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MINIREVIEWS

Prospects for clinical applications of butyrate-producing bacteria

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Abstract

As the major source of energy for colonic mucosal cells and as an important regulator of gene expression, inflammation, differentiation, and apoptosis in host cells, microbiota-derived butyrate can enhance the intestinal mucosal immune barrier, modulate systemic immune response, and prevent infections. Maintaining a certain level of butyrate production in the gut can help balance intestinal microbiota, regulate host immune response, and promote the development and maintenance of the intestinal mucosal barrier. Butyrate-producing bacteria act as probiotics and play important roles in a variety of normal biological functions. Bacteriotherapeutic supplementation by using fecal microbiota transplantation to restore butyrate-producing commensal bacteria in the gut has been very successful in the treatment of recurrent and refractory *Clostridium difficile* (*C. difficile*) infection or *C. difficile*-negative nosocomial diarrhea. Administration of probiotics that include butyrate-producing bacteria may have a role in the treatment of inflammatory bowel diseases and in the prevention of necrotizing enterocolitis and late-onset sepsis in premature infants. Furthermore, modulating gut microbiota with dietary approaches may improve intestinal dysbiosis commonly seen in patients with obesity-associated metabolic disorders. Supplementation with a butyrate-producing bacterial stain might be used to increase energy expenditure, improve insulin sensitivity, and to help control obesity and metabolic syndrome.

Key Words: Butyrate; Butyrate-producing bacteria; Gut microbiota; Intestinal mucosal barrier; Metabolic syndrome; Probiotics

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Core Tip: This minireview summarizes the potential clinical applications of butyrate-producing bacteria in disorders related to pediatrics and possible underlying mechanisms. Acting as probiotics, butyrate-producing bacteria play important roles in a variety of normal biological functions that include balancing gut microbiota, maintaining the mucosal barrier, modulating the host immune response, preventing infections, and regulating energy expenditure. Therefore, butyrate-producing bacteria may have a potential therapeutic value in a wide range of clinical conditions associated with intestinal dysbiosis such as inflammatory bowel disease, necrotizing enterocolitis, late-onset sepsis in the premature infant, nosocomial diarrhea, and obesity-associated metabolic disorders.

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INTRODUCTION

Short chain fatty acids (SCFAs), in particular butyric acid, play important roles in human intestinal health. They are the major source of energy for the colonic mucosal cells[1]. Maintaining a certain level of butyric acid production in the lumen can help to balance gut microbiota, regulate host immune response, and enhance intestinal mucosal barrier function. When butyrate is taken orally in food or as a medicine, it is digested and absorbed by the body before it reaches the colon, making it difficult for butyrate to perform its functions in the hindgut. Butyrate-producing bacteria are capable of fermenting undigested carbohydrates in the intestinal lumen, producing acidifying SCFAs such as butyric acid. Therefore, butyrate-producing bacteria may be used as probiotics with the goal of promoting gut health, and thus having a wide range of potential clinical applications[2]. This minireview focuses on recent research on butyrate-producing bacteria and their potential clinical applications, especially in disorders related to pediatrics.

BUTYRATE-PRODUCING BACTERIA AND THEIR MAIN PHYSIOLOGICAL FUNCTIONS

Butyrate-producing bacteria are not a coherent phylogenetic group but rather a group of commensal intestinal flora that can ferment carbohydrates and produce butyric acid [2,3]. Both lactic acid and acetic acid can be used as substrates in the biochemical synthesis of butyric acid[3]. The majority of *Firmicutes* are butyrate-producing bacteria. At the genus level, *Ruminococcus*, *Clostridium*, *Eubacterium*, and *Coprococcus* are common butyrate-producing bacteria. *Clostridium butyricum* (*C. butyricum*) is relatively common in the *Clostridium* genus[4]. Others include *Faecalibacterium*, *Butyrivibrio*, *etc.*, [5]. In the genus *Eubacterium*, *Eubacterium Hallii* (*E. Hallii*) and *Eubacterium Rectale* are among the most abundant butyrate-producing bacterial strains in human feces[6]. *Actinomycetes*, *Bacteroidetes*, *Proteobacteria*, *Spirochetes* also have been identified as potential butyrate-producing bacteria[2].

The butyrate-producing commensal bacteria are mainly anaerobes. The acidic environment generated by butyrate-producing bacteria during metabolism keeps a balanced microbiota and maintains a normal microecological environment in the intestinal tract. Therefore, butyrate-producing bacteria act as probiotics and play important roles in a variety of normal biological functions, such as maintaining the mucosal barrier, improving immunity, and facilitating nutrient digestion and absorption in animals[7]. Like other probiotics, butyrate-producing bacteria can ferment carbohydrates to produce SCFAs and synthesize folic acid, pyridoxol, vitamin B1 and other vitamins[8,9]. By using an *in vitro* model of the colonic mucosa barrier, Lewis *et al*[10] have shown that butyrate can ameliorate increased translocation of bacteria across metabolically stressed intestinal epithelia. With a similar model, we have shown previously that butyrate can enhance the intestinal barrier function by facilitating the assembly of tight junctions through the activation of AMP-activated protein kinase (AMPK) and have demonstrated that butyrate is important in the maintenance and regulation of the barrier function of the colonic epithelium[11]. Also, Wang *et al*[12] recently demonstrated that butyrate dynamically regulates intestinal homeostasis through regulation of synaptopodin, an actin-binding protein that is critical for barrier integrity and cell motility. Therefore, it is evident that production of butyrate in the intestinal lumen is vital for the maintenance of the intestinal mucosal barrier.

Butyrate is a potent histone deacetylase inhibitor, which can promote the proliferation and activation of regulatory T-cells (Treg cells) and thereby play an important role in the immune regulation[13,14]. Microbiota-derived butyrate can reduce the release of pro-inflammatory cytokines by regulating the activity of G protein-coupled receptors, NF-κB, JAK/STAT and other inflammation-related pathways, thereby inhibiting intestinal inflammation and maintaining intestinal immune balance[15]. In addition to the direct effects on the mucosal barrier, microbiota-derived butyrate can be absorbed and directly transmitted to mesenteric lymph nodes, into the lymphatic system, and then into the systemic circulation, affecting other organ systems. NF-kB pathway is involved in the expression of tumor necrosis factor (TNF), interleukin (IL)-1, IL-6 and other inflammation-related genes in the immune and inflammatory responses. The role of butyrate is to inhibit NF-κB from entering the nucleus. Without active NF-κB, the mRNA of pro-inflammatory factors cannot be transcribed and pro-inflammatory factors will not be expressed, resulting in inflammatory response inhibition[15]. Studies have shown that butyrate regulates the function of T cells in the induction of colitis by differentially regulating Th1 and Th17 cell differentiation, thus modulating the production of inflammatory cytokines[16,17]. Moreover, butyrate can inhibit the release of IL-12, TNF-α, IL-1β and nitric oxide in monocytes, up-regulate the expression of IL-10, and reduce the activity of NF-κB, thereby playing an anti-inflammatory role in other organ systems, such as the respiratory system[18]. In short, as the major source of energy for the colonic mucosa and as an important regulator of gene expression, inflammation, differentiation and apoptosis in host cells, microbiota-derived butyrate enhances the role of the intestinal mucosal immune barrier, modulates the systemic immune response, and thus prevents bacteria and their metabolites from entering the bloodstream and causing inflammation[19,20].

