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World Journal of Clinical Pediatrics (*World J Clin Pediatr*, *WJCP*, online ISSN 2219-2808, DOI: 10.5409) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Clinical Pediatrics
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
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Baishideng Publishing Group Inc
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E-mail: bpgoffice@wjgnet.com
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ORIGINAL ARTICLE

Retrospective Study

Rhabdomyolysis with different etiologies in childhood

Demet Alaygut, Meral Torun Bayram, Belde Kasap, Alper Soylu, Mehmet Türkmen, Salih Kavukcu

Demet Alaygut, Meral Torun Bayram, Belde Kasap, Alper Soylu, Mehmet Türkmen, Salih Kavukcu, Department of Pediatric Nephrology, Dokuz Eylul University Faculty of Medicine, 35340 İnciralti İzmir, Turkey

Author contributions: Alaygut D and Torun Bayram M contrubuted equally to this work; Alaygut D wrote the paper; Kasap B contributed new analytic tools; Soylu A and Türkmen M analyzed the data; Kavukcu S designed the research.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Dokuz Eylul University Hospital.

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Correspondence to: Demet Alaygut, MD, Department of Pediatric Nephrology, Dokuz Eylul University Faculty of Medicine, Mithatpaşa cad. İnciraltı mah., 35340 İnciralti İzmir, Turkey. demet.alaygut@deu.edu.tr
Telephone: +90-232-4126197
Fax: +90-232-4126005

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Abstract

AIM

To investigate different etiologies and management of the rhabdomyolysis in children.

METHODS

Eight pediatric rhabdomyolysis cases who applied to the Dokuz Eylul University Faculty of Medicine Department of Pediatric Nephrology with different etiologies between January 2004 and January 2012 were evaluated in terms of age, gender, admission symptoms, physical examination findings, factors provoking rhabdomyolysis, number of rhabdomyolysis attacks, laboratory results, family history and the final diagnosis received after the treatment.

RESULTS

Average diagnosis ages of eight cases were 129 (24-192) ± 75.5 mo and five of them were girls. All of them had applied with the complaint of muscle pain, calf pain, and dark color urination. Infection (pneumonia) and excessive physical activity were the most important provocative factors and excessive licorice consumption was observed in one case. In 5 cases, acute kidney injury was determined and two cases needed hemodialysis. As a result of the further examinations; the cases had received diagnoses of rhabdomyolysis associated with mycoplasma pneumoniae, sepsis associated rhabdomyolysis, licorice-induced hypokalemic rhabdomyolysis, carnitine palmitoyltransferase Ⅱ deficiency, very long-chain acyl-CoA dehydrogenase deficiency, congenital muscular dystrophy and idiopathic paroxysmal rhabdomyolysis (Meyer-Betz syndrome).

CONCLUSION

It is important to distinguish the sporadic and recurrent

rhabdomyolysis cases from each other. Recurrent rhabdomyolysis cases should follow up more regardful and attentive.

Key words: Rhabdomyolysis; Children; Etiology; Acute kidney injury; Treatment; Hemodialysis

Core tip: This is a retrospective study to evaluate rhabdomyolysis in childhood. Rhabdomyolysis could be caused by a number of reasons, which could be classified as sporadic and hereditary/recurrent. The initial point that is to attract attention in this manuscript is the importance of the rhabdomyolysis type (recurrent/sporadic). Even though rhabdomyolysis is not routinely involved in textbooks concerning neuromuscular diseases, it is an integral part of these diseases. It should be taken into consideration in the first diagnosis and clinical follow-up of patients. It is possible to encounter with a rhabdomyolysis attack in every case. But its treatment is different from that of a primary disease.

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INTRODUCTION

Rhabdomyolysis is a pathological condition that occurs as a result of musculoskeletal damage. Substances such as creatine kinase (CK), myoglobin, aspartate aminotransferase, alanine aminotransferase, and potassium pass from cells into circulation as a result of this damage[1]. Among them, particularly myoglobin is substantially toxic for kidneys and causes acute kidney injury (AKI)[2]. The syndrome generally presents with the triad muscle pain, weakness and dark urin[3] Nearly half of patients with rhabdomyolysis have these symptoms[4]. For the clinician, suspicion starts with increase of creatinine kinase level. This suspicion is verified by measuring serum or urine myoglobin level[4]. Rhabdomyolysis can result from a wide range of disorders. While 80% of the cause of rhabdomyolysis in adults is trauma and drugs, it is infections and congenital disorders in children[4,5]. If rhabdomyolysis is recurrent, it is recommended to carry out some further examinations (muscle biopsy, metabolic and genetic tests). Early diagnosis is crucial to prevent AKI. Prevention is important in patients with inherited forms[4]. The purpose of this article is to present eight pediatric cases with rhabdomyolysis diagnosis depending upon different etiologies.

MATERIALS AND METHODS

The study consisted of eight patients with rhabdomyolysis. Medical files of cases, who were referred to Pediatric Nephrology of Medicine Faculty of Dokuz Eylul University, were retrospectively examined between the years of 2004 and 2012. The following parameters were recorded as age, gender, presenting symptoms, provocative factors, attacks number, positive physical examination findings, background and family history, laboratory results on admission, management, and final diagnosis. All cases were inquired at the admission time in terms of drug usage, infections, excessive physical activity, alcohol usage and herbal treatments. Family history was evaluated in terms of the individuals diagnosed with rhabdomyolysis in his/her family and neuromuscular diseases. In terms of etiology; further examinations were performed other than basic laboratory evaluation especially for the cases with recurrent rhabdomyolysis attacks. These consisted of serologic screening (Hepatitis, TORCH, EBV, Mycoplasma, Trichinella) in terms of infection parameters, bleeding profile and sepsis screenings, toxic screening, thyroid function test, ANA and ENA panels, lactic acid, ammonia, pyruvic acid levels, organic acid profile, acylcarnitine, total and free carnitine levels, metabolic screening (in terms of glucose and fat metabolism defects), electrography and echocardiography, electromyography (EMG), muscle biopsy and genetic studies. SPSS 18.0 - software package program was used to conduct statistical analysis.

RESULTS

Average diagnosis ages of eight cases, five of them being female, in the patient series was 129 (24-192 mo) ± 75.5. Examining the admission symptoms; all the patients in older age group had specified muscle pain, myalgia, calf pain, fatigue, and dark urination complaints. In two younger cases (case 1 and 7); dark color urination finding was the most remarkable finding. Cases 4 and 5 were also presented with muscle weakness. Additionally, first, second and seventh cases had cough and fever and third case had vomiting complaints. Examining the factors provoking rhabdomyolysis attack; infection (pneumonia) in three cases (case 1, 2, 7), excessive physical activity in three cases (case 4, 5, 8), both infection and excessive physical activity in one case (case 6), and excessive licorice consumption in one case (case 3) were observed. Assessing their physical examination findings on admission; three patients had fever over 38 degrees and bilateral crepitation in their pulmonary examination (case 1, 2, 7). Muscle strength loss was determined in upper and lower extremities in 2 cases (case 4, 5). Findings of volume loss were present in the third case but blood pressure was normal and the physical examinations of sixth and eighth cases were normal except for their muscle sensitivities. In the evaluation of personal backgrounds; case 7 was followed for epilepsy due to microcephaly. In cases 4, 5, 6 and 8, recurrent rhabdomyolysis attack was present. Also hemodialysis (HD) treatment was applied to case 6 at a different center due to a rhabdomyolysis attack 10 mo ago. Parents of cases 4, 5 and 6 were relatives. Cases 4 and 5 were siblings. In 4 of the cases;

