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EVIDENCE REVIEW

Can omalizumab be used effectively to treat severe conjunctivitis in children with asthma? A case example and review of the literature

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Abstract

A 14-year-old girl with poorly controlled asthma attended the difficult-to-treat asthma clinic for review. Although she has eosinophilia and significantly raised immunoglobulin E levels, she is not currently a candidate for omalizumab (Xolair). She also suffers from chronic urticaria, eosinophilic eosophagitis and severe conjunctivitis. You wonder if omalizumab would be effective in treating her multiple atopic conditions, in particular her troublesome conjunctivitis. PubMed was searched using the following search terms: (Omalizumab) or (Xolair) and (conjunctivitis). Searches were conducted in November 2020. Abstracts were selected for full text review if the study population identified asthma as a comorbidity. Non-paediatric studies and those that were not written in English were excluded. The use of omalizumab has the potential to be effective in the treatment of conjunctivitis associated with asthma and other atopic conditions. However, research is needed to address the question, in the form of multicenter, double-blind randomized control trials.

Key Words: Omalizumab; Conjunctivitis; Allergy; Asthma; Pediatrics; Atopy

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Core Tip: Asthma is often associated with multiple atopic conditions which can be more debilitating than the asthma itself. The use of omalizumab has the potential to be effective in the treatment of conjunctivitis associated with asthma and other atopic conditions. However, research is needed to address the question, in the form of multicenter, double-blind randomized control trials.

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INTRODUCTION

Scenario

A 14-year-old girl with poorly controlled asthma attended the difficult-to-treat asthma clinic for review. Although she has eosinophilia and significantly raised immunoglobulin E (IgE) levels, she is not currently a candidate for omalizumab (Xolair) due to poor adherence. She attends immunology clinic for spontaneous urticaria which has not improved despite high dose antihistamine. Gastroenterology are treating her for eosinophilic oesophagitis with proton pump inhibitors. During the consultation, you note that she also has severe vernal keratoconjunctivitis (VKC). She reported itching, burning and tearing of her eyes and it was evident at the review that she had marked conjunctival hyperaemia and blepharitis. Although adherence has been an issue in relation to her asthma treatment, she is reportedly compliant with both enteral and topical antihistamine therapy for her conjunctivitis.

You wonder if omalizumab would be effective in treating her multiple atopic conditions, in particular her troublesome conjunctivitis.

STRUCTURED CLINICAL QUESTION

Does treatment with omalizumab (intervention) in children with allergic conjunctivitis as a comorbidity of asthma (population) improve their conjunctivitis symptoms (outcome) compared to current treatment (control)?

SEARCH

PubMed was searched using the following search terms: (Omalizumab) or (Xolair) and (conjunctivitis). Searches were conducted in November 2020.

RESULTS

The literature search returned a total of 31 studies. Abstracts were selected for full text review if the study population identified asthma as a comorbidity. Non-paediatric studies and those that were not written in English were excluded. Following abstract review, 5 papers were deemed relevant for full text analysis and all were felt to address the question. Included studies are summarized in Table 1 and graded according to the Oxford Centre for Evidence-based medicine Levels of Evidence[1].

Table 1 Studies assessing the use of omalizumab in conjunctivitis as a comorbidity

Ref.	Study group	Study type (level of evidence)	Intervention	Outcome	Results
Doan *et al* [13], 2017	4 patients with severe VKC, asthma, rhinitis and AD	Non-controlled, open-label, retrospective case series (Level 4)	2 weekly treatment with Omalizumab for range of 16-42 mo	Ocular VAS scale. Bonini grading. ACT score	3/4 had improvement in VAS score and Bonini grading. 3/4 had total control
Sánchez and Cardona [18], 2012	1 patient. 16 years old with severe refractory VKC, asthma, AD and rhinitis	Case report (Level 4)	2 weekly treatment with Omalizumab for 18 mo	Ocular VAS scale. Objective physician evaluation including cessation of immunosuppressive therapies	Ocular VAS improvement. Reduction of red eyes, photophobia and papillae. Cessation of ciclosporin and corticosteroids
de Klerk *et al*[19], 2013	1 patient. 12 years old with severe refractory VKC, asthma and rhinitis	Case report (Level 4)	Monthly treatment with Omalizumab for 18 mo	Juniper's rhinoconjunctivitis QOL score. Reduction in immunosuppressive ocular therapy	Improvement in Juniper's rhinoconjunctivitis score. Cessation of ciclosporin and olapatadine
Occasi *et al* [20], 2015	1 patient. 15 years old boy with asthma, severe VKC and AD	Case report (Level 4)	2 weekly treatment with Omalizumab for 3 mo	Achieving asthma control. Resolution of AD and VKC symptoms	Asthma control achieved at 3 mo. Resolution of VKC symptoms at 3 mo
Rossberg *et al*[11], 2020	2 patients with severe VKC, asthma and AD	Case report (Level 4)	2 weekly treatment with Omalizumab for 11 mo and 6 mo	Bonini grading	Improvement in Bonini grading

QOL: Quality of life; VKC: Vernal keratoconjunctivitis; VAS: Visual analogue scale; ACT: Advanced communication training.

DISCUSSION

Hypersensitization of IgE plays an important role in many allergic diseases. This means that patients often have multiple atopic conditions (multimorbidities). Patients with allergic asthma frequently present with other atopic conditions including: Rhinoconjunctivitis/allergic rhinitis, atopic dermatitis, food allergies, chronic spontaneous urticaria, eosinophilic oesophagitis and allergic bronchopulmonary aspergillosis [2]. Having these multimorbidities adversely impacts on asthma control and can contribute significantly to the overall burden of the disease[2].

IgE secreted by plasma cells in response to an exposure to allergens play an integral role in the allergic inflammatory cascade. Allergen-specific IgE binds to the surface of mast cells, causing degranulation of certain mediators (including histamine, chymase and tryptase) which are responsible for the classic symptoms of itching, redness and oedema. Omalizumab is a recombinant monoclonal antibody that sequesters free IgE and accelerates the dissociation of the IgE-Fcε receptor I complex[3]. This disrupts the IgE-mediated inflammatory cascade. Based on an extensive body of evidence, NICE now recommends use of omalizumab for patients with asthma and chronic spontaneous urticaria (CSU) who meet specific criteria[4,5] (Table 2). Guidance for its use in chronic rhinosinusitis with nasal polyps is expected[6]. These conditions are considered in isolation and current guidelines do not account for patients with multiple severe atopic conditions.

