults and children, have been published by professional associations such as the North American and European Societies of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN)[4]. Not many studies were conducted in Indonesia, but it has been estimated that the prevalence of constipation ranges between 12% and 48%, depending on multiple variables[5,6]. Although constipation is rarely an emergency, when it is not managed properly it can cause serious complications in the long term such as significant abdominal pain, lowered self-esteem, depression, and decreased quality of life[4,7]. Functional constipation has been identified as an important health problem during childhood and contrary to common belief, has a significant impact on quality of life of children and their families[8]. There is currently no Indonesian guideline. This study aims to evaluate the diagnosis and quality of management of constipation in children among pediatricians in Indonesia, in order to include our findings in National Guidelines.

MATERIALS AND METHODS

We developed a comprehensive anonymous questionnaire consisting of both multiple-choice and open questions (Table 1: Questionnaire). The questionnaires were distributed to 103 general pediatricians during a national meeting of the Indonesian Society of Pediatrics, both from academic and non-academic centers, working in 20 different cities in Indonesia. They were asked to fill in the questionnaire on the spot and returned the document as soon as it was completed to the research staff.

The first series of question asks about the symptoms making the pediatrician suspicious of the possible diagnosis constipation as cause for the symptoms. Participants could indicate more than one symptom out of a proposed list: Number of bowel movements, consistency of the stools, difficulties in defecation, blood in the stools, encopresis... The second series of questions regarded treatment, duration of treatment, and outcome. Specific information about recommendations regarding toilet training was asked for as an open question.

RESULTS

The response rate was 97%; 3 out of 103 general pediatricians returned the questionnaire with incomplete answers. The participants worked as general pediatricians for a mean duration of 78.34 ± 18.00 mo in hospitals distributed over the Western, Middle, and Eastern parts of Indonesia.

The pediatricians suspected constipation when a child over 6 mo of age presents with a decrease in frequency of bowel movement (87% of the participants) with a mean of 3.59 ± 1.0 d between two defecations (Question 1), hard stools (83%), presence of blood in the stools (36%), encopresis (33%), and/or difficulty in defecating (47%) (Table 2).

Table 1 Questionnaire about constipation in children older than 6 mo

We are studying the diagnostic criteria and management of constipation in children over 6 months of age. This questionnaire will be handled anonymously. Please tell us more about your experience in dealing with children with constipation. Many aspects in the diagnosis and management of constipation are debated. Therefore, there is no right or wrong answer. We look forward to your participation in completing this short questionnaire, which will take you around 5 to 10 min.

1 Please specify your profession: General Pediatrician Yes / No
How long are you working as General Pediatrician? ___ year(s) and __ month(s)

In which city do you work?_____

2 Which criteria do you use to diagnose constipation in children older than 6 months? (more than one answer is possible):
- o Infrequent defecation, less than once in every ____ day(s)
- o Hard consistency of stool
- o Bleeding when passing stools
- o Fecal incontinence
- o Difficulties in defecation
- o Crying before passing stool with normal consistency
- o Other (please specify)

3 Which treatment do you recommend as first approach? (more than one answer is possible):
- o Take a high-fiber diet
- o Increase fluid intake
- o Apply abdominal massage for babies
- o Start appropriate toilet training
- o Other (please specify)_____

4 If you answered "toilet training" in question 3, please explain briefly the method of toilet training which you suggested :

5 When do you start pharmacological therapy in a constipated child > 6 months old?
- o Immediately when the diagnosis of constipation is established
- o If non-pharmacological treatment does not respond after _____ day(s)/ week(s)/ month(s)
- o I do not recommendany pharmacological therapy
- o Other (please specify) _____

6 The pharmacological treatment that I recommend is :
- o Lactulose
- o Sorbitol
- o Magnesium salt
- o Laxative suppository
- o Other (please specify) _____

7 The rectal pharmacological treatment that you mostly recommend is:
- o Enema with a combination of sodium citrate, sodium lauryl sulfoacetate, and sorbitol (Microlax®)
- o Trifenylmethaan (Dulcolax®)
- o Docusate Sodium, Sorbitol (Yal®)
- o Glycerin suppository
- o I do not recommend such treatment
- o Other (please specify) _____