Table 1 General characteristics of patients

Case no	Age (mo)	Gender	Presenting symptoms	Provacative factors	Positive physical examination findings	Past/family history	Attacs number
1	24	F	Dark colored urine, fever, cough	Infection	Fever, bilateral crepitationsin chest examination	Unremarkable	1
2	84	F	Fever, cough,myalgia, calf pain, fatigue, dark colored urine	Infection	Fever, bilateral crepitationsin chest examination	Unremarkable	1
3	192	M	Myalgia, calf pain, fatigue, dark colored urine, vomiting	Excess licorice use	Volume depletion signs, normal blood pressure	Unremarkable	1
4	132	F	Myalgia, calf pain, fatigue, muscle weakness, dark colored urine	Prolonged physical exercise	Muscle strengths 3-4/5 bilateral in upper and lower extremities	Recurrent rhabdomyolysis, parents are consanguineous	7
5	192	M	Myalgia, calf pain, fatigue, muscle weakness dark colored urine	Prolonged physical exercise	Muscle strengths 3-4/5 bilateral in upper and lower extremities	Recurrent rhabdomyolysis, parents are consanguineous	6
6	192	F	Myalgia, calf pain, fatigue dark colored urine	Infection, prolonged physical exercise	Muscle pain	Recurrent rhabdomyolysis, hemodialysis treatment 10 mo ago due to attack, parents are consanguineous	6
7	24	M	Dark colored urine, fever, cough	Infection	Fever, bilateral crepitationsin chest examination	Epilepsy, micocephalia	1
8	192	F	Myalgia, calf pain, fatigue dark colored urine	Prolonged physical exercise	Muscle pain	Recurrent rhabdomyolysis	3

M: Male; F: Female.

rhabdomyolysis attack was seen for the first time (case 1, 2, 3, 7), but it was the seventh rhabdomyolysis attack for the forth case, sixth rhabdomyolysis attack for the fifth and sixth cases and third rhabdomyolysis attack of the eighth case. Table 1 illustrates general characteristics of the patients. In line with rhabdomyolysis; CK values of all the patients was > 1000 U/L, and their blood and urine myoglobin levels were additionally high. In none of the patients; hypoglycemia and cardiac enzyme increase were observed. In five cases, AKI was present (case 1, 2, 3, 4, 7). Table 2 illustrates laboratory results at the time of admission.

Hydration, alkalinization, electrolyte replacement if needed, antibiotics treatment and allopurinol were applied to all the patients. HD was applied to cases three and four. Examining in terms of etiology; the patients were diagnosed with rhabdomyolysis associated with mycoplasma pneumoniae, sepsis associated rhabdomyolysis, licorice-induced hypokalemic rhabdomyolysis, carnitine palmitoyltransferase Ⅱ deficiency, very long-chain acyl-CoA dehydrogenase deficiency, congenital muscular dystrophy and idiopathic paroxysmal rhabdomyolysis (Meyer- Betz syndrome) (Table 3).

DISCUSSION

Rhabdomyolysis is a clinical result that may appear in numerous situations. In this article, eight cases with developed rhabdomyolysis related to different etiologies were assessed. Rhabdomyolysis is diagnosed when serum CK level exceeds 1000 U/L in case of absence of myocardial infarction[5].

Some studies accept that serum myoglobin level of > 300 ng/mL and urine myoglobin level of > 10 ng/mL are diagnostic[6].

Presence of myoglobin in serum and its infiltration to urine turns the color of urine into red. While heme reaction occurs in urine sticks, it is typical not to observe erythrocyte in microscopy[7]. Compared to CK, myoglobin is eliminated more quickly and if there is no myoglobinuria at high CK level, the diagnosis of rhabdomyolysis is not excluded[8]. CK levels of all the patients was > 1000 and their concurrent blood and urine myoglobin levels were over the reference values. All of them had red or brown urine findings and no erythrocyte was observed in microscopy. Common symptoms include myalgia, muscle tenderness, and weakness. While numerous patients experience lower-leg pain, some patients may have nonspecific symptoms such as fever, fatigue, vomiting, and nausea[8]. All the patients had applied with the above-mentioned common symptoms. Only the diagnosis of the 24-mo-old first and seventh cases was established with the red urine and laboratory values.

AKI is the most significant complication of rhabdomyolysis. It is defined as creatinine level above 97 percentile with respect to age and gender[5]. Previous studies identified that rhabdomyolysis-related AKI was 17%-35% in adults and 42%-50% in children[6,7,9]. If AKI is also comorbid in the cases with CK level above 100000 U/L, mortality rates reach up to 80%[4]. In five of the cases in this series, AKI was determined at the time of admission.

We stated that infections were more critical in etiology of rhabdomyolysis in children compared to adults. Several causes of infection may be associated with rhabdomyolysis. Viral infections are responsible for one

Table 2 Laboratory results of patients on admission

Case No.	Hb g/dL	WBC /mm^3	Plt /mm^3	Glu mg/dL	BUN mg/dL	Creat mg/dL	CPK U/L	AST IU/L	ALT IU/L	LDH U/L	Uric acid mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	Urine myog.	Blood myog.
1	8.6	17.5	225	86	36	2.3	1158	451	3903	1227	6.1	139	4.2	110	8.6	4.5	193	155
2	12.9	6.5	93	102	65	4.7	12976	788	215	933	6.8	149	4.8	114	7.8	8.3	679	274
3	15.2	20.6	307	95	150	3.7	8379	780	250	1100	10	125	2.2	65	8.2	8.8	1370	3740
4	12.6	3.6	163	90	57	7	42670	998	249	1303	2.6	136	3.9	107	8.7	4.3	1200	1200
5	13.2	10.6	213	75	12	0.5	3012	210	664	1466	3.5	141	4.9	104	9.9	4.3	1200	1200
6	12.4	17.5	127	119	10	0.7	25983	338	87	1797	5	136	3.9	105	9.4	3.5	1200	1200
7	9.3	9.6	146	85	38	1.1	31119	683	235	1853	6.9	144	2.9	115	8.4	3.7	767	800
8	14.2	18.6	332	90	12.5	0.8	51228	1108	341	2381	2.3	135	3.7	107	10.1	3.6	800	1200

Hb: Hemoglobin; WBC: White blood cell; Plt: Platelet; Glu: Glucose in urine; CPK: Creatine phospho kinase; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase.

Table 3 Management and final diagnosis of patients

Case	Management	Renal replacement therapy	Final diagnosis
1	Antibiotic treatment, hydration, alkalinization	No	Rhabdomyolysis associated with Mycoplasma pneumoniae pneumonia
2	Antibiotic treatment, hydration, alkalinization, fresh frozen plasma	No	Sepsis, pneumoniae, rhabdomyolysis
3	Hydration, alkalinization, antiemetic, hemodialysis	Yes, HD	Licorice-induced hypokalemic rhabdomyolysis
4	Hydration, alkalinization, hemodiyalysis	Yes, HD	Rhabdomyolysis with carnitine palmitoyltransferase II deficiency
5	Hydration, alkalinization	No	Rhabdomyolysis with carnitine palmitoyltransferase II deficiecy ?
6	Hydration, alkalinization	No	Rhabdomyolysis with very long-chain acyl-CoA dehydrogenase deficiency
7	Hydration,alkalinization	No	Rhabdomyolysis due to congenital muscular dystrophy
8	Hydration, alkalinization	No	İdiopathic paroxysmal rhabdomyolysis "Meyer- Betz Syndrome

HD: Hemodialysis.

third of the cases[5,10] (Many infections are associated with rhabdomyolysis. While influenza takes place on the top among viral infection agents, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV) are the other causes[4]. Although the pathophysiology is not presently clear, bacterial infections have also been associated with rhabdomyolysis. In a review in which 60 cases were reported, Legionella spp, Francisella spp, Streptococcus spp, Salmonella spp, and Staphylococcus aureus were determined as the most frequent factors[11]. Rhabdomyolysis was also reported with Enterococcus species, Pseudomonas aeruginosa[12], Neisseria meningitidis[13], *Escheria coli*[14], and Haemophilus influenzae[15], Mycoplasma pneumoniae[16], leptospirosis[17], and Coxiella burnetii (Q fever)[18]. In this case series; two cases (case 1, 2) had infection-associated rhabdomyolysis. Case 1 had applied with cough and high fever complaints and anemia (Hb 8.6 g/dL) reticulocytosis (8.5%), leukocytosis (17500) and acute renal insufficiency (BUN 36, creatinine 2, 3) were found in the laboratory examinations. Blood gas and urine analysis were normal. Concurrently AST, ALT, LDH, CPK and uric acid values were also found high. Empirical antibiotics treatment (Ⅳ clarithromycin), hydration and alkalinization were started to be given. Hemolysis findings were found in the peripheral smear which was examined due to anemia, and direct combs test was found as + 2 positive. In the tests sent in terms of the infection agents; mycoplasma pneumoniae IgM was positive. The outcome was rapidly favorable, and she did not experience another attack. The family history was negative for the rhabdomyolysis. Mycoplasma pneumonia infection may lead to multiple organ involvement as well as it may be asymptomatic. 25% of the patients develop extrapulmonary complications (cardiovascular, gastrointestinal, hematologic, and central nervous system). These complications may occur before, during, and after the infection. Sometimes, they appear with autoimmune events without pulmonary findings[19]. Formation of cold agglutinin which is observed in 10% of the patients also occur with this infection agent and is responsible for antibody-induced hemolysis[20].