Dosing of omalizumab in Asthma is based on age, baseline, pre-treatment serum IgE levels and body weight[7]. As a result, a mg/kg dosing value is not usually given. Usual doses range from between 75-600 mg and depending on weight and serum IgE levels, dosing intervals may be fortnightly or monthly. At the upper extremes of weight and serum IgE levels, the theoretical dose *via* extrapolation is not licensed and therefore not recommended[7]. Currently, there is no guidance for this situation, however other biologics targeting different pathways may be trialed. Dosing in CSU is not dependent on serum IgE levels or body weights[7]. Recommendations are to administer 150 mg or 300 mg by subcutaneous injection every 4 wk. Dosing tables for asthma and chronic idiopathic urticaria are included in the appendix.

VKC is a chronic, relapsing condition mainly affecting children. Its pathophysiology involves both IgE and non-IgE mediated reactions[8]. The binding of specific allergens to specific IgE's causes degranulation of mediators leading to symptoms of redness and itching. Later, mediators cause infiltration of eosinophils, neutrophils and macrophages into the tissue. Eosinophils in particular play a major role in inflammation and tissue lesions such as epitheliopathy in VKC[9]. The mainstay of treatment is topical immunosuppressive medications and topical steroids. However, these are

Table 2 Current Indications for prescribing omalizumab

Ref.	Age	Previous treatment
NICE[4]	> 6 yr	Optimised standard treatment with documented compliance
		Continuous or 4 or more courses of oral steroids in the previous year
NICE[5]	> 12 yr	Poor response to standard treatment with H1-antihistamines and leukotriene receptor antagonists
		Objective severity score (weekly urticaria activity score) > 28

associated with significant side effects including ocular hypertension, glaucoma and cataract formation. Additionally, a large prospective study by Bonini *et al*[10] showed that 31% of patients with VKC requiring treatment with topical steroids had no improvement[10].

Four case reports and one case series followed a total of 9 patients with severe conjunctivitis as a comorbidity of asthma. Prior to omalizumab, all patients had worsening ocular symptoms despite topical and oral medications including immunosuppressants and corticosteroids. Omalizumab was associated with clinical improvement in 8 out of the 9 children including a reduction in the use of topical steroids and immunosuppressive therapies. Associated allergic multimorbidities also improved in 6 patients. Asthma control was achieved and lid eczema and atopic dermatitis completely resolved.

In the case report by Rossberg *et al*[11], effect on asthma symptoms was not reported. One patient required commencement of Dupilumab (an alternative monoclonal antibody that inhibits Interluekin-4 and Interleukin-13 signalling[12] mainly due to worsening AD, and reached complete control[11].

One patient in the case series by Doan *et al*[13] did not respond to omalizumab for either their conjunctivitis or their associated atopic conditions[13]. Notably, this patient did not have detectable sensitization to any allergen. This shows the complex and multifactorial pathogenesis of VKC, of which IgE plays a role[8,9].

A study by Heffler *et al*[14] in 2016 discusses treatment with omalizumab in 2 patients with severe VKC[14]. They did not meet our inclusion criteria as neither patient had concomitant asthma, however one patient was a child, in her first decade of life. Omalizumab was administered at 300 mg *per* month for 6 mo. Ocular visual analogue scale (VAS) scores, ophthalmologic examination and conjunctival scrape smears for cytologic examination were the outcomes measured. This is the first case report where cytologic examination has been used as an outcome. After 6 mo, the patient experienced improvement in all outcomes. Ocular VAS scores improved from 8 to 0, eye redness and cobblestone papillae were abolished, and eosinophil levels decreased from 69% to 3% on cytologic examination.

None of the five studies in this literature review report any adverse effects to treatment with omalizumab in children for conjunctivitis. The most common previously reported adverse effects to omalizumab include upper respiratory infections, headaches, arthralgia, pain, fatigue and abdominal discomfort[15]. The risk of anaphylaxis is 0.14% in patients receiving omalizumab, similar to other biologic drugs [16]. The British National Formulary reports further, rarer side effects, including eosinophilic granulomatosis with polyangiitis (usually associated with reduction of oral corticosteroids) and hypersensitivity reactions[17].

These findings are limited as the studies available were heterogeneous and of low quality. Sample size was small, with only case reports or small case series conducted. The dose, duration and frequency of omalizumab varied between the studies. Some studies used omalizumab as a single therapy and others as combination therapy. An array of different outcome measures were used and different grading systems were applied. Compliance to medication prior to commencing omalizumab was a concern in one case report, making conclusions of symptom improvement due to omalizumab more difficult.

CONCLUSION

The use of omalizumab has the potential to be effective in the treatment of conjunctivitis associated with asthma and other atopic conditions. However, research is needed to address the question, in the form of multicenter, double-blind randomized control trials.

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REVIEW

Celiac disease in children: A review of the literature

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Abstract

Celiac disease is an immune-mediated systemic disease triggered by intake of gluten in genetically susceptible individuals. The prevalence of celiac disease in the general population is estimated to be 1% in the world. Its prevalence differs depending on geographical and ethnic variations. The prevalence of celiac disease has increased significantly in the last 30 years due to the increased knowledge and awareness of physicians and the widespread use of highly sensitive and specific diagnostic tests for celiac disease. Despite increased awareness and knowledge about celiac disease, up to 95% of celiac patients still remain undiagnosed. The presentations of celiac disease have significantly changed in the last few decades. Classical symptoms of celiac disease occur in a minority of celiac patients, while older children have either minimal or atypical symptoms. Serologic tests for celiac disease should be done in patients with unexplained chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting, chronic abdominal pain, abdominal distension, chronic constipation, recurrent aphthous stomatitis, and abnormal liver enzyme elevation, and in children who belong to specific groups at risk. Early diagnosis of celiac disease is very important to prevent long-term complications. Currently, the only effective treatment is a lifelong gluten-free diet. In this review, we will discuss the epidemiology, clinical findings, diagnostic tests, and treatment of celiac disease in the light of the latest literature.

Key Words: Celiac disease; Children; Intestinal biopsy

Core Tip: Celiac disease is a systemic lifelong disease. The prevalence of celiac disease has increased significantly in the last three decades due to the increased awareness of physicians and widespread use of highly sensitive and specific diagnostic tests for celiac disease. Despite increased awareness and widespread use of diagnostic tests, up

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to 95% of celiac patients still remain undiagnosed. Early diagnosis is very important to prevent long-term complications. The only effective treatment is still a lifelong gluten-free diet. In this review, we will discuss the epidemiology, clinical findings, diagnostic tests, and treatment of celiac disease in the light of the latest literature.

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INTRODUCTION

Celiac disease is an immune-mediated systemic disease triggered by intake of gluten and related prolamines in genetically susceptible individuals, characterized by presence of various combinations of small intestinal damages, celiac specific antibodies, human leukocyte antigen (HLA)-DQ2 or HLA-DQ8, and gluten-dependent clinical manifestations[1]. Gluten is found in wheat, barley, rye, and oats[2].