POTENTIAL CLINICAL APPLICATIONS OF BUTYRATE-PRODUCING BACTERIA

Maintenance of the intestinal mucosal barrier

A monolayer of intestinal epithelial cells separates the body tissues from the dense communities of bacteria in the intestinal lumen. Therefore, maintenance of the mucosal epithelial barrier that prevents the invasion of host tissues by resident bacteria is vital for normal intestinal function. It is well known that the main energy source for the colonic epithelium is derived directly from the lumen rather than from blood. More than 90% of SCFAs produced in the intestinal lumen by bacterial fermentation are normally absorbed by intestinal epithelial cells. Lack of luminal SCFAs or the inability to oxidize butyrate leads to a nutritional deficiency of the colonic epithelium, causing mucosal atrophy in the short term and ‘nutritional colitis’ in the long term[1]. In patients with ulcerative colitis, the ability of the colonic epithelial cells to oxidize butyrate is weakened, so the energy obtained through oxidation is reduced; and thus the ability of butyrate to repair colonic mucosa is decreased[21]. The depletion of gut commensal flora by a prolonged course of broad spectrum of antibiotics can lead to more severe intestinal mucosal injury in a dextran sulfate sodium (DSS)-induced mouse colitis model[22]. Furthermore, reduced abundance of butyrate-producing commensal bacteria species has been found in the fecal microbial community in patients with inflammatory bowel disease (IBD)[23,24].

Probiotics have been advocated in clinical practice for prevention or treatment of intestinal mucosal injury associated with IBD or neonatal necrotizing enterocolitis (NEC)[25,26]. In children with IBD, a specific probiotic preparation (VSL#3) combined with *Lactobacillus* was shown to have a significant effect in achieving a clinical response[27]. A study in an animal model of DSS-induced colitis has shown that administration of *C. butyricum*, one of the butyrate-producing bacterial strains, can increase the luminal production of butyrate in the cecum and alleviate DSS-induced injury to colonic mucosa[28]. *C. butyricum* may induce intestinal macrophages to secrete IL-10, thereby inhibiting the occurrence of experimental colitis[29]. Geirnaer *et al*[30] used an *in vitro* system to examine the response of microbiota from patients with

Crohn's disease to the treatment with different combinations of butyrate-producing bacterial stains. They assessed the effects of butyrate-producing bacteria supplementation on short-chain fatty acid production, bacterial colonization of the mucus environment and intestinal epithelial barrier function. They demonstrated that treatments with butyrate-producing bacteria improved epithelial barrier integrity *in vitro*. More recently, Steppe *et al*[31] isolated and characterized the butyrate-producing strain *Butyricicoccus pullicaecorum* 25-3(T) and identified it as a potential probiotic for patients with IBD.

Regulation of intestinal immune response

The human intestine normally harbors billions of commensal bacteria. Intestinal epithelia cells actively sense those commensal bacteria and play an essential role in maintaining host-microbial homeostasis at the mucosal interface[19]. Commensal bacteria such as butyrate-producing bacteria can ferment undigested carbohydrates to produce small molecular metabolites such as lactic acid and SCFAs in the intestine, promote the proliferation of beneficial intestinal bacteria such as *bifidobacterium*, lactobacillus and fecal bacillus, and inhibit the growth of pathogenic bacteria such as *Staphylococcus, Escherichia coli, Salmonella typhus* and *Clostridium difficile* (*C. difficile*)[32,33]. Thus, butyrate-producing bacteria promote intestinal microecological balance and participate in the regulation of the production of amines, indole, hydrogen sulfide and other potential harmful substances. Therefore, they not only can improve intestinal digestive and absorptive capacity, but also play important roles in improving the body's immunity and preventing infections[8].

SCFAs promote intestinal peristalsis and reduce the duration of the presence of toxin in the intestinal tract. Among the SCFAs, butyrate is a potent mediator involved in the effects of gut microbiota on intestinal mucosal immune functions[34]. Butyrate can act as a ligand to activate specific G-protein-coupled receptors, activate intestinal mucosal immune activity, and enhance immunity[34]. Enhanced butyrate production by colonic butyrate-producing bacteria after diet manipulation is associated with increased levels of the anti-inflammatory cytokine IL-10 in mice[35]. Using intestinal mucosa biopsy tissues obtained from the patients with Crohn's disease, Segain *et al*[15] have shown that butyrate can ameliorate the inflammatory response of isolated lamina propria cells and that of cultured peripheral blood mononuclear cells. NF-κB pathway is involved in the inhibition of immune cell activation[15].

Butyrate regulation of Toll-like receptor (TLR) expression in human colonic epithelial cells may be one of the key mechanisms mediating the cross talk and interplay between normal gut microbiota and a host's innate and adaptive immune systems[36]. TLRs in intestinal epithelial cells and mucosal immune cells are pattern-recognition-receptors that are critical components of the symbiosis between the host and commensal microflora[37]. Therefore, bacterial production of butyrate plays a key role in maintaining intestinal homeostasis. Other factors such as antimicrobial peptides produced by commensal bacteria or the host may also be involved in the process[38-40]. More recently, a clinical study found that higher fecal SCFA concentrations were associated with the efficacy of immunotherapy in solid tumor cancer patients, indicating that gut microbiota might have wide-ranging impacts on host immune response[41].

Dysbiosis of intestinal microbiota and infection

Dysbiosis of intestinal microbiota may lead to so-called leaky gut and therefore microbial translocation, contributing to the development of infection. It is well accepted that an impaired interaction between intestinal microbiota and the host immune response can lead to an increased risk of infection caused by gram-negative bacteria or other pathogens[37,42]. It has been shown that reductions in mucosal butyrate from diminished colonic butyrate-producing bacteria contribute to HIV-associated mucosal pathogenesis[43]. SCFA uptake coupled with sodium absorption is one of the major mechanisms for salt and water uptake in the colon. The association between the depletion of intestinal microbiota and nosocomial diarrhea is well recognized. Normally abundant gut commensal organisms, including the butyrate-producing C2 to C4 anaerobic fermenters, are significantly depleted in the patients with *C. difficile* infection or *C. difficile*-negative nosocomial diarrhea[44]. Furthermore, dysfunction of the intestinal mucosal barrier and impaired mucosal immunity can lead to pathological translocation of intestinal bacteria or endotoxins, causing sepsis and multiple organ dysfunction syndrome in patients who experienced severe trauma, serious burn, major surgery or hemorrhagic shock[45]. Loss of the intestinal microbiota diversity and a subsequent loss of health-promoting SCFAs, such as butyrate, contribute to the dysregulated immune response and organ failure associated with sepsis

[46].

Bacteriotherapeutic supplementation may restore normal gut microbiota. For example, using fecal microbiota transplantation (FMT) to restore butyrate-producing bacteria in the gut and therefore the normal host immune response has been tested in clinical practice for the treatment of diseases related to dysbiosis of the intestinal microbiota[47]. FMT has been very successful in the treatment of recurrent and refractory *C. difficile* infection[48]. FMT has also been trialed for aiding in the recovery of septic patients[49]. However, concerns for lethal complications associated with FMT prevent its use other than for quite restricted clinical indications. Oral administration of health-promoting next-generation probiotics to ameliorate dysbiotic microbiota may be a safe alternative[9]. As summarized by a recent systematic review and meta-analysis, administration of probiotic mixtures, not single-strain products, has a beneficial effect of reducing the incidence of late-onset sepsis in human milk-fed very low birth weight preterm infants[50].

Role in obesity-associated metabolic disorders

Diet can modulate and support the symbiotic microbial communities that colonize the digestive tract. Modulating gut microbiota with dietary approaches may improve health, and prevent or treat diseases related to intestinal dysbiosis[51]. Dietary prebiotics are a group of nutrients that are degraded by gut microbiota. It is defined as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improving host health[52]. Most complex carbohydrates and plant polysaccharides ingested are metabolized by fermentation of commensal bacteria in the colon, which generate butyrate and other SCFAs (Figure 1). Consumption of a diet rich in fiber or prebiotic supplementation can boost the growth and metabolism of beneficial commensals in the colon, specifically targeting butyrate production[35,51].