It has not been understood exactly yet why rhabdomyolysis develops during mycoplasma infections, however direct invasion of muscles by the organism or muscular damage resulting from immune reactions are considered as responsible[16]. Although it is rare, rhabdomyolysis-induced AKI or glomerulonephritis, interstitial nephritis and nephrotic syndrome may develop with this infection[20,21].

Renal biopsy was not administered to patient due

to normal complement levels, absence of nephrotic syndrome, and existence of an AKI that does not require dialysis. Diagnosis of the patient was supported with positive serum mycoplasma IgM titration, antibody-induced hemolysis, and rapid response to anti-mycoplasma antibiotic treatment. Second case was a 84-mo-old girl. While she was being followed up for pneumonia; sepsis chart (thrombocytopenia, hypotension, bradycardia and disseminated intravascular coagulation) was developed. Then, diagnosis of rhabdomyolysis was made due to acute renal insufficiency and high CK, LDH, AST, ALT values. The patient had recovered without the need of appropriate antibiotherapy, hydration and alkalinization treatments and renal replacement treatment. Rhabdomyolysis attack of this patient did not repeat, and her family history was also negative. Sepsis-associated rhabdomyolysis was reported in numerous case reports[22-25]. In this case, we could not show any specific agent in the blood culture that may cause sepsis. Also no causative agent was reported in some studies about sepsis and rhabdomyolysis[26]. But specific causes such as blood pressure, electrolyte abnormalities, tissue hypoperfusion, hyperthermia, hypoxia, dehydration, and acidosis are known to induce rhabdomyolysis in any patient with a critical condition[27]. However, sepsis-associated microorganisms were identified in very few original studies. Even though these studies reported that bacterial sepsis-induced rhabdomyolysis can develop with numerous types of microorganisms, Betrosian *et al*[11] stated that it may occur mostly with gram positive organisms and Kumar *et al*[27] indicated that they may develop mostly with gram negative organisms[12,28].

Drugs, toxins and foods are other important causative factors for rhabdomyolysis. There are many drugs associated with development of rhabdomyolysis[8]. Drugs cause rhabdomyolysis due to direct or indirect muscle damage. Toxin poisoning related rhabdomyolysis has been reported by using honeybees[29], rattlesnakes[30], and brown recluse spider bites[31]. Carbon monoxide poisoning is another reason[32]. All the patients were examined during the anamnesis in terms of drug and toxin exposure and there were no patients with positive findings. Foods may also be a triggering factor. The most remarkable example about this issue is consumption of licorice root which may lead to hyperaldosteronism, hypokalemia, and rhabdomyolysis[33-35]. Third case was a 16-year-old male patient with chronic heavy cola consumption-associated rhabdomyolysis and AKI that were reported previously by Kasap *et al*[32] Due to the laboratory results that are concordant to hypokalemia, metabolic alcalosis, acute kidney insufficiency; diagnosis of hypokalemia associated metabolic alkalosis was made.

It was then learned from the history of patient that he/she was drinking about 1 lt of cola every day for 2-3 years. A substance was suspected causing the aldosterone effect with low serum plasma renin activity, normal aldosterone, and existence of hypokalemia. Licorice root in the cola consumed by the patient daily was emphasized. The patient was diagnosed with hypokalemic rhabdomyolysis induced by the use of licorice root. HD was applied because of volume load and oliguria developing when the patient was treated with intravenous fluid therapy. Acute tubular damage was determined in the renal biopsy performed in order to exclude the underlying chronic renal disease.

Hereditary diseases, most of which are metabolic diseases, develop another group that cause rhabdomyolysis. It should be especially considered in the cases with positive rhabdomyolysis in the family history and with recurrent rhabdomyolysis attacks[8]. Some individuals tend to have muscle damages especially after exercise. This low exercise tolerance is tried to be explained by CK-MM gene polymorphism and angiotensin-converting enzyme (ACE) polymorphism. C49T and C3788A genotypes of myosin light chain kinase cause CK level increased in response to exercise[36]. When 114 asymptomatic patients varying between ages of 3 and 70 and with incidental CK level increase were evaluated; 18% metabolic or neuromuscular diseases were determined.

The most frequent diagnoses were carnitine palmitoyltransferase deficiency and malignant hyperthermia[37]. Carnitine palmitoyltransferase deficiency was the most frequently observed disease in 36-patient series of idiopathic rhabdomyolysis[38].

Long chain fatty acids (LCFA) are the major source of energy for muscles in case of prolonged exercise. These fatty acids which cannot passively pass into mitochondria move inside actively *via* carnitine palmitoyltransferase pathway in the outer membrane of mitochondria. This pathway consists of enzymes of carnitine palmitoyltransferase Ⅰ located in the outer membrane and carnitine palmitoyltransferase Ⅱ located in the inner membrane.

Autosomal recessive carnitine palmitoyltransferase Ⅱ deficiency is the most frequent disorder in LCFA metabolism[39]. Clinic of rhabdomyolysis accompanying this condition is considerably variable. CK levels are normal or slightly high between attacks of rhabdomyolysis induced by this enzyme deficiency, increase between attacks, and muscle pains occurring after exercise start as from the childhood[40].

Enzyme analysis and mutation scanning should be performed for the diagnosis. Forth case in this article was an 11-year-old girl and we have learnt that she had complaints of not walking for a long distance, generalized muscle weakness from time to time, muscle cramps and dark colored urination problems from her early childhood ages. Her parents were relatives and her two brothers also had similar complaints. One of these brothers was the case five in our patient group. In CPT 2 gene; homozygote mutation was determined for SI13L. Genetic analysis was planned for his brother and possible CPT Ⅱ deficiency was accepted.

Case six was a 16-year-old female patient who had applied with sixth rhabdomyolysis attack and was within acyl-CoA dehydrogenase (ACAD) family and taken the diagnosis of very long chain acyl-CoA dehydrogenase

(VLCAD) deficiency. Very long chain acyl-CoA dehydrogenase deficiency is an autosomal recessive disorder progressing with inability for beta oxidation of fatty acids in the mitochondria. Its three phenotypes that are associated with different mutations were identified. The first one is the most critical phenotype starting in newborn period and having high mortality progressing with hypertrophic cardiomyopathy and hypoketotic hypoglycemia. The second one is observed during infancy period. There is no cardiomyopathy. Hypoketotic or nonketotic hypoglycemia develops. Rhabdomyolysis occurring in case of hunger or after exercise in preadolescence period, like in our patient, exists in the muscle type with late onset[41]. In the fibroblast culture of the case; very long chain acyl-CoA dehydrogenase activity was 4.3 nmol/min per milligram protein (controls: 5.1-21.7) (n = 28) and heterozygote carrier was found. Case seven was a patient who was followed up due to epilepsy, microcephaly and hypotonia and who had been diagnosed with infection-induced rhabdomyolysis. Myopathic findings were found in the electromyography and dystrophic changes were specified in the muscle biopsy. Visual examination and hearing test of the patient were normal. Congenital muscular dystrophies are a disease group which is clinically and genetically heterogeneous and is evident with early-onset and progressive muscle weakness. It has numerous genetic types that have been defined till now[42]. Thus, it was decided to conduct a genetic study on the patient in order to determine the sub type.