PATHOGENESIS

The key elements of the celiac disease, an autoimmune disease, are genetics HLA-DQ2 and HLA-DQ8 genotypes, environmental factors (gluten intake), and autoantigen to tissue transglutaminase (tTG), which are known to play an important role in the pathogenesis[3]. In addition to genetic susceptibility and gluten exposure, loss of intestinal barrier function, gluten-induced proinflammatory innate immune response, inappropriate adaptive immune response, and unbalanced gut microbiome all seem to be components of the celiac disease autoimmunity[3]. More than 99% of celiac patients have HLA-DQ2 or HLA-DQ8 compared to 40% in the general population[4].

It has been suggested that breast milk, mode of delivery, and the age of gluten intake in infants are a risk for developing celiac disease and may affect the incidence of celiac disease. However, there is a limited information in retrospective studies that those factors affect the risk of developing celiac disease[5-7].

Furthermore, it has been suggested that gastrointestinal system (GIS) infections such as rotavirus may increase the risk of developing celiac disease, and therefore rotavirus vaccine may significantly reduce the risk of celiac disease especially in infants with gluten intake before 6 mo[8].

EPIDEMIOLOGY

The prevalence of celiac disease in the general population is estimated to be 1% in the world[9]. The seroprevalence of celiac disease and a biopsy-proven prevalence of celiac disease in the world is 1.4% and 0.7%, respectively[10]. Its prevalence varies depending on geographical and ethnic variations. The highest prevalence is in Europe (0.8%) and Ocenia (0.8%), and the lowest prevalence is in South America (0.4%). The biopsy-proven prevalence of celiac disease was found to be 1.5 times higher in women than men, and approximately two times higher in children than adults. The reason for this difference may be genetic factors [human leukocyte antigen (HLA) and non-HLA genes], environmental factors such as wheat consumption, age at gluten intake, gastrointestinal infections, proton pump inhibitor and antibiotic use, and the rate of cesarean section[10-12].

Celiac disease can occur at any age from early childhood to old age. It has two peaks; the first peak occurs after gluten intake within the first 2 years of life, the second is seen in the second or third decade of life. The diagnosis of celiac disease is difficult because symptoms vary from patient to patient[13].

The prevalence of celiac disease has increased significantly in the last 30 years, the reason for this is not only the increased knowledge and awareness of physicians about celiac disease but also due to the widespread use of highly sensitive and specific

diagnostic tests for celiac disease[14,15]. For example, the incidence of pediatric celiac disease in Canada has increased 3-fold after the use of the endomysial antibody (EMA) test[16]. Despite increased awareness and knowledge about celiac disease, up to 95% of celiac patients still remain undiagnosed[17-19]. The delay in celiac disease diagnosis is reported to be 4-10 years in some studies[20,21]. There are many undiagnosed cases even in developed countries. Very few patients have clinically significant signs of celiac disease. The majority of cases have atypical signs or vague symptoms, so the diagnosis could not be made or diagnosis is delayed[22,23]. The reason for delayed or overlooked diagnosis may be the limited accessibility to serological diagnostic tests in developing countries and the lack of experienced specialists in this field[24].

The risk of developing celiac disease is higher in first- and second-degree relatives of celiac patients, Down syndrome, type 1 diabetes mellitus (DM), selective immunoglobulin (Ig)A deficiency, autoimmune thyroiditis, Turner syndrome, and Williams syndrome (Table 1)[25-28]. Screening tests for celiac disease at risk groups such as type 1 DM, autoimmune thyroid diseases, and first degree relatives of celiac patients also contributed to the increase in prevalence of celiac disease[27,29,30].

The prevalence of celiac disease in first degree relatives of celiac patients is as high as 10%-20%[1,31]. In a recent study of Sahin *et al*[32] the prevalence of celiac disease (CD) in siblings of pediatric celiac patients is reported to be 3.9%. The prevalence of CD in monozygotic twins has been found as high as 75%-80%[33,34].

In recent years, there has been a marked increase in the number of people having gluten-free diet. Furthermore, it has been observed that first-degree relatives of celiac patients start on a gluten-free diet before serologic tests for celiac disease were performed[35]. Therefore, before performing a serological test for celiac disease, it should be paid attention to whether they are on a gluten-free diet. Otherwise, the result of serological tests may be negative, and it would be difficult to diagnose celiac disease. Patients should take gluten-containing foods for 2-8 wk before serological tests[36].

CLINICAL MANIFESTATIONS

Symptoms usually occur in children after ingestion of gluten containing grains between 4 and 24 mo. There may be a delay or latent period between gluten intake and the onset of symptoms[37].

GIS and extra-intestinal manifestations are common in celiac disease[38]. The main GIS manifestations of celiac disease are chronic diarrhea, recurrent abdominal pain, nausea, vomiting, and abdominal distension. Common extra-intestinal manifestations are failure to thrive, short stature, chronic anemia, osteopenia, osteoporosis, delayed puberty, dental enamel defect, irritability, chronic fatigue, neuropathy, arthritis, arthralgia, amenorrhea, and increased liver enzymes[1,38].

Symptoms are usually different in infants than older children. Diarrhea, anorexia, abdominal distension, and abdominal pain are usually seen in younger children. If the diagnosis is delayed, failure to thrive, irritability, and severe malnutrition can be seen. GIS symptoms such as diarrhea, nausea, vomiting, abdominal pain, abdominal distension, weight loss, and constipation may occur in older children depending on the amount of gluten intake[28,37]. GIS signs of celiac disease such as diarrhea are seen in approximately 50% of patients[39-41].

The presentations of CD have significantly changed in the last few decades[41-48]. Classical symptoms of celiac disease occur in a minority of celiac patients, while older children have either minimal or atypical symptoms. GIS symptoms are mild or nonspecific[48,49].

It has been shown that pediatric patients diagnosed with celiac disease who are younger age at the diagnosis have less severe symptoms in the last 20 years. Also, it has been reported that the rate of asymptomatic patients, closer follow up, and strict adherence to gluten-free diet is higher in the last 10 years and that normalization of serological tests is faster than in the last decade[42].

Recently, the clinical symptoms of children with celiac disease are observed to change from GIS symptoms to extra-intestinal symptoms[39,50]. The exact reason for this is unclear, but it has been suggested that there may be increased awareness and widespread use of highly sensitive and specific serologic tests. It has been reported that isolated short stature is seen in up to 47.5% of celiac patients[41,51].