8 When do you recommend rectal treatment?
- o When impacted feces are diagnosed on physical examination
- o When patient had no bowel movement during ____ days
- o When stool is too hard to pass
- o When patient has to much difficulties to produce stools
- o Other (please specify) _____

9 Is there any other information/ education that you provide to the patients/parents?

10 In average, how long does it take for your patients to show a positive response to your first therapeutic approach? _____ days/ week(s)/ month(s)

11 In average, how long do you treat your patients for constipation? _____ week(s)/ month(s)/year(s)

12 When do you stop treatment?

Thank you so much for your participation

Seventeen participants (17%) did choose a combination of symptoms: Decreased frequency, hard stool and difficulties in defecation. Another 17 pediatricians chose only decreased frequency and hard stools. Eleven percent indicated only decreased frequency, while 14% answered they considered any of the symptoms or any combination as possibly indicating the diagnosis of constipation. Other participants combined any other variation of symptoms (Figure 1).

Regarding treatment, only 26% of the general pediatricians prescribed pharmacologic treatment as a first option. Non-pharmacologic treatment was recommended for a period of one to two weeks by 68% of the participants: high-fiber diet (96% of the participants), increased fluid intake (90%), toilet training (74%) and abdominal massage (46%) (Figure 2). However, seventy percents of the pediatricians indicating toilet training as therapeutic intervention could mention only some elements of the toilet training recommendations for constipated children. Only 15% were able to explain it fully and correctly, which includes age-appropriate technique and timing for toilet training according to the guidelines published by NASPGHAN and ESPGHAN[4]. Lactulose was the most frequent (87% of participants)

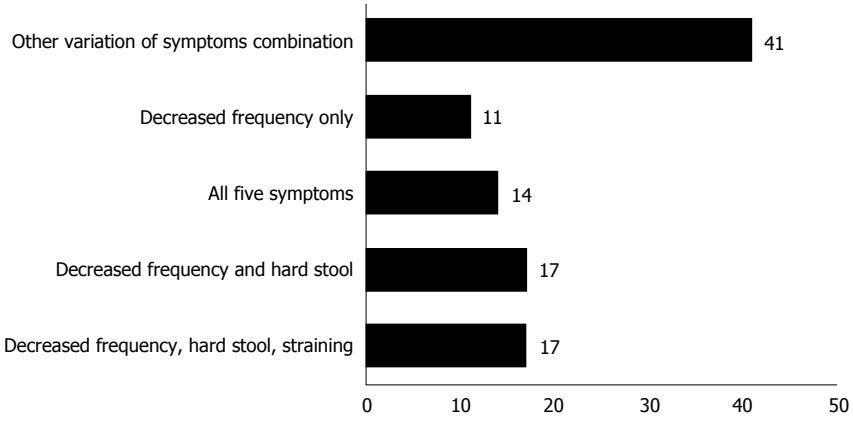

Figure 1 Constipation symptoms according to the participants.

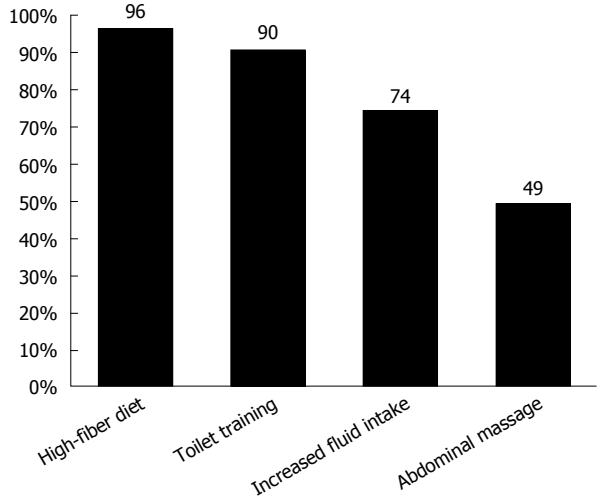

Figure 2 Preferred non-pharmacological treatment by the general pediatricians.