Despite all the further examinations; it cannot be possible to find the reason of recurrent rhabdomyolysis in some patients and idiopathic recurrent rhabdomyolysis is known as "Meyer Betz Syndrome". In fact, this is an exclusion diagnosis. Case eight was reported by Kasap *et al*[43] previously. The patient was applied with rhabdomyolysis finding that was induced by excessive physical activity at the first attack and after two months, he had applied again with a moderate CK increase. Metabolic screening of the patient (blood acylcarnitine analysis, total and free serum carnitine levels, and blood lactic acid level were normal, or tests conducted in terms of fatty acid oxidation defect -) was normal. EMG was normal. Ischemic effort test was applied in order to exclude McArdle's disease. Blood lactate and ammonia levels examined before and after exercise were above the normal. This picture is not expected in McArdle disease. Thus, muscle biopsy was applied to the patient and no glycogen deposit was observed.

If rhabdomyolysis is suspected in terms of the history and laboratory independently from underlying etiology, aggressive fluid treatment should be immediately started with isotonic saline[8]. Electrolyte abnormalities should be closely monitored and treated[8]. After urine output was observed, the urine may be alkalized with sodium bicarbonate. Many authors suggest a high hydration value, like 200 mL/h, until CK level decreases below 1000 U/L. Of course, this should be performed in a more controlled manner in pediatric cases. The indications for HD were severe hyperkalemia and prolonged oligo-anuric renal failure[4]. Two patients in this series were applied with HD treatment because of prolonged oligoanuric phase and hypertension in case three and high creatinine level and also hypertension in case four.

As a consequence; although the rhabdomyolysis picture is basically presented to us together with the same clinical and laboratory results, clarification of the etiology should be the primary factor. Especially it is very important to distinguish the sporadic and hereditary cases from each other. It should be considered that the primary organ to be rescued in the acute period is the kidney and aggressive fluid therapy, alkalinization and when needed, HD should be taken into consideration.

COMMENTS

Background

Rhabdomyolysis could be caused by a number of reasons, which could be classified as sporadic and hereditary/recurrent. All of the diseases causing rhabdomyolysis lead formation of cell membrane damage, hypoxia and lytic enzymes such as phospholipase A2, and decrease of energy source ATP as a result of cell's exposure to mechanical stress. Final outcome is disruption of intracellular ion balance, Ca concentration occurring within cell, hyperactivity in Ca-dependent proteolytic enzymes, and formation of oxidative free radicals. In the next periods, on the other hand, cell death occurs as a result of free radicals and proteases. It was intended to convey clinical and laboratory outcomes of rhabdomyolysis to reader and to identify extreme conditions within the scope of basic information. In this study, the authors evaluated clinical differences and etiologies of rhabdomyolysis in childhood.

Research frontiers

Rhabdomyolysis is an important clinical process in childhood. Clinicians must be keep in mind that sporadic and recurrent cases have different clinical properties.

Innovations and breakthroughs

Rhabdomyolysis is an important clinical situation. Clinician must be investigate it carefully. Unless a convenient treatment is performed, it will result in an acute kidney injury.

Terminology

Although the rhabdomyolysis picture is basically presented to us together with the same clinical and laboratory results, clarification of the etiology should be the primary factor. Especially it is very important to distinguish the sporadic and hereditary cases from each other. To concisely and accurately describe, define or explain the specific, unique terms that are not familiar to majority of the readers, but are essential for the readers to understand the article. AKI: Acute kidney injury; ACAD: Acyl-CoA dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BM: Blood myoglobin levels; BUN: Blood urea nitrogen; Ca: calcium; CPT II: Carnitinepalmitoyltrans ferase II enzyme; Ch: Chlor; CMV: Cytomegalovirus; Creat: Creatinine; CK: Creatinine kinase; EMG: Electromyography; EBV: Epstein-Barr virus; FDA: Food and Drug Administration; HD: Hemodialysis; Hb: Hemoglobin; HIV: Human immuno deficiency virus; K: Potassium; LDH: Lactate dehydrogenase; LCFA: Long-chain fatty acids; Na: Sodium; P: Phosphorus; PRA: Plasma renin activity; Plt: Platelet; UM: Urine myoglobin levels; VLCAD: Very long chaiin acyl-coA dehydrogenase; WBC: White blood cell.

Peer-review

The manuscript is a series of 8 case-reports occurring in children. I would thank the authors for these clinical cases that remembers us that rhabdomyolysis also occurs in children and that the etiologies are quite different from adults.

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ORIGINAL ARTICLE

Observational Study

Transition from early intervention program to primary school in children with autism spectrum disorder

Valsamma Eapen, Rachel Grove, Elizabeth Aylward, Annette V Joosten, Scott I Miller, Gerdamari Van Der Watt, Kathryn Fordyce, Cheryl Dissanayake, Jacqueline Maya, Madonna Tucker, Antonia DeBlasio

Valsamma Eapen, Academic Unit of Child Psychiatry, South West Sydney (AUCS), ICAMHS, Mental Health Centre, L1, Liverpool Hospital, Liverpool 2170, Australia

Valsamma Eapen, Rachel Grove, School of Psychiatry, University of New South Wales, Sydney 2052, Australia

Valsamma Eapen, Rachel Grove, Elizabeth Aylward, Annette V Joosten, Kathryn Fordyce, Cheryl Dissanayake, Jacqueline Maya, Madonna Tucker, Antonia DeBlasio, Cooperative Research Centre for Living with Autism (Autism CRC), Long Pocket 4850, Australia

Elizabeth Aylward, KU Marcia Burgess Autism Specific Early Learning and Care Centre, Liverpool 2170, Australia

Annette V Joosten, School of Occupational Therapy and Social Work, Curtin University, Perth 6000, Australia

Scott I Miller, Gerdamari Van Der Watt, Western Australia Autism Specific Early Learning and Care Centre, Bedford 6052, Australia

Scott I Miller, Gerdamari Van Der Watt, Autism Association of Western Australia, Perth 6000, Australia

Kathryn Fordyce, St Giles Society North West Tasmania Autism Specific Early Learning and Care Centre, Burnie 7320, Australia

Cheryl Dissanayake, Jacqueline Maya, La Trobe University, Melbourne 3000, Australia

Madonna Tucker, AEIOU Foundation, Nathan 4111, Australia

Antonia DeBlasio, AnglicareSA Daphne St Autism Specific Early Learning and Care Centre, Prospect 5082, Australia

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Correspondence to: Valsamma Eapen, MBBS, PhD, FRCPsych, FRANZCP, Academic Unit of Child Psychiatry, South West Sydney (AUCS), ICAMHS, Mental Health Centre, L1, Liverpool Hospital, Elizabeth Street, Liverpool 2170, Australia. v.eapen@unsw.edu.au
Telephone: +61-2-96164205
Fax: +61-2-96012773

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Abstract

AIM

To evaluate the characteristics that are associated with successful transition to school outcomes in preschool aged children with autism.

METHODS

Twenty-one participants transitioning from an early intervention program were assessed at two time points; at the end of their preschool placement and approximately 5 mo later following their transition to school. Child characteristics were assessed using the Mullen Scales of Early Learning, Vineland Adaptive Behaviour Scales, Social Communication Questionnaire and the Repetitive Behaviour Scale. Transition outcomes were assessed using Teacher Rating Scale of School Adjustment and the Social Skills Improvement System Rating Scales to provide an understanding of each child's school adjustment. The relationship between child characteristics and school outcomes was evaluated.

RESULTS

Cognitive ability and adaptive behaviour were shown to be associated with successful transition to school outcomes including participation in the classroom and being comfortable with the classroom teacher. These factors were also associated with social skills in the classroom including assertiveness and engagement.