Table 1 Groups with higher risk of developing celiac disease

Groups with higher risk of developing celiacdisease
First-degree relatives of celiac patients
Second-degree relatives of celiac patients
Type 1 diabetes mellitus
Autoimmune thyroid disease
Autoimmune liver disease
Down syndrome
Turner syndrome
Williams syndrome
Selective IgA deficiency
Systemic lupus eryhtematosus
Juvenile chronic arthritis

EXTRA-INTESTINAL MANIFESTATIONS

Extra-intestinal findings are seen in up to 60% of pediatric celiac patients (Table 2)[52]. Short stature is the most common finding in children[52-54]. It has been reported that 10%-47.5% of pediatric celiac patients have short stature at the time of diagnosis[41,54-57]. Nineteen percent to 59% of the non-endocrinologic causes of short stature are reported to be celiac disease[55,56,58-60]. Starting a gluten-free diet in the early period causes rapid growth and weight catch up, especially in the first 6 mo. The target height is usually reached within 3 years after diagnosis. If the target height is not reached despite a strict gluten-free diet, endocrinological evaluation should be done to rule out growth hormone deficiency[55,61-63].

Hypogonadism in girls and delayed puberty in boys due to androgen resistance is a common finding in undiagnosed or untreated pediatric celiac patients[55,64,65]. Delayed puberty is seen in 10%-20% of celiac patients[52,66]. Generally, the development of puberty occurs within 6-8 mo after starting a gluten-free diet. If delayed puberty persists, the patient should be referred to pediatric endocrinology for further evaluation of other disorders of the reproductive system[55,67].

Iron deficiency anemia is seen in up to 40% of pediatric celiac patients[52,53,68,69]. Since iron is absorbed from the first part of the duodenum, which is mainly affected by celiac disease, iron deficiency anemia is common in celiac patients. It has been reported that 84% of pediatric celiac patients have the complete recovery of iron deficiency anemia with a strict gluten-free diet and iron supplementation therapy within 12-24 mo[52].

Hypertransaminasemia is seen in 9%-14% of celiac patients[70]. Mostly, liver damage is reversible, and liver failure rarely occurs[71]. It has been suggested that as a result of exposure to more hepatotoxins through the portal circulation due to the altered intestinal permeability, inflammation and liver damage may occur[54,72]. The response to a strict gluten-free diet is excellent. The increased liver enzymes return to normal by the rate of 75%-90% within 12-24 mo with a strict gluten-free diet[73].

Osteopenia and osteoporosis are usually seen in patients with celiac disease. Approximately 75% of celiac patients have osteopenia and 10%-30% have osteoporosis [74]. Secondary hyperparathyroidism occurs due to the insufficient absorption of vitamin D and calcium from the damaged duodenal mucosa. It is commonly seen in 12%-54% of celiac patients[75]. Normal blood levels of vitamin D and calcium is observed within the first year after a strict gluten-free diet[76,77].

The most common joint and muscle disorders seen in celiac disease are myopathy, arthralgia, and non-erosive arthritis[55,78]. Since arthralgia is mostly seen after the age of 12, the most common finding in pediatric celiac patients is subclinical synovitis. It is most commonly seen in the knee joint. Its incidence is 5%-10%[54]. Since symptoms are mild, ultrasonography is important in the diagnosis of joint disorders.

The most common finding of neurological manifestations is headache, which is seen in up to 20% of celiac patients. More rarely, ataxia and neuropathy (0.1%-7.4%) are seen[79,80]. The prevalence of epilepsy is reported to be 1.43 times higher in children with celiac disease compared to the general population[81]. The relationship between

Table 2 Extra-intestinal manifestations of celiac disease

Extra-intestinal manifestations of celiac disease
Short stature
Anemia
Osteopenia/osteoporosis
Delayed puberty
Dental enamel defects
Dermatitis herpetiformis
Recurrent aphtous stomatitis
Neurological manifestations; peripheral neuropathy, epilepsy, ataxia, headache
Arthritis, arthralgia
Infertility
Amenorrhea
Elevated liver enzymes
Alopecia
Anxiety, depression

epilepsy and CD is still unclear.

The exact prevalence of enamel defects in celiac disease is unknown. In recent studies, it has been reported that enamel defects are seen in 55%-64% of celiac patients [82,83].

Aphthous stomatitis is seen in up to 46% of celiac patients[84]. Although its mechanism is not known exactly, it is usually completely cured with a strict gluten-free diet[52].

Dermatitis herpetiformis is thought to be an extra-intestinal manifestation of celiac disease, but it is relatively rare in pediatric celiac patients in Finland[85]. Unlike celiac disease, its annual incidence is decreasing. The reason for this is unknown exactly[85]. In contrast to that study, it has been reported that it is more common in childhood[86].

ASSOCIATED DISEASES WITH CELIAC DISEASE

The risk of another autoimmune disease is three to 10 times higher in patients with celiac disease compared to the general population[87,88].

The most common accompanying disease is type 1 DM since it has common genetic factors and pathogenic mechanisms with celiac disease[89]. HLA-DQ2 is present in approximately 90%-95% of celiac patients and 50% of type 1 DM patients, but HLA-DQ8 is detected in approximately 10% of celiac patients and approximately 70% of type 1 DM patients[90]. In a systematic review, the prevalence of celiac disease in patients with type 1 DM was reported to be approximately six times higher than in the general population[91]. The prevalence of celiac disease was reported to be 2.4%-16.4% in children with type 1 DM[92-95]. There is consensus about initial screening for celiac disease in newly diagnosed DM patients, but it is not clear when and how often to screen for celiac disease and initiate a gluten-free diet in asymptomatic patients[93]. It has been recommended that screening test for CD should be done at the time of type 1 DM diagnosis and then every 2 years[96]. In another study, it was recommended that children diagnosed with type 1 DM should be screened for celiac disease once a year for the first 5 years[92]. In other studies, it has been recommended that serological screening tests for celiac disease should be done within the first 2 years when the diagnosis is made, then 5 years after the diagnosis and if there is any symptom suggestive of CD[93,97]. Since 58%-85% of type 1 DM patients diagnosed with CD are asymptomatic, early diagnosis of CD is very important to prevent long-term complications such as failure to thrive, osteopenia, infertility, and malignancy[29,77,92,93,98,99].

There is good evidence that autoimmune thyroid diseases are associated with celiac disease[1,100]. The prevalence of celiac disease in patients with autoimmune thyroid

disease is found to be 3.0%-4.8%[30,101,102].

Also, the prevalence of celiac disease in patients with selective IgA deficiency is reported to be 10-20 times higher than in the general population[103].

There is a close relationship between Down syndrome and celiac disease. The prevalence of celiac disease in patients diagnosed with Down syndrome is reported to be 5%-12%[104-108]. The North American Society for Paediatric Gastroenterology, Hepatology and Nutrition and The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend screening tests for celiac disease in children with Down syndrome due to the increased risk of developing celiac disease [28]. In a study conducted in 2020, involving 1317 pediatric patients with Down syndrome aged 3 and over, the prevalence of celiac disease was found to be 9.8% in children with Down syndrome[109]. If screening test for celiac disease is not done, the diagnosis of celiac disease is either overlooked or delayed in 82% of the patients with Down syndrome, thus causing increased morbidity[109].