Numerous studies have demonstrated the beneficial effects of a diet rich in fiber on obesity-associated metabolic syndrome. A fiber rich diet is beneficial in the prevention of obesity, improving insulin resistance, and control of abnormal blood lipid profile commonly seen in metabolic syndrome[53]. We previously have proposed that increased production of SCFAs as a result of colonic bacterial fermentation of dietary fiber might, in part, account for some of the beneficial effects of dietary fiber on the metabolic syndrome[53]. Indeed, while on a high-fat diet, supplementation of butyrate prevented development of insulin resistance and obesity in mice. Fasting blood glucose, fasting insulin, and insulin tolerance were all preserved in the treated mice. In the obese mice, supplementation of butyrate led to an increase in insulin sensitivity and a reduction in adiposity[54]. Oral administration of *E. Hallii*, a butyrate-producing bacterial stain, can improve insulin sensitivity and increase energy expenditure in diabetic *db/db* mice[55]. As a potential therapeutic strategy for obesity and metabolic syndrome, FMT has also been trialed in a few randomized controlled human studies with some mixed beneficial results[56]. Promotion of energy expenditure, induction of mitochondrial function by activation of AMPK, and serving as an agonist of free fatty acid receptors, may be some of the mechanisms underlying the beneficial effects of butyrate on the abnormalities characterizing the metabolic syndrome[54,57-59].

CONCLUSION

This minireview summarizes the potential clinical applications and possible underlying mechanisms of butyrate-producing bacteria in disorders related to pediatrics. As the major source of energy of the colonic mucosa and as an important regulator of gene expression, inflammation, differentiation and apoptosis in host cells, microbiota-derived butyrate enhances the role of the intestinal mucosal immune barrier, modulates the systemic immune response, and thus prevents bacteria and their metabolites from entering the bloodstream and causing inflammation. Butyrate regulation of energy metabolism may play a role in the beneficial effects of a high fiber diet on metabolic syndrome. Therefore, acting as probiotics, butyrate-producing bacteria play important roles in a variety of normal biological functions that include balancing gut microbiota, maintaining the mucosal barrier, modulating the host immune response, preventing infections, and regulating energy expenditure. Thus, butyrate-producing bacteria may have a potential therapeutic value in a wide range of clinical conditions associated with intestinal dysbiosis such as IBD, NEC, late-onset sepsis in premature infant, nosocomial diarrhea, and obesity-associated metabolic disorders.

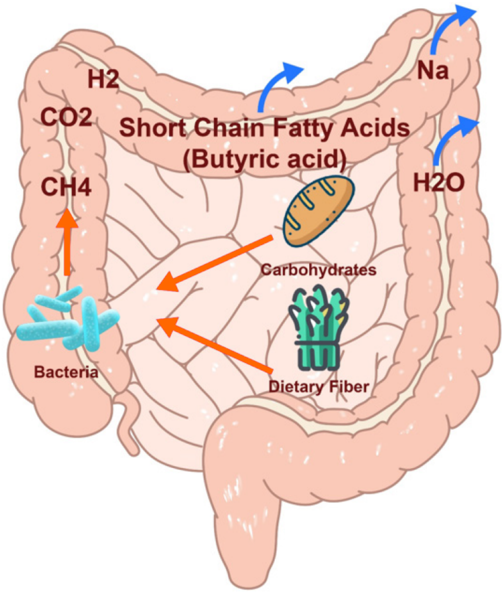

Figure 1 Butyric acid production by bacterial fermentation.

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ORIGINAL ARTICLE

Observational Study

Influence of education and residence on the parental search for pediatric surgical information on the internet

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Abstract

BACKGROUND

The internet is a valuable tool for access to health-related information. There is limited literature regarding its use by parents of children with surgical conditions.

AIM

To investigate internet usage by parents seeking information about the surgical conditions of their offspring in relation to epidemiological factors such as family residential area and parental educational level and to subsequently review the literature regarding this topic.

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METHODS

An anonymous questionnaire about internet usage was completed by eligible parents of children who were admitted to our clinic for minor surgical procedures during a six-month period.

RESULTS

Our results demonstrated that the internet has been mostly used by mothers for children's health information. Google was the most commonly used search engine, while pediatricians were the first parental choice for 'live' information. Only one-quarter of the parents informed their doctor about the information found online. Nine of ten parents had a positive opinion of an official website managed by the doctors of our clinic. Our results mostly agreed with the international literature.

CONCLUSION

In conclusion, the establishment of official websites (designed and managed by specialists) that parents can access to receive appropriate health information is mandatory in the internet era.

Key Words: Internet; Child; Health; Mothers; Fathers

Core Tip: The internet is a valuable tool for accessing health-related information. Parents of children with forthcoming surgery often seek online information about the specific conditions and symptoms of their children. Herein, we describe the influence of education and residence on the parental search for pediatric surgical information on the internet in a multicultural region of northern Greece, and we compare our results with the recent literature.

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INTRODUCTION

Fifty years have passed since the onset of the internet, and the increase in numbers of people who access it worldwide is remarkable. According to the hellenic statistical authority, the last decade (2009–2018) saw a 100.8% increase in internet access at home. In Greece, more than 76.5% of homes accommodate internet access. The vast majority of adults (96.6%) use the internet more than once a week, and the internet is a popular source of health-related information[1]. Recent studies have demonstrated that up to 91% of adults access online sources of health information[2-4]. In Greece, the proportion of internet health users increased from 23% in 2007 to 65.2% in 2018[1,5]. Parents of children with chronic medical conditions are motivated by a desire to increase their knowledge and relieve their anxiety[6-13]. Nevertheless, there is limited literature regarding the use of the internet for pediatric surgical conditions[4,14-17]. Previous studies in Europe have shown that the use of the internet for health information varies significantly in different parts of the continent[5,18]. No similar studies have been recorded in South Europe, a region with diverse cultural and socioeconomic environments. Previous studies on parental internet exploration have mostly focused on three parameters: (1) Identification of the websites used; (2) Evaluation of the information found in relation to its readability and accuracy; and (3) The influence of the information on the parents' decisions to visit the emergency department when their child is sick[6-9]. The objectives of this study were first to evaluate the epidemiological characteristics of parents in relation to the magnitude of internet usage for health-seeking information and second to review the literature regarding this topic.

MATERIALS AND METHODS

Participants

The survey was conducted from January 2018 to June 2018 in the Department of Pediatric Surgery, Alexandroupolis University Hospital, Greece. Eligible participants were parents of children (ages: 0–14 years) who were admitted to our clinic for minor elective surgical treatment (herniotomy, orchidopexy, hypospadias repair, circumcision) or emergency surgery (appendectomy, gonadal torsion, traffic accident, or fall-related injuries) and lived in the regions of Eastern Macedonia and Thrace. We excluded illiterate parents and parents who had already been included in the study group. Additionally, we excluded parents of children with chronic health problems and those of children who were admitted for major surgical procedures due to their increased anxiety. If both parents were present, only one of them could complete the questionnaire. In this cohort study, parents were divided into two categories according to their residency (urban or rural).

Questionnaire

The questionnaire was designed by MA and KK (authors) and was anonymous and voluntary. The questionnaire was designed and adjusted according to the characteristics and needs of people of our region regarding the difficulties they confront in communicating with a hospital doctor to accomplish sufficient and satisfactory medical information. In this region, with many scattered and isolated villages, the inhabitants form a multicultural society with different habits. The questionnaires were designed to be simple, unintimidating and easy to complete. There was no need for stratification, and the questionnaire consisted of a paper that required approximately 4 to 6 min to complete. It included 17 questions addressing three areas: (1) The use of the internet and its accessibility at home/work/elsewhere. Personal computers (PCs) at home, frequency of internet use, engagement in social media, parental engagement in social media and parental groups; (2) The use of the internet for access to medical information by family members, the use of the internet on a regular basis and 24 h prior to admission and which search engines were used; and (3) The use of the internet by parents addressing information for a specialist pediatric surgeon, other sources of information and the need for an official website with online, up-to-date medical information. In addition, there were questions about demographic data [gender, age and parental educational level, family income, residence, child insurance, type of admission (elective or emergency)]. The questionnaire was in Greek. Nevertheless, the option for a questionnaire written in Turkish was offered for some parents who were more fluent in that language. To reduce bias from the influence of medical staff of our clinic on the participants, a team consisting of two doctors and two medical students from the university was responsible for distributing these questionnaires (in paper) to the parents. The parents, if they agreed to participate, were asked to complete and return the questionnaires up to the day after their child's admission.