CONCLUSION

Supporting children on the spectrum in the domains of adaptive behaviour and cognitive ability, including language skills, is important for a successful transition to school. Providing the appropriate support within structured transition programs will assist children on the spectrum with this important transition, allowing them to maximise their learning and behavioural potential.

Key words: Autism spectrum disorder; School transition; Primary school; Outcomes

Core tip: Assess, address and communicate children's strengths and difficulties during the transition to school process for better outcome including language skills, cognitive ability and adaptive function.

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INTRODUCTION

Children with autism often find change difficult. This makes transitioning between different settings and stages of life particularly challenging[1]. In this regard, transition to primary school from preschool settings or early intervention programs is particularly significant as this is a major transition point in the child's life. A successful start to school has been defined as consisting of feeling secure and comfortable in the new school environment, increased academic and social skills, increased independence, engagement and motivation to participate in class and school activities[2]. It is also associated with academic progress, positive relationships with peers and teachers, positive attitudes and feelings about school and learning, and a sense of wellbeing, belonging and inclusion[2]. There is evidence to suggest that children who have a positive start to school are likely to engage well and experience academic and social success[3,4]. While there have been some efforts to provide specific programs to support transition to school, this is often targeted broadly for children with a disability and not specific to children on the autism spectrum, who arguably have individualised transition support needs[3]. Children with autism attend a variety of school settings including mainstream schools, specialised support classes within mainstream settings, specialised schools or centres[5].

Children with autism have a greater risk of poor school outcomes, including emotional and behavioural problems[6], bullying[7], school exclusion[8] and peer rejection[9]. It is therefore critical that both the barriers and protective factors for a positive transition for children with autism are well understood. However, there is a lack of empirical research that examines the transition to school for children with autism, and existing research on primary school transition has tended to adopt cross-sectional survey based methodology[3,4,10,11], rather than longitudinal designs with specific measurement of children's social, emotional, adaptive, cognitive and academic progress. A large number of school transition practices has been identified and endorsed from these survey studies; however, the adequacy of these practices has not been established. There is a need to understand the specific support needs of children on the autism spectrum in order to develop evidence based programs to enhance the school transition process. Additionally, a more systematic monitoring of developmental and behavioural progress, using standardised instruments, is also required in order to understand transition outcomes for children with autism[12].

This project aimed to evaluate transition to school outcomes for children transitioning from early intervention settings to primary school. It also aimed to

determine the individual characteristics associated with successful transition to school in children on the autism spectrum.

MATERIALS AND METHODS

Participants

Data were collected from children with a confirmed diagnosis of autism who were transitioning to school from six early intervention centres [Autism Specific Early Learning and Care Centres (ASELCCs)] across six states in Australia in 2016. The early intervention programs provided at each ASELCC were varied and included manualised programs like the Early Start Denver Model[13] and the SCERTs program[14], through to other programs based on evidence based principles that are still to be manualised. This total sample of 21 participants included 3 females (14%) and 18 males (86%). The mean age of the sample at exit from the centres was 5.4 years (SD = 0.4). Children had been attending the centre for a mean duration of 23 mo (SD = 9.9).

Design

Data were collected at two time points; at the end of the preschool placement and approximately 5.4 (SD = 1.8) months later following their transition to school. A number of measures were administered at the end of the early intervention program. These included the Mullen Scales of Early Learning (MSEL)[15], Vineland Adaptive Behaviour Scales (VABS)[16], Social Communication Questionnaire (SCQ)[17,18], and the Repetitive Behaviour Scale (RBS)[19] There were a number of outcome measures that were collected following transition to school. Teachers were asked to complete the Teacher Rating Scale of School Adjustment (TRSSA)[20] and the Social Skills Improvement System Rating Scales (SSIS)[21]. Parents were also asked to rate their child on the parent form of the SSIS. Parents were also asked questions about their child's school placement.

Measures

MSEL: The MSEL[15] is a standardised assessment which provides a measure of cognitive and motor development in children from birth to 68 mo. The MSEL consist of four subscales evaluating visual reception, fine motor, and receptive and expressive language skills. Developmental quotients (DQs) were calculated for each subscale of the MSEL by dividing each child's age equivalent score by their chronological age at the time of testing and multiplying by 100[22] given that a number of children in the sample did not receive MSEL subscale raw scores that were high enough for calculation of a meaningful *t* score (*i.e.*, they were performing at a level < 0.1 percentile).

VABS: The VABS second edition[16] evaluates parent perceptions of their child's adaptive functioning in a number of domains including communication, daily living skills, socialisation and motor skills. A norm-referenced standardised score with a mean of 100 and SD of 15 is calculated for each domain. This is also calculated for the overall adaptive behaviour index. VABS scale scores with a mean of 15 and an SD of 3 are calculated for each sub-domain. Higher scores are indicative of better adaptive function.

Social communication questionnaire: The SCQ[17,18] is a 40 item parent report measure evaluating autism symptoms, with a total score above 15 indicating probable autism[18].

RBS: The RBS[19] is a 44 item parent report questionnaire designed to evaluate repetitive behaviour in children with autism. The RBS consists of six subscales including stereotyped, self-injurious, compulsive and ritualistic behaviour, as well as restricted interests. Higher scores indicate a greater presence of repetitive behaviours.

SSIS: The parent and teacher SSIS[21] were included in the project to collect information on children's social skills development following their transition to school. The SSIS includes subscales evaluating social skills, including communication, cooperation, assertion, responsibility, empathy, engagement and self-control. It also evaluates problem behaviours, including bullying, hyperactivity/inattention, and symptoms of autism. A measure of academic competence is also included on the teacher rating form. Standard scores and percentile ranks are calculated for the social skills and problem behaviours composite scales.

TRSSA: TRSSA[20] is a 52 item measure that assesses adjustment to the school or classroom setting. It consists of five subscales including independent participation, cooperative participation, teacher's perception of children's school liking, teacher's perception of children's school avoidance, and teacher's perception of children's interest/comfort with the teacher. Higher scores on these subscales indicate a higher frequency of this behaviour.

Semi-structured interview: Parents completed a semi-structured interview following their child's transition to school. This was included in order to provide details regarding their child's school placement setting and experience of starting school.

Statistical analysis

The TRSSA and teacher rated SSIS were assessed as outcome variables of successful school transition. Cognitive ability, adaptive behaviour, autism symptoms and repetitive behaviours at exit from early intervention were entered into correlation analyses to evaluate their relationship with the TRSSA and teacher SSIS at school follow up. In order to account for the multiple comparisons and minimise type I errors alpha was set at $P = 0.01$ across all analyses.

RESULTS

School placement details

A large proportion of the sample (94%) transitioned

Table 1 Correlation between Teacher Rating Scale of School Adjustment and child characteristics at exit (n = 21)

	Cooperative participation	Independent participation	Likes School	Avoids School	Comfortable with teacher
Cognitive ability (MSEL)					
Visual reception	0.317	0.442	0.26	0.406	0.574[a]
Fine motor	0.318	0.486	0.454	0.421	0.622[a]
Receptive language	0.469	0.488	0.364	0.289	0.598[a]
Expressive language	0.453	0.603[a]	0.316	0.284	0.635[a]
Early learning composite	0.453	0.603[a]	0.316	0.284	0.635[a]
Adaptive function (VABS)					
Communication	0.596[a]	0.588[a]	0.124	-0.018	0.493
Daily living skills	0.531	0.505	0.051	-0.212	0.355
Socialisation	0.411	0.555[a]	0.22	0.045	0.519
Motor skills	0.568[a]	0.721[b]	0.445	-0.004	0.621[a]
Adaptive behaviour composite	0.567[a]	0.727[b]	0.332	-0.031	0.621[a]
Autism symptoms (SCQ)					
Total score	0.027	-0.156	-0.286	-0.254	-0.493
Repetitive behaviours (RBS)					
Stereotypic	-0.206	-0.248	0.209	0.129	-0.044
Self-injurious	0.204	0.301	0.353	0.454	-0.025
Compulsive	-0.188	-0.101	0.313	0.09	-0.065
Ritualistic	0.28	0.319	0.343	0.4	0.021
Restricted interests	-0.177	-0.258	0.189	0.49	-0.381

[a]$P < 0.05$, [b]$P < 0.01$. MSEL: Mullen Scales of Early Learning; VABS; Vineland Adaptive Behaviour Scales; SCQ: Social Communication Questionnaire; RBS: Repetitive Behaviour Scale.

from the early intervention centres to a full time (5 d a week) school program. Fifty-six percent transitioned to a mainstream setting, with 29% enrolled in a specialised school setting, 10% attending a mixed mainstream and special school, and 5% a special class in a mainstream school setting. Parents reported that the experience of starting school ranged from very good (53%) to fairly good (37%), with a smaller proportion indicating that their experience was just ok (5%) or not very good (5%).