Table 2 Symptom that raise the suspicion of constipation

Symptom at presentation	Frequency
Decreased bowel movement	87%
Hard stool	83%
Difficulties in defecation	47%
Blood in stool	36%
Encopresis	33%

pharmacologic intervention used and a micro-enema with a combination of sodium citrate, sodium lauryl sulfoacetate and sorbitol was the most frequent rectal treatment (85%) prescribed. Only 51 of the pediatricians did recommend rectal treatment for fecal impaction. Some would only recommend rectal treatment after failure of lactulose.

The majority of the pediatricians (69%) answered to expect a positive response during the first week after starting therapy, with a mean (± SD) of 4.1 (± 2.56) d. Most participants (86%) recommend treatment during one month or even less. And the majority (67%) also stops the treatment when the frequency and/or consistency of the stools have become normal, or if the patient had no longer complaints.

DISCUSSION

Constipation is common during childhood and has an important impact on quality of life with a negative impact on psychological wellbeing. Functional constipation in young individuals influences quiet substantially familial stress[8]. The NASPGHAN and ESPGHAN Joint Guideline recommends the use of Rome III diagnostic criteria for functional constipation, based on history and physical examination[4]. The number of physician visits due to childhood constipation has doubled between 1958 and 1986[9]. About 3% of the visits to a general pediatric practice and as many as 30% of consultations to a pediatric gastroenterologists are because of sysmptoms suggestive for constipation[2]. Many authors have hypothesized that this important increase in childhood constipation might be due to changing patterns in toilet training, imbalanced diet, or that parents nowadays are more likely to consult because of symptoms of constipation.

Little is known about the knowledge of pediatricians (and general practitioners) on the diagnosis and management of childhood constipation or the management. In most children, constipation is usually associated with stool retention, incomplete evacuation of stool, and fecal incontinence[4]. Fecal incontinence is involuntary or voluntary passage of feces into the underwear or in socially inappropriate places[10]. Fecal incontinence is also known as encopresis and fecal soiling. In our study, only 33% of the respondents suspected childhood constipation in the presence of fecal incontinence. This is a major lack of knowledge as fecal incontinence is reported to occur in up to 29.6% of the children with of constipation[11]. According to other data, about 2% of an unsleected population suffers fecal incontinence, albeit relate dto constipation is as much as 82%[12]. According to data from a tertiary care center, as many as 85% of the children diagnosed with fecal impaction presented

with fecal incontinence[13]. Thus, not recognizing this symptom fecal incontinence as aa symptom of constipation will lead to underdiagnosis of constipation.

Treatment success corresponds to how aggressively the child was treated. The Indonesians pediatricians expect a positive response to fast and treat over a to short period[4]. Any form of colonic evacuation followed by daily laxative therapy results in a better outcome than less aggressive management[2]. The long term efficacy of treatment remains an issue. After treatment during two months, more than one third (37%) is still considered as constipated[2]. Laxatives or stool softeners are the most used approach, in up to 87% of children. Frequent used laxatives are magnesium hydroxide (77%), senna syrup (23%), mineral oil (8%) and lactulose (8%)[2]. About 68% of the participants preferred non-pharmacological treatment as first intervention, before giving any medication. The rise in prevalence of constipation in the past decade may lead to speculations about the role of decreased fiber intake in constipation. We found a discrepancy in diet management between recommendations by the ESPGHAN/NASPGHAN guideline and the answers provided by the participants in our study. The guideline states that evidence does not support the use of extra fiber above the recommended intake in the treatment of functional constipation[4], while the majority of the Indonesian pediatricians recommended families a high-fiber diet (96%). However, at least in the Western world, most of the children do have a low fibre intake, resulting in a recommendation to increase the fibre intake up to the normal, recommended level. The efficacy of extra fibre has not been shown, mainly because it was poorly studied[4]. Therefore this dietary intervention cannot be recommended. However, data have never suggested that constipation worsened with a high fibre diet. As a consequence, the advice to have a high fibre diet should be considered as "not recommended", but it does not mean that this recommendation is erroneous. The NASPGHAN/ESPGHAN guideline also mentions that extra fluid intake above the recommended intake has not been shown to be beneficial in the treatment of constipation, while most Indonesian participants recommended an increase in fluid intake (90%)[4]. The comment that was made regarding fibre can be repeated regarding water. Dietary modifications should only be done to ensure a balanced diet and so that sufficient fibers and fluid are consumed[4]. However, other authors had described the benefits of consuming a high dietary fiber[14].