Sample size derivation and statistical analysis

With 600 admissions for minor surgical treatment in the University Pediatric Surgery Clinic annually, 234 completed questionnaires were required to achieve a 5% margin of error with a 95% confidence interval[19]. The main emphasis was on parents who searched the internet for children's health-related information in the past (202/235, 86%). Two parameters were analyzed: (1) The residence of the family; and (2) The educational level of the parent who searched the internet for child-related medical information. Descriptive statistics such as frequency, proportions, chi-squared test for categorical variables, and Mann–Whitney U test [nominal scale, when the point of interest was the residence (urban or rural)] or Kruskal–Wallis H (nominal scale, when the point of interest was the education level of the parent; categorized into three groups: (1) Completed high school or less; (2) Completed college or some college; or (3) Advanced degree or beyond) were employed to analyze data. We used R software (version 3.4.1), and a P value < 0.05 was considered statistically significant. The study was completed with a review of the existing literature on this topic.

Review of literature

Study design and inclusion criteria: The inclusion and exclusion criteria were defined before the initiation of the research. Only research studies were included. Commentaries, conference abstracts, any type of review, editorials, letters to the editor, case series, and case reports were not considered. The selection criteria were defined by applying the problem/population, intervention, comparison, and outcome framework. Participants included parents or guardians of children who required pediatric surgeon management. Intervention consisted of telephone interviews, live interviews, questionnaires or surveys. Any comparison between different populations was acceptable. Desired outcomes were socioeconomic status; residence (urban or rural area); internet usage; internet search platforms; internet sites and any other result reported in the questionnaire, survey or interview.

Literature search strategy and study selection: A literature search was performed based on the PubMed and Cochrane libraries using the following search terms: Internet health service; internet health information; internet; network; net; search; E-health; e-mail; mail; parents; guardians; family; questionnaire; survey; interview; pediatric; pediatric; and pediatric surgery. Articles published in English were retrieved from inception to October 2020. The records found were checked for duplicates. Then, the remaining articles were screened. Any article that met our criteria was included.

RESULTS

Demographics

All parents completed the questionnaire (235 of 235, 100%). Two hundred two (86%) parents searched the internet for children's health-related information. Descriptive data for all participants are presented in Table 1.

Family residence and parental internet usage

Internet usage and accessibility. There was a statistically significant difference between parents living in urban and rural areas regarding several parameters (Table 2): (1) Internet access according to the location of the participants. Most of the parents in urban and rural districts (95.2% and 86.6%, respectively) had internet access at home. Nevertheless, only 1.9% of urban residents used the internet elsewhere as well (library, internet cafes, friend's home), and 9.3% of rural residents used the internet elsewhere (P = 0.022); (2) Ownership of PC at home. Only 7.6% of the city homes did not possess a PC in comparison to 27.8% of rural homes (P = 0.0001); (3) Frequency of internet usage. The usage of the internet was more than once a week among 94.3% and 85.6% of parents in urban and rural areas, respectively. However, the relevant percentages for internet usage less than three times per month were 5.7% and 14.4%. (P = 0.038); and (4) Participation in parents' groups on social media. Participation in parental social media groups varied significantly in the two groups: 66.7% in urban areas and 34% in rural areas (P < 0.0001).

Internet usage to access medical information. Almost half of the parents (42.1%) searched for medical information 24 h prior to admission, but 49.5% had doubts about this information. There was a statistically significant difference between parents living in urban or rural areas with respect to several parameters, as shown in Table 3: (1) Regular internet search activity for basic medical information in the past. Almost nine of ten parents (86.7%) from urban areas searched the internet for medical conditions on a regular basis, in contrast to 67% of parents from rural areas (P = 0.0009); and (2) Search engines. Multiple answers were possible. Google was the most frequently used search engine by both groups. Parents from urban districts used Wikipedia more often (23.8%) than those from rural areas (12.4%). Rural area participants (12.4%) searched through other unspecified engines, while only 2.9% of the urban area participants used other unspecified engines (P = 0.0078).

Internet usage and examination by a pediatric surgeon. Comparing online sources of information with the information provided by a pediatric surgeon, 67.8% of the parents found both sources to be consistent. There were statistically significant differences between parents living in rural and urban areas with respect to several parameters, as shown in Table 4: (1) Searching the internet for a specialist before an appointment. Half the parents from rural areas (50.5%) searched for a specialist before their decision for an appointment, while only 32.4% of those from urban areas did so (P = 0.008); (2) Informing the doctor about the internet search. A great percent of parents from urban sites (29.5%) communicated with the specialists regarding their

Table 1 Demographic data of all participants (*n* = 235), *n* (%)

Demographic characteristics	All parents (*n* = 235)
Accompanying parent	
Mother	145 (61.7)
Father	90 (38.3)
Age of father, median (range)	40 (27-57)
Age of mother, median (range)	36 (21-52)
Family condition	
Married	222 (94.5)
Divorsed/Single	13 (5.6)
Educational level of father	
Completed high school or less	148 (63)
Completed college or some college	53 (22.6)
Advanced degree or beyond	34 (14.5)
Educational level of mother	
Completed high school or less	118 (50.2)
Completed college or some college	73 (31.1)
Advanced degree or beyond	44 (18.7)
Gross household income in Euro	
Less than 10000 €	98 (41.7)
10000 €-25000 €	101 (43)
25000 €-40000 €	31 (13.2)
Greater than 40000 €	5 (2.1)
Residence	
Rural	111 (47.2)
Urban	124 (52.8)
Insurance of child	
Public (government)	214 (91.1)
Private/no insurance	21 (8.9)
Type of admission	
Emergency	114 (48.5)
Elective	121 (51.5)

results from their internet search, in contrast to only 17.5% of parents from rural areas (P = 0.045); and (3) The need for an official website. Parents (97.1%) from urban sites believed that an official website managed by doctors from the clinic would be helpful, while 85.6% of parents from rural areas agreed with this opinion (P = 0.003).

Educational level of parents who performed research for medical information

Internet usage and accessibility. Regardless of education level, 90.1% of all parents used the internet more than once a week. There were statistically significant differences when comparing the results between parents from rural and urban areas with respect to several parameters, as shown in Table 5: (1) Ownership of a PC at home. All participants (100%) with an advanced degree owned a PC, in contrast to 92.1% of the parents with a college degree and 70.9% of the parents with a high school diploma (P < 0.0001); and (2) Participation in parental groups on social media. Participation in parental groups on social media was higher among parents with college degrees (71.4%) than among those with high school degrees (37.9%) and university

Table 2 Internet usage and accessibility regarding the residence (n = 202), n (%)

	Rural residence, n = 97	Urban residence, n = 105	Total	P value
Internet access				
At home	84 (86.6)	100 (95.2)	184 (91.1)	0.022
At work	23 (23.7)	39 (37.1)	62 (30.7)	
Elsewhere	9 (9.3)	2 (1.9)	11 (5.4)	
Personal computer at home				
Yes	70 (72.2)	97 (92.4)	167 (82.7)	0.0001
No	27 (27.8)	8 (7.6)	35 (17.3)	
Frequency of Internet usage				
Daily/1-3 times per week	83 (85.6)	99 (94.3)	182 (90.1)	0.038
1-3 times per month/rare	14 (14.4)	6 (5.7)	20 (9.9)	
Engaging in social media (Facebook, Twitter, Instagram)				
Yes	79 (81.4)	86 (81.9)	165 (81.7)	0.93
No	18 (18.6)	19 (18.1)	37 (18.3)	
Are you member of parents groups in social media?				
Yes	33 (34)	70 (66.7)	103 (51)	< 0.0001
No	64 (66)	35 (33.3)	99 (49)	

degrees (52.8%) (P = 0.0001).