Predictors of transition outcomes at school follow up

Correlations were conducted to evaluate the relationship between the child measures at exit and teacher ratings on the domains of the TRSSA and SSIS following transition to school. Results are presented in Tables 1-3.

TRSSA: Table 1 outlines the relationship between the TRSSA and child characteristics including cognitive ability, adaptive function and autism symptoms. Results indicated a significant positive relationship between scores on the MSEL and the TRSSA, with visual reception, fine motor skills and receptive and expressive language shown to be positively associated with comfort with the teacher. Expressive language skills were also associated with increased independent participation in the classroom.

Communication skills, as measured by the VABS, were also positively associated with both cooperative and independent participation in the classroom. Motor skills and overall adaptive function were also positively related to both forms of classroom participation, as well as comfort level with the teacher. There was no relationship between autism severity or repetitive behaviours and the TRSSA.

SSIS: There were a number of associations between scores on the social skills subscales of the SSIS and child characteristics at exit (Table 2). All subscales of the MSEL were positively associated with the communication, assertion, empathy and engagement subscales of the SSIS. Receptive and expressive language skills were also related to overall teacher rated social skills.

Results indicated a significant positive relationship between all subscales of the VABS and communication and engagement on the teacher rated SSIS. The overall adaptive behaviour composite score was also shown to be associated with communication, assertion, empathy, engagement and social skills.

As noted for the TRSSA, there were no significant relationships between autism symptoms or repetitive behaviours and the social skills subscales of the SSIS. There was no significant relationship between cognitive ability, adaptive function, autism symptoms or repetitive behaviour and the problem behaviour subscales of the SSIS (Table 3).

DISCUSSION

This study evaluated the characteristics associated with transition to school outcomes in children transitioning from early intervention to their first year of school. There were a number of significant relationships between child characteristics at exit and school transition outcomes. Cognitive ability, including visual reception, fine motor skills and receptive and expressive language were positively associated with the level of comfort children showed with their classroom teacher. Expressive language skills and overall scores on the MSEL were also associated with increased independent participation in the classroom. This indicates that cognitive ability, and particularly

Table 2 Correlation between the social skills subscales of the Social Skills Improvement System Rating Scales and child characteristics at exit (n = 21)

	Communication	Cooperation	Assertion	Responsibility	Empathy	Engagement	Self-control	Social skills scale
Cognitive ability (MSEL)								
Visual reception	0.590[a]	-0.065	0.660[a]	0.114	0.591[a]	0.697[b]	0.161	0.468
Fine motor	0.606[a]	-0.03	0.671[a]	0.14	0.574[a]	0.733[b]	0.182	0.492
Receptive language	0.665[a]	0.101	0.718[b]	0.29	0.574[a]	0.792[b]	0.326	0.600[a]
Expressive language	0.784[b]	0.151	0.793[b]	0.259	0.651[a]	0.833[b]	0.321	0.655[a]
Early learning composite	0.784[b]	0.151	0.793[b]	0.259	0.651[a]	0.833[b]	0.321	0.655[a]
Adaptive function (VABS)								
Communication	0.732[b]	0.076	0.597[a]	0.416	0.563[a]	0.698[b]	0.319	0.591[a]
Daily living skills	0.656[a]	0.145	0.497	0.437	0.479	0.570[a]	0.372	0.548
Socialisation	0.677[a]	-0.099	0.695[b]	0.195	0.443	0.634[a]	0.096	0.464
Motor skills	0.799[b]	0.329	0.836[b]	0.35	0.529	0.717[b]	0.343	0.680[a]
Adaptive behaviour composite	0.815[b]	0.136	0.821[b]	0.338	0.580[a]	0.762[b]	0.261	0.647[a]
Autism symptoms (SCQ)								
Total score	-0.28	0.482	-0.4	0.218	-0.245	-0.256	0.289	-0.032
Repetitive behaviours (RBS)								
Stereotypic	-0.45	0.09	-0.331	-0.244	-0.358	-0.187	-0.346	-0.294
Self-injurious	0.107	0.29	0.168	0.222	-0.084	0.303	0.239	0.213
Compulsive	-0.291	0.099	-0.095	-0.194	-0.195	-0.03	-0.211	-0.153
Ritualistic	0.176	0.396	0.199	0.322	-0.044	0.319	0.317	0.289
Restricted interests	-0.38	0.035	-0.362	-0.029	-0.405	-0.121	-0.089	-0.201

[a]$P < 0.05$, [b]$P < 0.01$. MSEL: Mullen Scales of Early Learning; VABS: Vineland Adaptive Behaviour Scales; SCQ: Social Communication Questionnaire; RBS: Repetitive Behaviour Scale.

Table 3 Correlation between the problem behaviours subscales of the Social Skills Improvement System Rating Scales and child characteristics at exit (n = 21)

	Bullying	Hyperactivity/inattention	Externalising	Internalising	Problem behaviours scale	Academic competence scale
Cognitive ability (MSEL)						
Visual reception	0.233	0.005	0.218	-0.145	0.001	0.158
Fine motor	0.232	0.013	0.245	-0.28	0	0.101
Receptive language	0.097	-0.086	0.145	-0.167	-0.066	0.201
Expressive language	0.158	-0.119	0.146	-0.204	-0.08	0.093
Early learning composite	0.158	-0.119	0.146	-0.204	-0.08	0.093
Adaptive function (VABS)						
Communication	-0.083	-0.315	-0.095	-0.476	-0.374	-0.214
Daily living skills	-0.099	-0.374	-0.201	-0.452	-0.415	-0.025
Socialisation	0.243	-0.006	0.245	-0.237	-0.051	0.013
Motor skills	0.166	-0.186	0.113	-0.078	-0.104	0.384
Adaptive behaviour composite	0.149	-0.164	0.125	-0.257	-0.171	0.227
Autism symptoms (SCQ)						
Total score	-0.382	-0.296	-0.443	0.497	-0.138	0.404
Repetitive behaviours (RBS)						
Stereotypic	-0.228	0.023	-0.05	0.088	0.113	0.334
Self-injurious	0.004	-0.112	-0.031	0.255	0.033	0.41
Compulsive	-0.032	0.133	0.136	0.267	0.256	0.314
Ritualistic	-0.147	-0.188	-0.098	0.237	-0.045	0.36
Restricted interests	-0.140	0.075	0.031	0.317	0.17	0.179

MSEL: Mullen Scales of Early Learning; VABS: Vineland Adaptive Behaviour Scales; SCQ: Social Communication Questionnaire; RBS: Repetitive Behaviour Scale.

language skills, play a role in successful transition to school for children with autism. This is consistent with previous research highlighting that children on the spectrum with a higher level of skills, particularly in communication, tend to make more progress over time[12]. Interestingly, the current research also indicates that these skills are also associated with being comfortable with the teacher in the school environment.

Communication skills, as measured by the VABS, were also positively associated with both cooperative and independent participation in the classroom. Motor skills and overall adaptive function were also positively related to both forms of classroom participation, as well as comfort level with the teacher. Previous research has highlighted that both independent and cooperative participation in the classroom are critical to a child's

achievement and educational progress[23]. These findings therefore have clinical implications for transition practices.