Toilet training is a frequent non-pharmacologic treatment recommended by the pediatricians. Seventy percent of participants choosing toilet training could mention some elements of toilet training technique, but only 15% of them were able to explain it thoroughly and correctly. This is extremely detrimental as toilet training is proven to be beneficial to increase bowel movement[4,14]. Therefore, pediatricians should further enhance their knowledge on toilet training in order to give proper education to parents.

The management of constipation with fecal impaction should be conducted more aggressively. Literature suggests to use enemas or oral medication with polyethylene glycol to obtain fecal disimpaction[4,15]. Most of the participants (87%) recommended lactulose for disimpaction. As much as 26% of the pediatricians prefer rectal treatment as first option in the therapy. Impaction, if left untreated, may lead to involuntary overflow soiling and pain in passing stools. Therefore, general pediatricians should give a more intrusive approach in order to resolve fecal impaction. An electronic questionnaire which was developed to test the diagnostic and management approaches for functional constipation without or with fecal incontinence was send out to over 8000 persons[16]. Almost 1000 answered (80% trainees and 20% physicians). A large majority (84%) of the respondents acknowledged to not or insufficiently know about the NASPGHAN guidelines that were published in 2006[16]. A questionnaire testing the awareness of pediatric Rome criteria for the diagnosis of functional gastrointestinal disorders showed comparable results: Less than 30% of the general pediatricians knew about the Rome criteria, in contracts to almost all pediatric gastroenterologists[17]. Adequate dissemination of recommendations and guidelines is to be a major problem. These recommendations may be perceived as difficult and even inappropriate to implement. Physicians may simply also just not agree with some of the recommendations because of missing evidence. As a consequence, physicians may refuse to include recommendations from guidelines in their daily practice[18]. Functional constipation and functional gastrointestinal disorders are common problems. Childhood constipation does have a major impact on health care budgets: the management of childhood constipation is estimated to be cost about $2500/year[19].

A shortcoming of this research is that the questionnaire was not validated. in Another weakness of the design of this study is that no information was collected regarding the fibre and fluid intake at baseline. However, considering that the questionnaire collects information on the theoretical criteria used by pediatricians for the diagnosis and management of constipation, it was not possible to collect information on the daily fibre and fluid intake of Indonesian children (with constipation).

This study provides an insight of the pattern and quality of diagnosis and management of constipation in Indonesian children. Although constipation is a frequent condition, knowledge about appropriate diagnosis and treatment is weak among young general pediatricians. Non-evidence based advices are often given to patients and their family, resulting in less effective treatment. Especially fecal incontinence is insufficiently recognized as a symptom of constipation. The appropriate management of fecal impaction still needs to be stressed among pediatricians. Pediatricians need more comprehensive knowledge on proper toilet training advices to be able to teach patients. Therefore, the knowledge of general should be improved as well as the implementation

regarding available constipation guidelines is important to be assessed to ensure early diagnosis and prompt treatment. Data from this research confirm that training regarding diagnosis and management of functional constipation is needed. A better knowledge of medication to obtain rapid solution of the problem, the need for effective disimpaction and erroneous considerations regarding adverse effects will improve the outcome[16]. Awareness campaigns informing the population about the magnitude and impact of childhood constipation have to be considered considering its social and economic impact[8]. A better dissemination of recommendations is a priority[18].

ARTICLE HIGHLIGHTS

Background

Criteria for the diagnosis and management of functional constipation are not well known by general pediatricians and primary health care, despite published guidelines.