Internet usage to access medical information. Google was the most commonly used search engine by the three groups (85.6%), followed by Wikipedia (18.3%). There was a statistically significant difference between parents living in urban and rural areas with respect to several parameters, as shown in Table 6: (1) Regular internet search activity for basic medical information in the past. One of three parents (35.9%) from the lower education level never previously searched the internet for medical information, in contrast to parents with a college (6.3%) or an advanced degree (13.9%) (P < 0.0001); (2) Internet usage the day before admission. Parents with a higher education level were less likely to search the internet prior to admission (19.4%) than parents with medium (54%) and lower (42.7%) education levels (P = 0.004); and (3) Website validity. Most parents from the higher education levels (77.8%) negatively evaluated the websites in terms of validity. The evaluation from the two other groups was not decisive (P = 0.0009).

Internet usage and examination by a pediatric surgeon. Regardless of the education level of parents, 41.1% of all participants searched for a specialist on the internet. There was a statistically significant difference in parents living in urban and rural areas with respect to several parameters (Table 7): (1) Informing the doctor about the internet search. We noticed that parents from higher education levels (advanced degree or higher) were less likely to inform doctors about the medical information they found online (8.3%), in contrast to parents who had college degrees (23.8%) and high school diplomas (29.1%) (P = 0.041); (2) Agreement between information provided by the doctor and that from the internet. A total of 55.3% of the parents from the lower, 85.7% from the medium and 72.2% from the higher educational level thought information found on the internet and that provided by the doctor were compatible (P = 0.0002); and (3) The need for an official website. All parents from all educational groups consisting of an advanced degree or higher and who completed college or some college (100%) agreed that an official website is necessary for reliable information, while 83.5% of parents from the lower education level agreed with this opinion (P = 0.0001).

Other interesting results

Regardless of the education levels and the residence of the parents, several factors were generally applicable: (1) Most parents (81.7%) were actively engaged in social media (Facebook, Twitter, Instagram); (2) The family member most likely to search the internet for children's health information was the mother (73.8% when the comparison

Table 3 Internet usage to access medical information regarding the residence of the family (n = 202), n (%)

	Rural residence, n = 97	Urban residence, n = 105	Total	P value
Previous medical information searching on Internet				
Yes	65 (67)	91 (86.7)	156 (77.2)	0.0009
No	32 (33)	14 (13.3)	46 (22.8)	
Internet usage in 24 h prior to admission				
Yes	40 (41.2)	45 (42.9)	85 (42.1)	0.81
No	57 (58.8)	60 (57.1)	117 (57.9)	
Which family member searched on Internet mostly?				
Mother	68 (70.4)	81 (76.7)	149 (73.8)	0.25
Father	29 (29.6)	24 (23.3)	53 (26.2)	
Search engines used				
Google	80 (82.5)	93 (88.6)	173 (85.6)	0.0078
Wikipedia	12 (12.4)	25 (23.8)	37 (18.3)	
Other	12 (12.4)	3 (2.9)	15 (7.4)	
Do you trust the websites in terms of validity?				
Yes	53 (54.6)	49 (46.7)	102 (50.5)	0.26
No	44 (45.4)	56 (53.3)	100 (49.5)	
Were the health information comprehensive?				
Yes	75 (77.3)	71 (67.6)	146 (72.3)	0.12
No	22 (22.7)	34 (32.4)	56 (27.7)	
Level of satisfaction with the medical information				
High	21 (21.6)	25 (23.8)	46 (22.8)	0.12
Medium	70 (72.2)	56 (53.3)	126 (62.4)	
Low	6 (6.2)	24 (22.9)	30 (14.9)	

was according to residence and 68.3% when the comparison was according to the educational level of the parent who searched the internet); (3) Evaluation of the websites in terms of comprehension. Most parents (72.3%) stated that they understood completely, or they thought they understood, the information provided; (4) Level of satisfaction with medical information. Only two of ten parents (22.8%) were satisfied/very satisfied with the medical information they found; and (5) Other resources for health information. Multiple answers were possible. Most parents (97.5%) approached a pediatrician or a general practitioner (GP) for health information about their child's condition. The next most popular source of information consisted of friends and family (37.6%).

Review of the literature

The combined search identified 12 articles that matched our criteria[4,6-8,10-13,16,17,20,21]. In the recent literature, it is stated that highly educated parents are more likely to search online for child-related information on a regular basis (52.2%-97.7%) and less likely to search 24 h prior to admission of their child (11.8%-21%). Although parents from lower education levels were less likely to search the internet on a regular basis (64.1%), they were more likely to use the internet for health-related information 24 h prior to the child's admission (47.2%). In contrast, the proportion of parents from the higher education levels was 86.1% and 19,4% regarding searching on a regular basis and searching 24 h prior to child admission, respectively. It was also reported that lower rates of internet accessibility and PC ownership in rural districts made parents from these areas less likely to search the internet on a regular basis (67%) than parents from urban sites (86.7%)[7,8,10,11,16]. Russo *et al*[20] reported that parents who lived more than 44 km from the hospital were twice as likely to search online for information about their child's surgery than those who lived closer to the hospital[20].

Table 4 Internet usage and examination by a pediatric surgeon regarding the residence of the family (*n* = 202), *n* (%)

	Rural residence, *n* = 97	Urban residence, *n* = 105	Total	*P* value
Other medical information resources				
Pediatrician/GP[1]	95 (97.9)	102 (97.1)	197 (97.5)	0.13
Friends and family	27 (27.8)	49 (46.7)	76 (37.6)	
Parents groups	9 (9.3)	8 (7.6)	17 (8.4)	
Search for a specialist				
Yes	49 (50.5)	34 (32.4)	83 (41.1)	0.008
No	48 (49.5)	71 (67.6)	119 (58.9)	
Did you inform the specialist about the Internet search?				
Yes	17 (17.5)	31 (29.5)	48 (23.8)	0.045
No	80 (82.5)	74 (70.5)	154 (76.2)	
Was the information found on the Internet the same as the one given by the doctor?				
Yes	63 (64.9)	74 (70.5)	137 (67.8)	0.4
No	34 (35.1)	31 (29.5)	65 (32.2)	
Need for an official website, *n*				
Yes	83 (85.6)	102 (97.1)	185 (91.6)	0.003
No	14 (14.4)	3 (2.9)	17 (8.4)	

[1]GP: General practitioner.

Regarding search engines, parents mostly used Google and Wikipedia to locate medical websites[4,8,11,12,16,21]. The evaluation of the websites in terms of validity and general level of satisfaction of the information provided was low, especially when the education level of the parents was higher. Several authors have also reported that the quality of medical information found on the internet was poor, which may cause misinformation[6,11-13]. In contrast, Semere *et al*[16] reported that 98% of parents agreed or somewhat agreed that the information was comprehensible[16]. Regarding other sources of medical information, it was reported that pediatricians and GPs were mainly consulted according to several authors who studied the health information seeking behavior of parents[8,11,12,17]. Some studies conclude that there is a predominance of friends and family instead of pediatricians[4,10,13]. Wong *et al*[4] reported a similar conclusion that only 35.5% of the parents informed the doctor about online medical information because the doctor had already included it in his consultation[4]. Another reason why they were hesitant to discuss the information they found with their doctor might have been the warnings from doctors about the validity of the health-related webpages[21]. A consistency rate of 95.2% was reported when the information found on the internet and the information provided by the doctor were compared[4]. Furthermore, several authors pointed out the overwhelming interest of parents on websites provided by doctors or hospitals[8,10-12,16].