Interestingly, while there were a number of cognitive and adaptive characteristics that were associated with successful transition to school for children with autism, there was no relationship between autism severity or repetitive behaviours and transition outcomes. This has important clinical implications for transition practices, as it indicates that autism symptoms were not the most important predictors of transition outcomes for children with autism exiting early intervention. This highlights that it is cognitive, language and adaptive functioning that are critical to successful transition to school.

Taken together, these findings indicate the need to assess and address cognitive ability, communication skills and adaptive function for better transition to school outcomes for children on the autism spectrum. Understanding and supporting any communication and cognitive difficulties will be of significant benefit to children with autism transitioning to school.

There were also a number of significant associations between child characteristics at exit and the social skills subscales of the teacher rated SSIS. Cognitive ability, as measured by the MSEL, was positively associated with communication, assertion, empathy and engagement. Receptive and expressive language skills were also positively related to overall social skills. This indicates the importance of cognitive ability and language in the development of social skills, particularly in the classroom environment. This is consistent with previous research outlining the link between language and social skills in autism[24].

Results indicated a significant positive relationship between all subscales of the VABS and communication and engagement on the teacher rated SSIS, highlighting the importance of adaptive function in relating to others. The overall adaptive behaviour composite was also shown to be associated with communication, assertion, empathy, engagement and social skills. This highlights the importance of adaptive behaviours in the development of social skills and school transition.

As noted for the TRSSA, there were no significant relationships between autism symptoms or repetitive behaviours and the social skills subscales of the SSIS, highlighting that autism symptom severity is not a significant barrier to school transition and less important than the language, cognitive and adaptive skills of the child. There was also no relationship between child characteristics at exit and the problem behaviour subscales of the SSIS, indicating that cognitive ability and adaptive function are more important in the development of participation in the classroom, level of comfort with the teacher and social skills but do not play as much of a role in the number of problem behaviours reported by school teachers.

Limitations

The response rate for this study was low, resulting in a limited sample size. This made it difficult to include models with a large number of predictors and correlates. Future research is warranted to replicate these findings within a larger sample. The findings from the current study would also benefit from the inclusion of a comparison group of children without a diagnosis of autism, as well as children who may not have transitioned from targeted early intervention settings. Future research incorporating these comparisons would allow for a more fine grained understanding of the unique challenges that are associated with children attending more specialised intervention programs and those receiving support in the community.

The results of the study indicated that child characteristics, including cognitive ability and adaptive function had a significant influence on transition to school outcomes for preschool aged children with autism. It is important to target relevant issues as they emerge across both home and school contexts. Targeting these issues in early intervention programs will assist children on the spectrum with this important transition, allowing them to maximise their learning and behavioural potential.

COMMENTS

Background

Transition from early intervention programs to the school setting can be a challenging time for children with autism. While a number of programs have been implemented to support transition to school, these have not been specifically tailored for children with autism. Children who have a positive start to school are more likely to experience academic and social success. This highlights the importance of effectively supporting children on the spectrum to experience a positive transition from early intervention services to primary school.

Research frontiers

This study aimed to evaluate the characteristics that are associated with successful transition to school outcomes in preschool aged children with autism. This study addresses an area that is currently under researched.

Innovations and breakthroughs

Cognitive ability and adaptive behaviour were shown to be associated with successful transition to school outcomes for children with autism. These factors were also associated with social skills in the classroom including assertiveness and engagement.

Applications

Understanding the factors associated with successful school transition will enable the development of guidelines for service providers and families to assist children on the spectrum to achieve academic and social success.

Terminology

ASELCC: Autism Specific Early Learning and Care Centres; MSEL: Mullen Scales of Early Learning; VABS; Vineland Adaptive Behaviour Scales; SCQ: Social Communication Questionnaire; RBS: Repetitive Behaviour Scale; TRSSA: Teacher Rating Scale of School Adjustment; SSIS: Social Skills Improvement System Rating Scales.

Peer-review

The paper is well-written and has interesting findings.

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CASE REPORT

Neonatal pyknocytosis in a preterm dizygotic twin

Alberto Berardi, Eleonora Balestri, Goretta Bonacorsi, Claudio Chiossi, Giovanni Palazzi, Eugenio Spaggiari, Fabrizio Ferrari

Alberto Berardi, Eugenio Spaggiari, Fabrizio Ferrari, Unità Operativa di Terapia Intensiva Neonatale, Dipartimento Integrato Materno-Infantile, Azienda Ospedaliero-Universitaria Policlinico, 41100 Modena, Italy

Eleonora Balestri, Unità Operativa di Terapia Intensiva Neonatale, Azienda Ospedaliera Santa Maria Nuova, 42100 Reggio Emilia, Italy

Goretta Bonacorsi, Unità Operativa di Ematologia, Dipartimento di Scienze Mediche e Chirurgiche, Azienda Ospedaliero-Universitaria Policlinico, 41100 Modena, Italy

Claudio Chiossi, Unità Operativa di Pediatria, Nuovo Ospedale Civile, 41049 Sassuolo, Italy

Giovanni Palazzi, Unità Operativa di Pediatria, Dipartimento Integrato Materno-Infantile, Azienda Ospedaliero-Universitaria Policlinico, 41100 Modena, Italy

Author contributions: Berardi A, Balestri E, Spaggiari E and Ferrari F analyzed the data, designed the report and wrote the paper; Bonacorsi G, Chiossi C and Palazzi G collected the patient's clinical data and reviewed the manuscript.

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Correspondence to: Alberto Berardi, MD, Unità Operativa di Terapia Intensiva Neonatale, Dipartimento Integrato Materno-Infantile, Azienda Ospedaliero-Policlinico Universitario, Via del Pozzo, 41100 Modena, Italy. berardi.alberto@policlinico.mo.it
Telephone: +39-59-4224921
Fax: +39-59-4223770

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Abstract

Infantile pyknocytosis (IP) is a rare, self-limited neonatal haemolytic anaemia that may require multiple blood transfusions. Only a little more than 50 cases have been reported in the medical literature, and the great majority of them concerns term infants. The etiology of IP is not well understood; most likely it results from a transient extra-corpuscular factor, whose nature is unknown, transmitted from mother to child or, alternatively, from a deficiency of an anti-oxidative agent. We report the case of two preterm twins, one of which suffered from IP and developed severe anaemia at age 2 wk, while the other was unaffected. Although no specific agent was identified as the cause of anaemia and IP, we speculate that the transmission of an agent from mother to child was unlikely, as only twin one suffered from IP. Smelly greenish diarrhoea occurred just before the presentation of IP, suggesting that the same agent led to both the diarrhoea and the oxidative injury. Because IP may remain underdiagnosed, it should be considered in cases of early unexplained severe hemolytic anemia.

Key words: Infantile pyknocytosis; Glucose-6-phosphate

dehydrogenase deficiency; Anemia; Oxidative stress; Hemolysis

Core tip: This manuscript describes the first case of infantile pyknocytosis affecting only one of the twins, and contributes to understand the etiology of infantile pyknocytosis.

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INTRODUCTION

Premature neonates commonly experience a fall in haemoglobin concentration. This has been termed "physiologic" anaemia of prematurity, since it is commonly not associated with any abnormalities in the red blood cells (RBCs). Repeated blood sampling and many diseases of prematurity can worsen this "physiologic" anaemia. However, more rare underlying diseases may mimic anaemia of prematurity or increase its severity.

Infantile pyknocytosis (IP) was first described by Tuffy *et al*[1] and is characterized by a self-limited neonatal haemolytic anaemia, which may require multiple blood transfusions. The aetiology of IP is unclear. Pyknocytes most likely result from a transient extracorpuscular factor, whose nature is unknown[2]. An exogenous oxidative agent transmitted from mother to child or a deficiency of an anti-oxidative agent has been hypothesized[3].

We report the case of two Caucasian female preterm twins, one of whom suffered from IP and developed severe anaemia at age 2 wk. We discuss factors possibly associated with IP.

CASE REPORT

A dizygotic twin pregnancy resulted from an *in vitro* fertilization-embryo transfer. There was no familial history of unexplained transient neonatal anaemia.