Research frontiers

Our research was limited to one country.

Innovations and breakthrough

This research confirms the frequency of childhood constipation. Knowledge of primary health care physicians on the diagnosis and management is limited. Published guidelines are insufficiently disseminated.

Applications

It is likely that these findings can be extrapolated to the rest of the world, since similar data are reported for the United States and Indonesia.

Terminology

Childhood constipation, electronic questionnaire, primary healthcare, guidelines, laxative.

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ORIGINAL ARTICLE

Clinical Practice Study

Outcomes of transconjuctival sutureless 27-gauge vitrectomy for stage 4 retinopathy of prematurity

Parag K Shah, Vishma Prabhu, Venkatapathy Narendran

Parag K Shah, Vishma Prabhu, Venkatapathy Narendran, Department of Pediatric Retina and Ocular Oncology, Aravind Eye Hospital, Coimbatore, Tamil Nadu 641014, India

ORCID number: Parag K Shah (0000-0002-5014-6599); Vishma Prabhu (0000-0001-6845-0209); Venkatapathy Narendran (0000-0003-1201-9801).

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Correspondence to: Dr. Parag K Shah, DNB, Department of Pediatric Retina and Ocular Oncology, Aravind Eye Hospital, Avinashi Road and Postgraduate Institute of Ophthalmology, Coimbatore, Tamil Nadu 641014, India. parag@cbe.aravind.org
Telephone: +91-422-4360400
Fax: +91-422-2593030

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Abstract

AIM

To report our initial experience with lens-sparing vitrectomy for stage 4 retinopathy of prematurity using the 27-gauge (G) system.

METHODS

This retrospective case series involved nine eyes of five babies with active stage 4 ROP, who underwent 27-G lens-sparing vitrectomy. Surgery was done using 27-G valved cannulas and sclerotomies were made 1.5 mm from the limbus. Bilateral sequential vitrectomy was done in eight eyes.

RESULTS

At one-year follow-up, anatomical outcome was favourable in all nine (100%) eyes. High-speed cutting and smaller sclerotomies were helpful in reducing the intra and post-operative complications.

CONCLUSION

27-G vitrectomy is well suited for stage 4 ROP surgeries.

Key words: Vitrectomy; Retinopathy of prematurity; 27-gauge

Core tip: This is a retrospective study of nine eyes of five children with active stage 4 retinopathy of prematurity, who underwent 27-gauge microincision vitrectomy surgeries with excellent outcomes.

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INTRODUCTION

Pars plana vitrectomy was first described by Machemer *et al*[1] in 1971 when he used the 17-gauge (G) system, where the incisions were > 1 mm in size. Later, O'Malley and Heintz[2] introduced the 20-G system where the incisions became 0.9 mm in size. Although this remained the standard of care for almost three decades, the disadvantage was that apart from relatively bulky instruments, it needed conjunctival dissection followed by applications of sutures. A big change was seen when small-gauge (23 and 25 G) instrumentation was introduced[3,4]. With thinner instrumentation, the incision became smaller to 0.5 mm and transconjunctival entry with sutureless closure became a possibility. This is extremely beneficial in the small eyes of premature neonates[5]. The advent of 27-G vitrectomy with only 0.4 mm incisions has led to a new beginning of transconjuctival microincision vitrectomy surgery (MIVS) in retinopathy of prematurity (ROP). Oshima *et al*[6] in 2010 were the first to describe the safety and feasibility of the 27-gauge MIVS system with excellent visual and anatomical outcomes in adults. However, its use in ROP is still not established, although Yonekawa *et al*[7] have reported 25 and 27-G hybrid vitrectomy in complex surgeries including ROP.

The purpose of this study was to describe our initial experience in using the 27-G trocar and cannula system in pediatric eyes with stage 4 ROP.