The increased prevalence of celiac disease is also seen in autoimmune liver disease, Turner syndrome, and Williams syndrome[1,110-116].

THE DEFINITONS RELATED TO CELIAC DISEASE

Silent celiac disease

Silent celiac disease is defined by the presence of celiac antibodies and HLA-DQ2 or HLA-DQ8 and small intestinal biopsy findings compatible with celiac disease especially in patients with autoimmune disease or a genetic disorder or relatives of celiac disease but without any symptoms suggestive of CD[1].

Potential celiac disease

Potential celiac disease is defined by the presence of celiac antibodies, HLA-DQ2 or HLA-DQ8, but intestinal biopsy is not compatible with celiac disease. Marsh classification score 0 or 1 is detected in intestinal biopsy, and the risk of developing celiac disease is increased[117].

Clinical symptoms and signs of the celiac disease are not always seen. Even if there are clinical findings, they are usually mild. The diagnosis of potential CD has increased significantly in recent years due to increased use of serological screening for celiac disease in the general population. A lower prevalence of HLA-DQ2 and a higher prevalence of HLA-DQ8 are detected in potential celiac patients compared to active celiac patients[118].

It should be considered that the cause of negative intestinal biopsy may be the patchy involvement of the small intestinal mucosa, low gluten intake, and inappropriate biopsy orientation[119].

Its treatment is still uncertain and controversial. There is no consensus about how often celiac serological tests should be performed in potential celiac patients on a gluten-containing diet, and how often they should be evaluated clinically[120]. It has been reported that villous atrophy is observed in 33% of symptomatic potential celiac patients after 3 years[121]. Therefore, it has been suggested that symptomatic patients should be given a gluten free diet.

Refractory celiac disease

Refractory celiac disease is characterized by the persistence of symptoms and intestinal villous atrophy despite a strict gluten-free diet for at least 12 mo. Generally, celiac antibodies are negative in most patients at the time of diagnosis, but the presence of high-titer antibodies does not rule out the refractory celiac disease. In all cases, dietary adherence should be carefully questioned. It can cause complications such as ulcerative jejunoileitis, collagenous sprue, and intestinal lymphoma[117].

Seronegative celiac disease

It is characterized by the presence of clinical signs of severe malabsorption and intestinal villous atrophy and negative celiac antibodies[122]. It constitutes approximately 2%-3% of celiac patients. Seronegative celiac disease can be confirmed with improvement in both symptoms and histology 1 year after starting a gluten-free diet [122]. Compared with classical celiac disease, seronegative celiac patients are associated with a higher rate of autoimmune disease, and these patients have a higher risk of developing refractory celiac disease[122].

In this form of celiac disease, genetic analysis is the key step for the diagnosis, because if it is found as negative, celiac disease is ruled out. Other diseases causing villous atrophy are parasitic infections (*e.g.*, *Giardia lamblia*), autoimmune enteropathy, small intestinal bacterial overgrowth, common variable immunodeficiency, eosinophilic gastroenteritis, drug induced enteropathy (*e.g.*, olmesartan, mycophenolate), intestinal lymphoma, Crohn's disease, tropical sprue, human immunodeficiency virus enteropathy, and Whipple disease should be considered in the differential diagnosis (Table 3)[122-124].

Non-responsive celiac disease

Non-responsive celiac disease is defined by the persistence of GI symptoms more than 12 mo despite a strict gluten-free diet. The most common causes of non-responsive celiac disease are persistent gluten ingestion and incorrect diagnosis[125,126]. It needs to be differentiated from active celiac disease and other conditions associated with celiac disease.

DIAGNOSIS

The clinical symptoms of celiac disease are very diverse. Celiac patients may present with symptoms of GIS or extra-intestinal symptoms or no symptoms at all. Therefore, serologic tests for celiac disease should be done in patients with unexplained chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting, chronic abdominal pain, abdominal distension, chronic constipation, recurrent aphthous stomatitis, and abnormal liver enzyme elevation[1].

Furthermore, celiac disease should be investigated in patients with high risk of developing celiac disease, such as type 1 DM, Down syndrome, autoimmune thyroid disease, Turner syndrome, selective IgA deficiency, autoimmune liver disease, and first-degree relatives of celiac patients, even if they are asymptomatic[1].

Celiac disease is diagnosed by a variable combination of symptoms, positive celiac antibodies, presence of HLA-DQ2/DQ8, and duodenal histology[1].

ESPGHAN guidelines from 2012 recommend tissue tTG-IgA test, which is highly sensitive and specific and less costly compared to EMA IgA antibody test, as an initial screening test for suspected celiac disease, and the total IgA test to rule out selective IgA deficiency. The analysis of deamidated gliadin peptide (DGP) IgA test is recommended for children under 2 years of age. If there is IgA deficiency, the tTG-IgG test or the EMA-IgG test or the DGP-IgG test should be performed[1].

If serological tests are negative for tTG-IgA and total IgA level is normal, celiac disease is unlikely. In this condition, the reasons leading to the false negative tTG result should be considered. Those are low gluten intake, protein-losing enteropathy, use of immunosuppressive drugs, and patients under 2 years of age. If the tTG is found as positive [lower than 10 times upper limit of normal (ULN)], gastroduodenoscopy and multiple biopsies of the small intestine should be performed to confirm the diagnosis[1].

If the tTG is higher than 10 times ULN in a symptomatic patient, it should be discussed with the parents in order to make a diagnosis of celiac disease without biopsy. If the parents agree, EMA test and HLA-DQ2/DQ8 analysis are performed. To rule out false positivity of the tTG test, an EMA test is performed from a second blood sample. If EMA and HLA-DQ2 or HLA-DQ8 are positive, celiac disease is diagnosed without biopsy[1]. In practice, it has been reported that this reduces the need for endoscopy by 30%-50%[127].

Since celiac disease causes patchy involvement in the small intestine, at least four biopsies from the duodenum and at least one biopsy from the bulbus should be performed by gastroduodenoscopy. Biopsies are evaluated according to modified Marsh-Oberhuber classification (Table 4)[128]. Since the lesion of celiac disease can only be seen in the bulb, at least one biopsy should be taken from the bulb[129].

While interpreting the serological test results of celiac disease, serum total IgA levels, the amount of gluten consumption, use of immunosuppressive drugs, and age of the patient should be considered[1]. IgG class celiac antibody tests should be performed in patients with low serum IgA levels (total serum IgA < 0.2 g/L)[1].