Preterm labour occurred at 32 wk' gestation, and an emergency caesarean section was required due to breech presentation.

Twin 1 (first born). The Apgar score was 8 and 9 at the 1st and 5th min respectively, birth weight was 1735 g, length was 39 cm and cranial circumference was 25 cm. At birth, the red blood cell count and haemoglobin levels were normal (Figure 1). On day three the neonate suffered from jaundice and required phototherapy. The clinical course was uneventful until day 10, when stools became smelly and the baby required further phototherapy. The fecal occult blood test was positive.

On day 17 she was referred to our neonatal intensive care unit because of jaundice, foul-smelling greenish diarrhoea and worsening anaemia, which required a packed RBC transfusion.

The reticulocyte count was 169 per milliliter. Liver and renal function tests were normal. A direct antiglobulin test and search for irregular agglutinins were negative; haemoglobin electrophoresis as well as glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase activity were normal, while lactate dehydrogenase was mildly abnormal (518 U/L). Bacterial cultures were sterile; detailed viral investigations yielded normal results.

A peripheral blood smear demonstrated high rates (> 25%) of irregularly contracted, bite, and densely stained RBCs (Figure 2). The morphological changes in the RBCs accompanied with normal enzyme activity led us to suspect IP.

The jaundice worsened further on day 19, and additional phototherapy was administered. A further packed RBC transfusion was given on day 28. Subsequently the infant recovered spontaneously, and no further transfusions were given.

At age 5 mo both the haemoglobin level and RBC morphology were normal. G6PD test yielded normal result, confirming overall the initial diagnosis of IP. Twin 2 (second born). The Apgar score was 8 and 9 at the 1st and 5th min respectively.

The birth weight was 1760 g, the length 45 cm and cranial circumference 30 cm. The newborn had mild jaundice (maximum bilirubin levels 90.4 mg/L) on day five. Thereafter her clinical course was uneventful and she never suffered from anaemia. The haemoglobin level was 135 g/L on day 25.

DISCUSSION

Pyknocytes are small, irregular, distorted erythrocytes, which are densely stained in a peripheral blood smear. A low percentage of pyknocytes is commonly found in healthy full-term neonates (from 0.3% to 1.9%) and preterm neonates (from 0.3% to 5.6%) during the first weeks of life[1].

IP is a transient but often severe neonatal haemolytic anaemia associated with an accentuation of the physiologic presence of pyknocytes. Factors that increase oxidative stress may damage erythrocyte membranes, resulting in the formation of pyknocytes[3]. Since IP was first described, only a little more than 50 cases have been reported in the literature and the great majority of IP cases concern term infants[4]. The rarity of the disease as well as the lack of awareness about this cause of neonatal anaemia may lead to an underestimation.

IP may account for approximately 10% of cases of unexplained neonatal haemolytic anaemia[3]. Most cases present during the first days of life, with neonatal

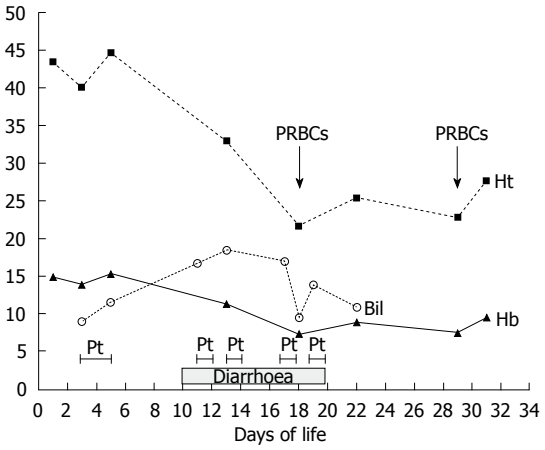

Figure 1 Twin 1 haematocrit, haemoglobin and bilirubin levels during the first month of life. Ht: Haematocrit; Hb: Haemoglobin; Bil: Bilirubin level; Pt: Phototherapy; PRBCs: Packed red blood cell transfusion.

jaundice as the first manifestation; approximately 70% of affected infants develop severe anaemia from the second to the fourth week. Of life, commonly requiring one or more packed RBC transfusions[1,3]. Anaemia resolves spontaneously by the age of 4 to 6 mo[5].

The aetiology of IP is unclear. A transient extra-corpuscolar factor damaging the erythrocyte membrane, rather than an intrinsic factor, has been implicated in the pathogenesis of the disease. Indeed, flow cytometric analysis has shown that morphological changes do not affect reticulocytes, suggesting that erythropoietin treatment could prevent severe anemia[3,6]. Furthermore, among the seven cases of pyknocytosis reported by Ackerman, two showed the same morphologic abnormalities even after exchange transfusion, suggesting that erythrocytes of donor origin may also be affected[2]. There are only 2 reports of IP in twins; in all reported cases both twins were affected[7,8].

Pyknocytes most likely result from a transient extra-corpuscular factor, whose nature is unknown. Causes such as an exogenous oxidative agent or a deficiency of an anti-oxidative agent have been hypothesized[3].

In the current case report, only twin one suffered from IP. Therefore the transmission of an oxidative agent from mother to child, as well as a familial susceptibility or a hereditary factor[8,9] seem unlikely. Even if no specific agent was identified as the cause of the severe anaemia, the occurrence of smelly greenish diarrhoea was just before a decrease in haemoglobin and a rise in bilirubin levels, suggesting that the same cause, most likely an exogenous agent (perhaps infectious), and acquired after birth, led to both the diarrhea and the oxidative injury. Preterm birth possibly contributed to worsening the IP, as premature infants are more susceptible to oxidative stresses[9].

In conclusion, this is first case of IP affecting only one of the twins. The most likely cause of IP was an exogenous oxidative agent associated with diarrhoea and not transmitted from mother to child.

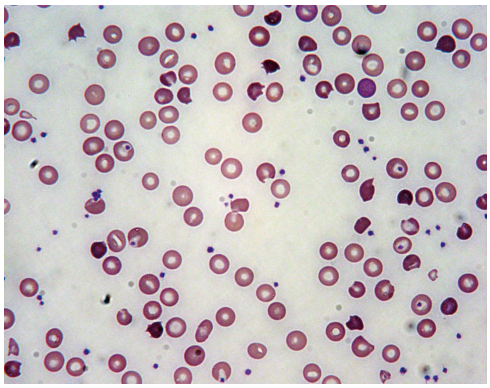

Figure 2 Twin 1 peripheral blood smear during the haemolytic phase of infantile pyknocytosis (magnetogastrogram x 400). Erythrocyte morphological changes: bite cells, irregularly contracted cells (pyknocytes). Changes are comparable to glucose-6-phosphate dehydrogenase deficiency.

COMMENTS

Case characteristics

A preterm female twin presented with recurrent jaundice and severe hemolytic anemia at age 2 wk.

Clinical diagnosis

The diagnosis was based on jaundice and hemolytic anemia.

Differential diagnosis

Common causes of jaundice and hemolytic anemia were excluded.

Laboratory diagnosis

Liver, renal tests, viral and bacterial cultures were normal.

Pathological diagnosis

A peripheral blood smear demonstrated high rates (> 25%) of irregularly contracted, bite, and densely stained red blood cells (supporting the diagnosis of pyknocytosis).

Treatment

The newborn underwent blood transfusions and phototherapy.

Related reports

Infantile pycnocytosis is a transient but often severe neonatal haemolytic anaemia associated with an accentuation of the physiologic presence of pyknocytes.

Term explanation

Infantile pyknocytosis is a rare, self-limited neonatal haemolytic anaemia characterized by high rates of pyknocytes (small, irregular, distorted, densely stained erythrocytes).

Experiences and lessons

Infantile pycnocytosis may remain underdiagnosed; it should be considered in cases of early unexplained severe hemolytic anemia.

Peer-review

The submitted paper by Alberto Berard *et al*, titled "Neonatal pyknocytosis in a preterm dizygotic twin", is very interesting, well structured, with clear presentation.

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