MATERIALS AND METHODS

This is a retrospective non-comparative case series of nine eyes of five babies. All eyes had stage 4 ROP. Four babies had bilateral disease and both eyes were operated sequentially under same general anesthesia[8]. Care was taken to rescrub and re-prepare the surgical field of the second eye as done for any new case. The entire team rescrubbed and a new set of surgical instruments were used for each eye. Written informed consent was obtained from their parents for the procedure. Ethics committee approval was obtained for this study. The study was conducted from January 2015 to December 2015. Patient records were reviewed and the data collected were date of birth, gestational age, birth weight, postconceptional age, postnatal age, and intra and postoperative status of each eye.

All surgeries were performed under general anesthesia by a single surgeon, using the Constellation Vision System with Vitrectomy 27-G Total Plus Vitrectomy Pak system (Alcon Laboratories, Texas, United States).

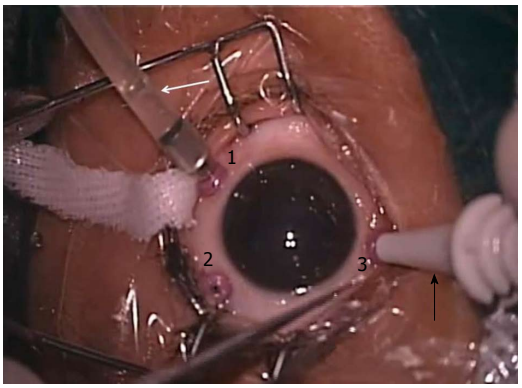

Figure 1 Intraoperative picture of a left eye. The three sclerotomies 1.5 mm from the limbus are labeled as 1 (inferotemporal port), 2 (superotemporal port) and 3 (superonasal port) of the 27-gauge vitrectomy system (silicon band pieces are not shown in this representative photograph). The white arrow shows the infusion tube through which balanced salt solution flows and maintains intraocular pressure. The black arrow shows the trocar handle inserting the last superonasal port.

Valved 27-G cannulas were used. The intraocular portions of the 27-G cannula, which are designed for adult eyes were shortened for these small pediatric eyes, similar to what has been described by Babu *et al*[9]. We took a 42 silicon band, which has a width of 4 mm and a thickness of 1.25 mm. The band was divided at 2 mm and again cut in the center to get two small pieces of 2 mm x 2 mm each. The trocar and cannula were passed through these pieces till the hub with the help of a toothed forceps. Cannulas were inserted at inferotemporal, superotemporal, and superonasal quadrants, 1.5 mm away from the limbus (Figure 1). The conjunctiva and Tenon's capsule were displaced over the sclera to avoid communication between conjunctival and scleral entry sites.

Trocar cannulas were inserted *via* a "straight in" (perpendicular to the sclera) or angled (less than 90 degrees to the sclera) approach in a 1-step procedure. First, a core vitrectomy was performed using a cutting speed of 5000 cuts per minute and a suction of 150 mmHg in core mode. Peripheral vitrectomy was done using 7500 cuts per minute with the same suction in shave mode of the machine. After the vitrectomy, partial fluid air exchange was done, the cannulas were removed, and sclerotomies were left sutureless after thorough examination for any leakage. Babies were examined on postoperative days 1, 14, and after one month.

RESULTS

Nine eyes of five babies were operated during the study period. Mean gestational age of these babies was 29.2 wk (range, 28-31 wk). Mean birth weight was 1177 g (range, 950-1850 g). Mean postconceptional age at the time of surgery was 39 wk (range, 36-43 wk), and mean postnatal age was 9.6 wk (range, 6-12 wk). Out of nine eyes, seven had stage 4a and two had 4b disease. Two eyes of case 1 had ROP in zone 1, while the rest of the

Table 1 Baseline characteristics and final outcome of the cases

Case No	GA (wk)	BW (gm)	PCA (wk)	Eye	Zone	Stage	Preoperative laser	Intraoperative anti-VEGF	Final outcome
1	30	1100	36	RE	1	4a	Y	Y	F
				LE	1	4a	Y	Y	F
2	31	950	43	RE	2	4a	Y	N	F
				LE	2	4a	Y	N	F
3	28	1000	37	RE	2	4b	Y	N	F
				LE	2	4a	Y	N	F
4	28	1850	38	RE	2	4a	Y	N	F
				LE	2	4a	Y	N	F
5	29	985	41	RE	2	4b	N	N	F

GA: Gestational age; BW: Birth weight; PCA: Postconceptional age; RE: Right eye; LE: Left eye; F: Favourable.