If the patient has the gluten-free diet for a long time or gluten-free diet for a short time before testing, false negative results may occur[130]. Therefore, patients should take definitely gluten-containing foods before the test. Gluten challenge test should be performed for patients with a gluten-free diet before serological tests, 3-7.5 g/d gluten-

Table 3 Other diseases causing villous atrophy

Other diseases causing villous atrophy
Parasitic infections (*Giardia lamblia*)
Autoimmune enteropathy
Small intestinal bacterial overgrowth
Common variable immunodeficiency
Cow's milk or soya protein hypersensitivity
Intractable diarrhea of infancy
Eosinophilic gastroenteritis
Drug induced enteropathy (*e.g.*, olmesartan, mycophenolate)
Intestinal lymphoma
Crohn's disease
Human immunodeficiency virus enteropathy
Tropical disease

Table 4 The modified Marsh classification

	IEL	Crypts	Villi
Type 0	< 40	Normal	Normal
Type 1	> 40	Normal	Normal
Type 2	> 40	Hypertrophic	Normal
Type 3a	> 40	Hypertrophic	Mild atrophy
Type 3b	> 40	Hypertrophic	Marked atrophy
Type 3c	> 40	Hypertrophic	Absent

IEL: Intraepithelial lymphocyte count/100 epithelial cells.

containing diet (approximately two slices of bread) is recommended for 2 wk[131].

If the patient is strongly suspected of celiac disease, multiple intestinal biopsy and HLA-DQ2/DQ8 analysis are recommended, even if the serological tests for celiac disease are negative. If the histology is compatible with celiac disease but HLA-DQ2/8 negative, celiac disease is unlikely and other causes of enteropathy should be investigated (Table 3)[1]. Celiac disease is diagnosed if the celiac serological tests are positive and the biopsy is compatible with celiac disease.

ESPGHAN guidelines from 2020 report that the tTG-IgA test and total IgA test combination give more accurate results than other test combinations as the initial test for suspected celiac disease regardless of age. If total IgA level is found to be low, tTG-IgG test or EMA-IgG test or DGP-IgG test should be performed (Figure 1)[119].

If the tTG test is found as positive (> 10 times ULN), HLA-DQ2/8 analysis is not recommended in the ESPGHAN 2020 guidelines even if the patient is asymptomatic. It has been suggested that the EMA test should be checked in a second blood sample and if the EMA test is detected positive and the family agrees, celiac disease can be diagnosed without biopsy. In other words, the presence of HLA-DQ2/8 analysis and clinical symptoms are not mandatory for celiac diagnosis in last guideline in 2020 (Figure 1)[119].

If HLA-DQ2/DQ8 test is negative, the probability of celiac disease is low, but a positive HLA-DQ2/DQ8 test does not confirm the diagnosis of celiac disease[132]. If the tTG test is detected positive (< 10 times ULN), multiple intestinal biopsy is recommended to rule out false positivity. It is not recommended to diagnose without biopsy in patients with selective IgA deficiency even if IgG-based antibody positivity is detected[119].

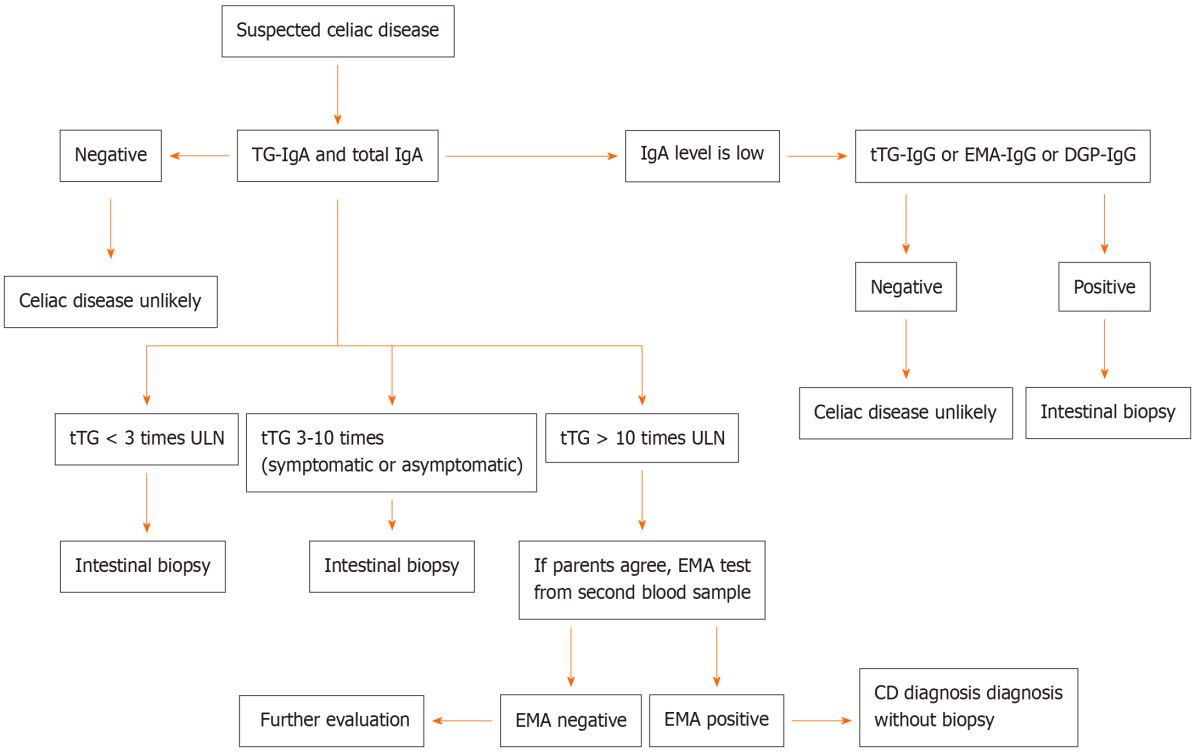

Figure 1 Algorithm for diagnosis of celiac disease. CD: Celiac disease; DGP: Deamidated gliadin peptide; EMA: Endomysial antibody; tTG: Tissue transglutaminase antibody; ULN: Upper limit of normal.

It has been considered that villous atrophy may be seen in other GIS diseases such as parasitic infections, autoimmune diseases, bacterial overgrowth in the small intestine, and Crohn's disease (Table 3)[133].

It has been reported that the pooled sensitivity and specificity of tTG or DGP or tTG + antigliadin antibodies for diagnosing celiac disease is 94.0% and 94.4%, respectively, in a systematic review[134]. It has been suggested that those tests can be used in places where access to laboratory tests is limited.

MANAGEMENT

Currently, the only effective treatment is a lifelong gluten-free diet. Significant improvements in symptoms, normalization of biochemical tests, and improvement in quality of life with a strict gluten-free diet are seen[135].

Rapid improvement in clinical symptoms is observed within 2-4 wk in children. Serological and histological responses are slower compared to clinical symptoms[136]. Although histological response in children is observed within 2 years by a rate of 95%, this rate is 60% in adults[137].