DISCUSSION

The results of this study confirm that the internet is a rapidly growing source of medical information, and parents are using it for child-related health information to make significant decisions regarding their child's health[4,11,12,16]. Parental internet access at home ranged from 84.5% to 100% and 86.6% to 95.2% in relation to education level and location of residence, respectively. The vast majority (82.7%) owned a PC at home. They used the internet more than once a week in 90.1% of the sample, while 81.7% participated in social media. Half the study group (51%), mostly parents in urban sites with college and university degrees, were members of health-related support and parental support groups. Our study was in contrast to a study concluding that parents of children living a long distance (≥ 44 km) from a hospital were twice as likely to search online for information about their child's forthcoming surgery than

Table 5 Internet usage and accessibility regarding the educational level of the parent (*n* = 202), *n* (%)

	Completed high school or less, *n* = 103	Completed college or some college, *n* = 63	Advanced degree or beyond, *n* = 36	Total	*P* value
Internet access					
At home	87 (84.5)	61 (96.8)	36 (100)	184 (91.1)	0.27
At work	27 (26.2)	20 (31.7)	18 (50)	65 (32.2)	
Elsewhere	7 (6.8)	4 (6.3)	0	11 (5.4)	
Personal computer at home					
Yes	73 (70.9)	58 (92.1)	36 (100)	167 (82.7)	< 0.0001
No	30 (29.1)	5 (7.9)	0	35 (17.3)	
Frequency of Internet usage					
Daily/1-3 times per week	88 (85.4)	61 (96.8)	33 (91.7)	182 (90.1)	0.055
1-3 times per month/rare	15 (14.6)	2 (3.2)	3 (8.3)	20 (9.9)	
Engaging in social media (Facebook, Twitter, Instagram)					
Yes	84 (81.6)	53 (84.1)	28 (77.8)	165 (81.7)	0.73
No	19 (18.4)	10 (15.9)	8 (22.2)	37 (18.3)	
Are you member of parents groups in social media?					
Yes	39 (37.9)	45 (71.4)	19 (52.8)	103 (51)	0.0001
No	64 (62.1)	18 (28.6)	17 (47.2)	99 (49)	

those who lived closer to a hospital[20]. In our study, this result probably occurred because families that live far from a hospital are those from rural areas where the parents are simpler and trust without doubt the hospital doctors, and additionally, the internet in their areas is not easily accessible. In our study, most mothers searched the internet regardless of their education level (68.3%) or residence (73.8%). Nevertheless, this result is in line with findings from previous studies[4,5,8,10]. Our questionnaire-based study found that the most commonly used search engines by parents were Google (85.6%) and Wikipedia (18.3%), who are less familiar with child-specific websites managed by specialists and hospitals or because they are not aware of what constitutes good health information. These results coincide with previous studies[4,8,11,12,16,21]. On the one hand, the evaluation of websites in terms of comprehension in our study was high since 72.3% of the parents understood or thought that they understood the online medical information. This finding agrees with the results from a study by Semere *et al*[16] in which 98% of parents agreed or somewhat agreed that the information was comprehensible[16]. In contrast, several studies have shown that the quality of medical information found on the internet is poor and that the results are misleading[6,11-13]. In addition to the internet, other resources for medical information according to our study were mainly pediatricians and GPs (97.5%) regardless of the education level or residence of the parents, while friends and family members were the next most frequently used resources, mostly from urban residents (46.7%), with lower EL (43.7%). The same conclusions were reported by several authors who studied the health information-seeking behavior of parents[5,8,11,12,17], in contrast to other studies in which there was a predominance of friends and family instead of pediatricians[4,10,13]. One study reported that nearly one-third of the parents discussed the information that they found online with their doctors[4]. Our study showed that the higher the education level of the parents, the less likely they were to inform the doctor about their internet searches. Additionally, urban residents discussed the child's health-related information more often (29.5%) than parents from rural sites (17.5%). When comparing the information found on the internet and that provided by the doctor, only half the parents from the lower education level (55.3%), 85.7% with college degrees, and 72.2% with advanced degrees found both sources to be consistent. Wong *et al*[4] reported a consistency rate of 95.2%[4]. Several authors have noted the

Table 6 Internet usage to access medical information regarding the educational level of the parent (*n* = 202), *n* (%)

	Completed high school or less, *n* = 103	Completed college or some college, *n* = 63	Advanced degree or beyond, *n* = 36	Total	*P* value
Previous medical information searching on Internet					
Yes	66 (64.1)	59 (93.7)	31 (86.1)	156 (77.2)	< 0.0001
No	37 (35.9)	4 (6.3)	5 (13.9)	46 (22.8)	
Internet usage in 24 h prior to admission					
Yes	44 (42.7)	34 (54)	7 (19.4)	85 (42.1)	0.004
No	59 (57.3)	29 (46)	29 (80.6)	117 (57.9)	
Which family member searched on Internet mostly?					
Mother	67 (65)	48 (76.8)	23 (63)	138 (68.3)	0.27
Father	36 (35)	15 (23.2)	13 (37)	64 (31.7)	
Search engines used					
Google	86 (83.5)	53 (84.1)	34 (94.4)	173 (85.6)	0.74
Wikipedia	15 (14.6)	15 (23.8)	7 (19.4)	37 (18.3)	
Other	12 (11.7)	7 (19.4)	3 (8.3)	22 (10.9)	
Do you trust the websites in terms of validity?					
Yes	58 (56.3)	36 (57.1)	8 (22.2)	102 (50.5)	0.0009
No	45 (43.7)	27 (42.9)	28 (77.8)	100 (49.5)	
Were the health information comprehensive?					
Yes	76 (73.8)	48 (76.2)	22 (61.1)	146 (72.3)	0.24
No	27 (26.2)	15 (23.8)	14 (38.9)	56 (27.7)	
Level of satisfaction with the medical information					
High	22 (21.4)	18 (28.6)	6 (16.7)	46 (22.8)	0.051
Medium	69 (67)	38 (60.3)	19 (52.8)	126 (62.4)	
Low	12 (11.7)	7 (11.1)	11 (30.6)	30 (14.9)	

overwhelming interest of parents on websites provided by doctors or hospitals[8,10-12,16]. Our study demonstrated that the vast majority of parents (91.6%) supported the idea of an official website designed and managed by the doctors of our clinic in which they would be able to find reliable and accurate child-related infor-mation.

Limitation

Our study included parents of children who were admitted to our clinic but excluded those who were not. It would be interesting to determine parent behaviors when they are not stressed out by their child's hospitalization.

CONCLUSION

Our study is in line with the international literature with some minor deviations. This demonstrates that most parents use the internet to query child-related surgical pro-blems. Internet access is difficult in rural areas of northeastern Greece, probably because many of these regions are isolated mountainous areas where the majority of the population is engaged in agricultural work and has different cultural habits. After

Table 7 Internet usage and examination by a pediatric surgeon regarding the educational level of the parent who searched on the Internet (*n* = 202), *n* (%)

	Completed high school or less, *n* = 103	Completed college or some college, *n* = 63	Advanced degree or beyond, *n* = 36	Total	*P* value
Other medical information resources					
Pediatrician/GP	98 (95.1)	63 (100)	36 (100)	197 (97.5)	0.11
Friends and family	45 (43.7)	20 (31.7)	11 (30.6)	76 (37.6)	
Parents groups	8 (7.8)	9 (14.3)	0	17 (8.4)	
Search for a specialist					
Yes	42 (40.8)	31 (49.2)	10 (27.8)	83 (41.1)	0.11
No	61 (59.2)	32 (50.8)	26 (72.2)	119 (58.9)	
Did you inform the specialist about the Internet search?					
Yes	30 (29.1)	15 (23.8)	3 (8.3)	48 (23.8)	0.041
No	73 (70.9)	48 (76.2)	33 (91.7)	154 (76.2)	
Was the information found on the Internet the same as the one given by the doctor?					
Yes	57 (55.3)	54 (85.7)	26 (72.2)	137 (67.8)	0.0002
No	46 (44.7)	9 (14.3)	10 (27.8)	65 (32.2)	
Need for an official website					
Yes	86 (83.5)	63 (100)	36 (100)	185 (91.6)	0.0001
No	17 (16.5)	0	0	17 (8.4)	

GP: General practitioner.

this survey and this review, the next developmental step that the medical community must support is clear. This is the creation of an easy-to-use (even by people with a low educational level) official website from which the parents could access appropriate health information to give substantial answers to their questions and by which they could contact online medical staff and address their questions. Parents will be reassured about their decisions regarding the right time to visit the hospital and consult the doctor they choose for their child's conditions.