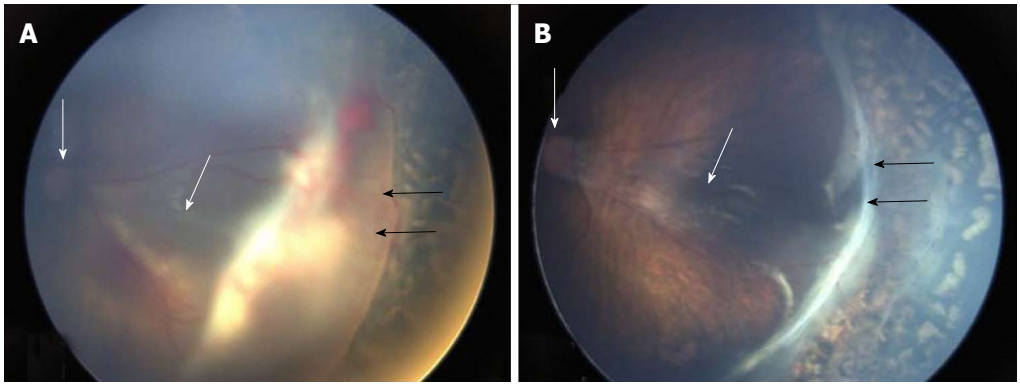

Figure 2 Anatomical success was achieved in all ten eyes at 4-mo follow-up. A: Preoperative picture of left eyes showing stage 4A ROP with partial retinal detachment (black arrows), and the optic disc is shown by the thin white arrow; B: Postoperative picture of the same eye showing settled retinal detachment with residual fibrous tissue (black arrows). The optic disc and fovea are shown by the white arrows, respectively.

eyes had ROP in zone 2. Eight eyes of four cases had undergone laser therapy prior to vitrectomy (Table 1). Two eyes of case 1 underwent vitrectomy along with intravitreal injection of ranibizumab as this case had excessive vascularity. At 4-mo follow-up, anatomical success was seen in all ten (100%) eyes (Figure 2). We did not encounter any postoperative hypotony in any of our cases. No other complications were noted in the follow-up period. At an average follow-up of 12 mo, all eyes showed stable regressed ROP.

DISCUSSION

The introduction of 27-G vitrectomy had major concerns like reduced endoillumination, instrument fragility, and reduced flow rate during surgery[10]. Oshima *et al*[6] in their study describe the various steps taken to improve the MIVS. This study done in 2010 with 31 adult eyes undergoing vitreoretinal surgeries for epiretinal membrane, macular hole, vitreous hemorrhage, focal tractional retinal detachment, and vitreomacular traction also analyzed the duty cycles of cutter, infusion and aspiration rates, and clinical outcome of 27-G MIVS. Brighter light sources such as xenon and mercury vapour bulb were used to increase the endoillumination. The smaller gauge did increase the fragility of the cutter during vitrectomy and to avoid this, the shaft of the cutter was reduced from 32 mm to 25 mm, which gives a good rigidity similar to that of a conventional 25-G vitrectomy.

High cutting rates of 27-G vitrectomy was proved to be a major advantage as it reduced the risk of iatrogenic damage to the retinal surface and intraoperative retinal tears by preventing uncut vitreous fibers entering the cutter port. Clinically and experimentally it has been proved that high cutting rates reduce retinal traction and thereby retinal breaks[11,12].

Postoperative complications seen with 23 and 25-gauge surgery like poor wound sealing causing leakage, hypotony, and endophthalmitis[13-15] were serious concerns, but one-step insertion technique in 27-G vitrectomy surgeries avoided these problems. Opening and closing procedures are simplified with the one-step insertion technique, consequently shortening the total operative time. Similarly, Rizzo and colleagues[16] in 2012 described 27-G vitrectomy in 16 patients and achieved a good clinical outcome. Additional surgical indications included were rhegmatogenous retinal detachment and tractional retinal detachment. No intraoperative and postoperative complications were encountered and no cases were converted to the 23 or 25-G system.