The amount of tolerable gluten varies from patient to patient. As little as 50 mg of gluten, present in a few amounts of bread crumbs or a small piece of cake or traces of contamination, may cause symptoms and/or enteropathy in asymptomatic patients [135,138]. It is unlikely that a gluten intake of less than 10 mg/d will cause significant histological abnormality[139].

Adherence to the gluten-free diet is better in children diagnosed with CD at an early age and those who continue to follow up regularly. It is less in adolescents compared to adults[135].

It has been reported that there is a direct relationship between the duration of exposure to the gluten-free diet and increased autoimmune disorders[140].

In a multicenter prospective study involving 6605 children with the HLA genotype associated with celiac disease, it was shown that the amount of gluten exposure in the first 5 years of life is associated with the development of celiac disease and celiac autoimmunity[141]. Since celiac disease is a multisytemic disease that affects multiple organs, a lifelong gluten-free diet may reduce malignant and non-malignant complications[142].

FOLLOW-UP

Currently, there are no standard evidence-based recommendations for the follow-up of pediatric celiac disease[143].

Patients with celiac disease should be followed up 6 mo after diagnosis and every 6 mo in terms of improvement in symptoms, compliance with the gluten-free diet, quality of life, and progressive normalization of celiac-associated antibodies. Screening tests should be done in terms of autoimmune thyroid disease. A control duodenal biopsy is not required after a gluten-free diet. However, if there is a partial or no response to the gluten-free diet, careful examination should be done for involuntary gluten contamination or poor compliance with the gluten-free diet. If the response to a strict gluten-free diet is poor, duodenal biopsy can be performed[135,143,144].

Earlier diagnosis of celiac disease in asymptomatic patients is associated with better quality of life as well as better compliance with the gluten-free diet[42,145,146].

It has been shown that pediatric patients who are lost to follow up are less adherent to the gluten-free diet and have positive celiac serological antibodies[147]. It has been shown that the regular control is very important.

Routine testing for vitamin and mineral deficiency is reported to be unnecessary in the vast majority of children who follow up to regular controls and have normal growth and development and have no symptoms[148].

The essential marker of the success of the gluten-free diet is still satisfactory height and weight gain in children and adolescents[135].

The best marker of proper follow-up and management is the decline in the antibody levels and the return of antibody levels to normal in follow-up. The presence of persistent positive antibodies usually indicates ongoing intestinal damage and gluten exposure. Serological follow-up should be done within 6 mo and 12 mo after diagnosis and then once a year[149].

tTG-IgA test is reported to be best test in follow up[150]. It has been shown that the average time to return to normal levels of the tTG test in patients with strictly adherent to the gluten-free diet is 1 year[151].

It has been detected that there is no correlation between symptoms and mucosal healing[152]. Gluten challenge test can be performed in cases when there is a doubt about the initial diagnosis of celiac disease. However, HLA typing should be done before evaluation of mucosal damage. Gluten challenge is not recommended under 5 years of age and during pubertal development[1].

In recent studies, it has been reported that gluten consumption can be shown in symptomatic and asymptomatic patients who are unaware of gluten intake by gluten immunogenic peptide tests in stool and urine[153,154]. Gluten intake of more than 50 mg/d for stool test and more than 25 mg/d for urine test seems to be necessary for the sensitivity of the test[153]. Dietary adherence to the gluten-free diet can be evaluated with this test. It can replace serological tests in follow-up, but its use in routine practice is still uncertain and further studies are needed.

DIETS AND NEW TREATMENTS

Currently, the only effective treatment is still to avoid gluten completely for life. The adherence to the gluten-free diet has some disadvantages; negative impact on quality of life, psychological problems, involuntary gluten contamination, possible vitamin and mineral deficiencies, metabolic syndrome, increased cardiovascular risk, and severe constipation[153,155-157].

Approximately 40% of celiac patients are not satisfied with the gluten-free diet due to the negative effect on their quality of life and seek alternative treatments[158,159].

Clinical studies are still ongoing in the treatment of celiac disease. Larazotide acetate is a zonulin antagonist that blocks the tight junction, thus restricting the passage of gluten through the permeable intestinal mucosa[160]. This drug is shown to be effective in controlling gluten-related symptoms[160]. There is also limited information that larazotide may allow patients to tolerate minimal amounts of gluten (involuntary gluten contamination or short-term feeding with a small amount of gluten).

ALV003 (latiglutenase) reduces gluten into small pieces in the stomach before it passes into the duodenum[161]. In a study involving 494 celiac patients, latiglutenase was compared with placebo. It has been shown that latiglutenase did not improve histological findings or symptoms[162]. Further studies are needed.

Vaccination (Nexvax2) is another therapeutic option intended to be used for desensitization in celiac patients against gliadin peptides. Although its major side effects are abdominal pain and vomiting, it passed phase 1. Given the effectiveness of vaccines, it can be a definitive cure for celiac disease[163].

COMPLICATIONS

Complication are usually manifested in late-diagnosed celiac patients (after the age of 50) and in patients not adhering to a strict gluten-free diet. These patients have a higher mortality than the general population[164], but complications are rare (< 1%)[165].

Complications of celiac disease include hyposplenism, refractory celiac disease, intestinal lymphoma, small bowel adenocarcinoma, and ulcerative jejunoileitis[166].

Despite adhering to a gluten-free diet and having complaints that cannot be explained by any other reason, complications should be considered in every patient whose symptoms persist.

CONCLUSION

Celiac disease is a lifelong multi-systemic disease triggered by intake of gluten in genetically susceptible individuals.

Serologic tests for CD should be done in patients with unexplained chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, iron deficiency anemia, nausea, vomiting, chronic abdominal pain, abdominal distension, chronic constipation, recurrent aphthous stomatitis, and abnormal liver enzyme elevation.

Since tTG-IgA test and total IgA test combination give more accurate results than other test combinations, ESPGHAN 2020 guideline recommends this combination as the initial test for suspected celiac disease regardless of age. While interpreting the serological test results of celiac disease, serum total IgA levels, the amount of gluten consumption, use of immunosuppressive drugs, and age of the patient should be considered.

Early diagnosis of CD is very important to prevent long-term complications such as failure to thrive, osteopenia, infertility, and malignancy.

Currently, the only effective treatment is a lifelong gluten-free diet.

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ORIGINAL ARTICLE

Retrospective Study

Indirect determination of serum creatinine reference intervals in a Pakistani pediatric population using big data analytics

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Author contributions: Ahmed S designed and conceived the idea, performed the literature review/comparison, interpreted the data and performed the majority of the write up in the first draft; Zierk J performed the statistical analysis, assisted in the write up of the first draft and critically reviewed the manuscript; Siddiqui I critically analyzed the results and reviewed the manuscript; Khan AH assisted with data acquisition and critically reviewed the manuscript; all the authors have accepted responsibility for the entire content of the submitted manuscript and approved submission.