ARTICLE HIGHLIGHTS

Research background

The internet is a valuable tool for access to health-related information. There is limited literature regarding its use by parents of children with surgical conditions.

Research motivation

Our study describes the influence of education and residence on the parental search for pediatric surgical information on the internet in a multicultural region of northern Greece, and we compare our results with the recent literature.

Research objectives

The objectives of this study were first to evaluate the epidemiological characteristics of parents in relation to the magnitude of internet usage for health-seeking information and second to review the literature regarding this topic.

Research methods

In this study, an anonymous questionnaire about internet usage was completed by eligible parents of children who were admitted to our clinic for minor surgical procedures during a six-month period. And the literature was reviewed.

Research results

The results of this study demonstrated that the internet has been mostly used by mothers for children's health information. Google was the most commonly used search engine, while pediatricians were the first parental choice for 'live' information.

Research conclusions

The establishment of official websites that parents can access to receive appropriate health information is mandatory in the internet era.

Research perspectives

It would be interesting to determine parent behaviors when they are not stressed out by their child's hospitalization in the future.

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CASE REPORT

Pediatric case with vaccine-related poliovirus infection: A case report

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Abstract

BACKGROUND

As long as oral poliovirus vaccine (OPV) is used, the potential risk for the emergence of vaccine-related polioviruses remains.

CASE SUMMARY

We report a case of Sabin-like type 1 poliovirus infection in an immunocompetent 17-mo-old child after receiving four scheduled doses of OPV. Somehow, the four doses did not confer full protection, possibly because of interference created by other enteroviruses.

CONCLUSION

The surveillance of vaccine-related polioviruses has important implications for improving health policies and vaccination strategies. Missed cases of vaccine-related poliovirus infection might pose a potential risk to global poliovirus eradication. Therefore, the global withdrawal of OPV and a shift to the inclusion of only inactivated poliovirus vaccine in the vaccination schedule is the main objective of the polio eradication program.

Key Words: Poliovirus; Oral poliovirus vaccine; Vaccine-associated paralytic poliomyelitis; Case report

Core Tip: In this study, we report an unusual case of Sabin-like type 1 poliovirus infection in an immunocompetent 17-mo-old child after receiving four scheduled doses of oral poliovirus vaccine (OPV). Somehow, the four doses did not confer full protection, which may have been caused by interference created by the other enteroviruses. The surveillance of vaccine-related polioviruses (VRPVs) has important implic-

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ations for improving health policies and vaccination strategies. Missed cases of VRPV infection might pose a potential risk to global poliovirus eradication. Therefore, the global withdrawal of OPV and a shift to including only inactivated poliovirus vaccine in the vaccination schedule is the main objective of the polio eradication program.

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INTRODUCTION

The extensive use of trivalent oral poliovirus vaccine (tOPV) in routine and supplementary immunization schedules has led to the control and eradication of wild poliomyelitis in almost all parts of the world[1]. Despite inducing durable mucosal and humoral immunity, conferring immunity to unvaccinated individuals as well as low cost and easy oral administration, oral poliovirus vaccine (OPV) strains are genetically unstable[2]. On rare occasions, OPV might revert toward virulent strains by recombination with other enteroviruses in the human gut or reversion mutations under tropical conditions and with poor sanitation, hygiene and water quality, or under conditions of low vaccination coverage and poor population immunity[1,3]. Vaccine-related polioviruses (VRPVs) can cause vaccine-associated paralytic poliomyelitis (VAPP) in normal and immunodeficient vaccine recipients or their close contacts. However, the risk is much higher in immunodeficient individuals[4,5].

The emergence and spread of VRPVs are the biggest threats to the global poliovirus eradication program. A switch from live-attenuated OPV to inactivated poliovirus vaccine (IPV) seems to be the best option to eliminate the risk of VAPP emergence. However, in reality, OPV cessation is not feasible as long as global polio eradication is not achieved[5-7]. In polio-endemic regions or neighboring countries at risk of wild poliovirus importation and spread, OPV remains the vaccine of choice to block wild polio infection and transmission caused by induction of prolonged intestinal immunity even beyond its recipients[5,8]. Currently, we are on the horns of a dilemma. In these circumstances, timely detection and response to VRPVs need to be emphasized in countries using OPV to prevent paralysis development and community spread[6,9]. Here, we report a pediatric case of Sabin-like type 1 poliovirus infection at 17 mo of age after receiving four doses of tOPV.

CASE PRESENTATION

Chief complaints

A 17-mo-old girl from Bushehr city was admitted to Shohadaie Khalij-Fars Hospital with symptoms of fever (38.5°C-40°C), drowsiness, irritability, cough, rhinorrhea, vomiting, and generalized weakness.

History of present illness

On history, the child was immunocompetent and had no known illness. The immunization history revealed that the child was vaccinated with four scheduled doses of tOPV, one dose at birth and three doses at 2, 4, and 6 mo of age. Approximately, 11 mo after receiving the fourth dose of tOPV at her local public health center, febrile enteritis along with anorexia and vomiting developed, and she was hospitalized a few days later.

History of past illness

The child had no history of prior illness.

Personal and family history

The child was immunocompetent and had no known illness.

Physical examination

A lumbar puncture (LP) was performed and antibiotic therapy with empiric antibiotics including vancomycin and ceftriaxone was initiated immediately. On the fourth day of hospitalization, her condition deteriorated, and the pediatrician referred her to the Pediatric Clinic of Namazi Hospital in Shiraz for further evaluation. On examination, reduced strength in all limbs, most notably in her lower extremities, and regression in her ability to sit and walk were noted. High-grade fever and conjunctivitis were the other clinical symptoms. An LP was repeated and cerebrospinal fluid (CSF) pleocytosis was reported.

Laboratory examinations

CSF analysis showed a clear appearance, lymphocytic pleocytosis, normal glucose, and a mild increase of protein levels. CSF bacterial culture was negative; viral culture and molecular assays were not performed. The diagnosis was aseptic meningitis.

Imaging examinations

There were no imaging examinations.

Further diagnostic workup

About 2 years after this event, a regional survey supported by Bushehr University of Medical Sciences (grant number 4359), was performed on leftover CSF samples of patients with a diagnosis of primary aseptic meningitis. The study was approved by the Ethical Committee of Bushehr University of Medical Sciences (reference number bpums.rec.1394.29). Sabin-like type 1 poliovirus was isolated from the CSF specimen of this patient by enterovirus reverse transcriptase-polymerase chain reaction assay (RT-PCR), targeting the 5′ untranslated region (5′ UTR) of the genome, followed by sequencing (Figure 1). The nucleotide sequence isolated from the CSF sample of this case was submitted to the GenBank sequence database (accession number: KX 011400.10).

The nucleotide sequence of this case (KX011400.1) and the nucleotide sequences of wild-type poliovirus (human poliovirus 1 Mahoney), vaccine-derived poliovirus, and vaccine-strain poliovirus (Sabin type 1) were aligned by the ClustalW program in MEGA software version 4.0 (Biodesign Institute, Tempe, AZ, United States). A change of an A to a G was shown at position 480 of the 5′ UTR of the isolated sequence (Figure 2). The CSF sample was negative for nonpolio enteroviruses, mumps, herpes simplex virus types 1 and 2, cytomegalovirus, and varicella-zoster virus.

FINAL DIAGNOSIS

We present a case of Sabin-like type 1 poliovirus infection that was initially consistent with the diagnosis of aseptic meningitis. On further evaluation, a diagnosis of Kawasaki disease was presumed. However, that diagnosis is unlikely, given that the high-grade fever persisted despite intravenous immune globulin (IVIG) therapy. This was a probable case of VRPV infection, and is supported by isolation of Sabin-like type 1 poliovirus from CSF specimen. The nucleotide sequence isolated from the CSF sample of this case had G at nucleotide position 480 of the 5′ UTR, which differentiates it from the wild-type poliovirus with A-480[10,11]. The probability of nonpolio enteroviral infections was ruled out by the negative RT-PCR enterovirus assay results on the CSF specimen.