A retrospective case series of 95 adult eyes by Khan *et al*[17] has been extremely valuable as it includes a large sample size of 27-G MIVS operated till date. This study evaluated the change in visual acuity, postoperative intraocular pressure (IOP), and the mean operative time by diagnosis. They reported an initial fall in IOP over

the first week, which started to increase after day 30. A recently published study of cases with 20, 23, and 25-G surgeries showed a decrease in baseline IOP over a period of 3 mo and then gradual regain[18]. Thus, they concluded that IOP regains faster to the baseline value in MIVS.

In our study, 27-G MIVS performed in pediatric eyes is the first of its kind and has not been reported till date. The problem of bending of the shaft is minimal as the plus system has a small cuff of metal supporting the base and ROP vitrectomy just needs a good core vitrectomy with keeping the instruments more perpendicular compared to adults in whom base shaving may be required. None of our case had hypotony in the postoperative period as compared to 5% in a study by Khan *et al*[17]. However, our sample size is much smaller compared to their study. Singh *et al*[19] showed that the different gauge vitrectomy systems are equally effective and safe. All of our cases were sutureless and at the end of the surgery none developed any wound leak, which was seen in about 0%-7.1% of cases of 23 and 25-G vitrectomy[20-22]. No sclerotomy-related retinal tears were noted while with 23 and 25-gauge vitrectomy 0%-3.1% have been reported[22-25].

In one case during vitrectomy, the cannula came out along with the vitrectomy cutter, and this could have been avoided by carefully removing the cutter. This could be more common in the 27-G system compared to the 25-G system, as Alcon 27-G cannulas are valved and hence get snuggly attached to the instruments. In four babies, bilateral simultaneous vitrectomy was performed as all these babies had bilateral acute disease. The anatomical outcome was 100% in our study, which is better than previously reported ROP vitrectomies with larger gauges[8,26-28].

Limitation of our study is small sample size. Thus to summarize, the 27-G system could be favourable for pediatric cases, since this technique has a favorable wound sealing structure with fewer postoperative complications and better surgical outcomes. However, studies with a larger sample size are needed to substantiate this.

ARTICLE HIGHLIGHTS

Research background

Retinopathy of prematurity (ROP) vitrectomy is challenging due to the altered and more compact structures in a pediatric eye. Hence, there is a need to invent smaller vitrectomy instruments to make the outcome of this surgery better. 27-gauge vitrectomy being the smallest gauge available commercially could have the most benefit in the pediatric age group.

Research motivation

27-gauge instruments are smaller in size and have capability of high speed cutting, which is ideal for pediatric eyes. Hence, this study was conducted to examine the feasibility of this instrument in ROP surgery.

Research objectives

The main research objective was to assess the feasibility of 27-gauge vitrectomy for ROP and to examine if the ease of surgery and surgical outcomes could be bettered.

Research methods

27-gauge vitrectomy has been reported mainly in adult eyes. Very few studies have explored its use in the pediatric age group and especially in ROP. This is one of the few studies which tried 27-gauge vitrectomy exclusively in stage 4 ROP.

Research results

The results of this study show that sutureless transconjuctival 27-gauge vitrectomy has good anatomical outcome in stage 4 ROP.

Research conclusions

27-gauge vitrectomy is beneficial for pediatric eyes. It is safe and effective. This study shows that smaller gauge instruments are most suitable for lens-sparing vitrectomy in ROP where the surgical space is very limited with the ever looming danger of damaging the lens anteriorly and the retinal posteriorly. Even with the limited surgical space, it become easier to maneuver with 27-gauge instruments without damaging the critical structures.

Research perspectives

In the future, 27-gauge vitrectomy has the potential to become the standard of care for all ROP-related lens-sparing vitrectomies.

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