TREATMENT

As Kawasaki disease was suspected, a single high-dose (2 g/kg) intravenous administration of immunoglobulin (IVIG) was given. However, the high-grade fever was not responsive to IVIG and persisted for approximately 8 d. Subsequently, the clinical symptoms were gradually improved. It is unclear whether immunoglobulin therapy facilitated the improvement of the clinical symptoms, or they improved spontaneously.

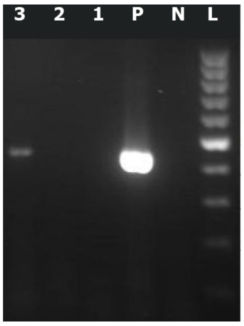

Figure 1 Reverse transcriptase-polymerase chain reaction assay amplification of Sabin-like type 1 poliovirus RNA isolated from cerebrospinal fluid samples of this case. 3: Amplified product (approximately 438 bp) on 2% agarose gel electrophoresis; L: 100 bp DNA ladder; N: Negative control; P: Positive control.

OUTCOME AND FOLLOW-UP

Following clinical improvement, the child was discharged from the hospital, but she had a mild fever, muscular weakness, and difficulty using her lower limbs for approximately 2 mo. At a 1-year follow-up, cardiac complications were not reported, and the strength of all her limbs was completely restored.

DISCUSSION

This is an unusual case of VRPV, as the child was immunocompetent and had received four doses of tOPV. Somehow, the four doses had not conferred full protection, possibly because of interference created by other enteroviruses. Of note, the child lives in a tropical area, where diarrheal diseases frequently occur. Neurovirulent reversion of OPV in the child’s gut is a possibility. However, the long interval between administration of the fourth dose of tOPV and onset of clinical symptoms, as well as the child’s immunocompetency make that unlikely. Other possibilities include the presence of a prolonged poliovirus excreter or the existence of circulating VRPVs in the environment. However, that is unlikely possibility given that no secondary cases were reported southern Iran before or after this event. She was a close contact of other OPV-vaccinated children in a crowded nursery, and therefore exposure of this patient to VRPVs originating from the other children is another possibility. Overall, the evidence is insufficient to trace the source of this strain. This case was detected through a regional survey to reveal the molecular epidemiology of viral causes of aseptic meningitis. This case was missed by routine surveillance of acute flaccid paralysis because the patient was not paralyzed at the time of admission and was evaluated following a misdiagnosis.

The VRPV surveillance has important implications for improving health policies and vaccination strategies. However, most cases of VRPV infection are captured through the acute flaccid paralysis surveillance system. Recognition of VRPVs remains an important challenge. Missed cases of VRPV infection pose a potential risk to global poliovirus eradication. As long as OPV is used, the potential risk of emergence of VRPVs remains[6]. VRPVs are clinically indistinguishable from wild polioviruses and are capable of causing paralytic poliomyelitis and circulating in society whenever the immunity coverage is reduced[2,6]. The emergence of VAPP is a health dilemma as devastating as wild polio. Therefore, the global withdrawal of OPV and shift toward the all-IPV schedule is the main objective of the polio eradication program[3].

CONCLUSION

In this study, we report an unusual case of Sabin-like type 1 poliovirus infection in an immunocompetent 17-mo-old child after receiving four scheduled doses of OPV. Somehow, the four doses did not confer full protection, possibly because of interference created by other enteroviruses. The surveillance and notification of VRPVs has important implications for improving health policies and vaccination strategies.

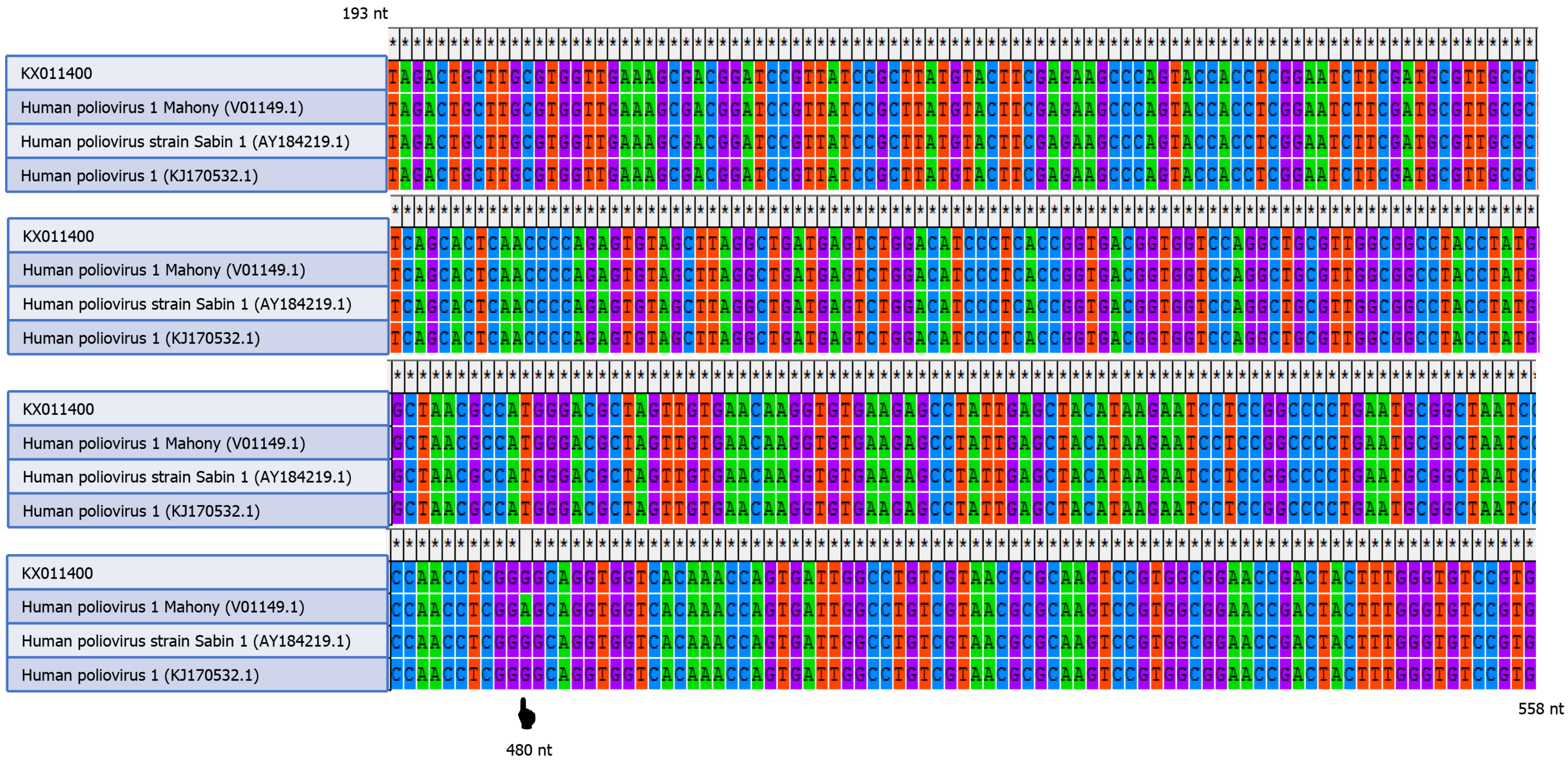

Figure 2 Alignment of the partial nucleotide sequences (193 nt to 558 nt) of this case (KX011400). Wild-type poliovirus (V01149.1), vaccine-strain poliovirus (AY184219.1), and vaccine-derived poliovirus (KJ170532.1) by MEGA software version 4.0 (Biodesign Institute, Tempe, AZ, United States) and appearance of a nucleotide difference at position 480 of the 5' untranslated region. A denotes wild-type poliovirus and G denotes vaccine-strain poliovirus.

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