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Abstract

BACKGROUND

The indirect methods of reference intervals (RI) establishment based on data mining are utilized to overcome the ethical, practical challenges and the cost associated with the conventional direct approach.

AIM

To generate RIs for serum creatinine in children and adolescents using an indirect statistical tool.

METHODS

Data mining of the laboratory information system was performed for serum creatinine analyzed from birth to 17 years for both genders. The timeline was set at six years from January 2013 to December 2018. Microsoft Excel 2010 and an indirect algorithm developed by the German Society of Clinical Chemistry and Laboratory Medicine's Working Group on Guide Limits were used for the data analysis.

RESULTS

Data were extracted from 96104 samples and after excluding multiple samples for the same individual, we calculated RIs for 21920 males and 14846 females, with stratification into six discrete age groups.

CONCLUSION

Serum creatinine dynamics varied significantly across gender and age groups.

Key Words: Creatinine; Pediatric; Reference intervals; Indirect; Data mining; Pakistan

identification anonymized.

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Core Tip: Good laboratory practices advocate the necessity for generation of population specific reference intervals (RIs). The indirect methods of RIs establishment based on data mining are utilized to overcome the ethical, practical challenges and the cost associated with the conventional direct approach. The population specific RIs generated for pediatric serum creatinine levels in this study will assist in more accurate comprehension of the variations in creatinine and facilitate patient care.

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INTRODUCTION

Reliable, accurate and population specific reference intervals (RIs) for laboratory analyses are pivotal for laboratory results interpretation and appropriate clinical decision-making. RIs for an analyte are based on the 2.5th and 97.5th centiles values from a set of pre-defined healthy individuals[1,2]. Furthermore, to improve the diagnostic efficiency of biomarkers, various partitioning criteria for RIs have been deployed, particularly aimed to evaluate the influence of increasing age and gender dependence[3,4]. In the pediatric population, this portioning becomes more essential as physiological developments after birth and during adolescence result in fluctuations in the levels of many biomarkers, especially serum creatinine (CREA)[5].

The most commonly utilized and recommended 'direct approach' for RIs generation follows a more robust strategy, with a pre-selected population, that undergoes sample collection, processing and analysis in a controlled environment[6]. However, to utilize this approach in pediatrics is a challenging task, owing to ethical, financial and practical issues. Whereas, the indirect approach can be more effectively and conveniently utilized as an alternative route[6,7]. Analyte specific results from laboratory health records that comprise results obtained from healthy individuals as well as pathologic test results from clinical care areas are extracted in the indirect method and no additional blood samples are drawn, which is of utmost concern in children. This approach is swift and cost-effective especially for low middle-income countries (LMIC). Moreover, use of a minimum of 400 reference subjects for each partition aimed at obtaining statistically reliable RI calculations is further recom-mended, which can be conveniently accomplished with this approach[8].

In most clinical settings, evaluation of kidney function is carried out by requisition of biochemical analysis of serum CREA and 24 h CREA clearance as an indirect measure for the estimation of glomerular filtration rate (GFR)[9]. However, the growth mediated changes in CREA, especially in infancy and during puberty, due notably to its renal tubular secretion and the influence of muscle mass and dietary intake, makes the interpretation even more challenging[10].

The majority of laboratories in LMIC, are unable to establish their population specific RIs and seldom rely on published literature or adopt the ones cited by the manufacturers in kit information sheets[11]. Whereas, some laboratories also imple-ment RIs calculated based on different analytical platforms and reagents than the ones in actual use. The inappropriate RIs adopted can lead to errors in report interpretation, ultimately leading to compromised patient safety, unnecessary further testing and costs, especially for LMIC. Our primary objective was to establish gender- and age-specific RIs for CREA specific to Pakistani children and adolescents using a validated indirect statistical approach[5,7,12].

MATERIALS AND METHODS

Study design and subjects

A team of investigators performed data mining of the laboratory information system at the Section of Clinical Chemistry, Aga Khan University. Ethical approval for the study was obtained from the Ethical review committee (ERC, #5348-Pat-ERC-18) of the university. All serum CREA measurements for both genders, including both in-house as well as ambulatory cases from birth to 17 years, were retrieved, regardless of the indication for test requisition. The timeline was set at six years from January 2013 to December 2018.

Biochemical analysis

The biochemical analysis was carried out on a Siemens ADVIA 1800 platform. The precision of the assay was 3.8% at 1.8 mg/dL (159 μmol/L) and 3.7% at 8.4 mg/dL (743 μmol/L), and the method was linear from 0-25 mg/dL (0-2210 μmol/L). As most of the laboratories in Pakistan are well versed with the conventional system of units, the levels of CREA are expressed in mg/dL. The laboratory is accredited by the College of American Pathologist and internal quality assurance is practiced in light of the Clinical & Laboratory Standards Institute standards.

Statistical analysis

The statistical analysis was performed using Microsoft Excel 2010 and the indirect algorithm proposed and pre-validated the German Society of Clinical Chemistry and Laboratory Medicine's Working Group freely available online as a software pack-age [5,7,12]. The method is based on utilizing an input dataset of laboratory values containing both non-pathologic and pathologic samples, but only one sample per patient. A Power Normal distribution, defined as Gaussian distribution following Box-Cox transformation was performed to model the distribution of non-pathologic samples in the dataset. As per the default settings, the abnormal values are expected outside the distribution of normal CREA results, with an adjustment of the algorithm for the generation of the upper limits of the RI, by setting the Pathological value to "high", compared to the physiological test results.

To calculate the respective 2.5th and 97.5th percentiles, the data were split into six age groups, for each gender, ranging from birth *i.e.*, 0 d- < 2 years, 2- < 5 years, 5- < 9 years, 9- < 12 years, 12- < 15 years and 15- < 17 years, respectively, as defined previously by Tahmasebi *et al*[11] in the CALIPER cohort of healthy children and adolescents[11].

For the evaluation of calculated RIs, we performed a comparison of our results with Tahmasebi *et al*[11] that has established pediatric RIs for CREA on the Siemens ADVIA 1800[11]. Additionally, we also compared our findings with a local study by Molla *et al* [13] that has established direct RIs for CREA in an apparently healthy Pakistani population, for the combined 0-14 and 15 years onwards age groups, respectively, without partitioning into fine grained age clusters[13]. Lastly, the RIs currently in use by our laboratory for children and adolescents adopted from the Tietz textbook of clinical chemistry and molecular diagnostics were also evaluated[14].

RESULTS

From a total of 96104 samples analyzed for CREA over the study timeline, patients with multiple samples were further scrutinized and only the first sample analyzed was included in the final analysis. The lower and upper RIs were calculated based on 36766 CREA results obtained, including 21920 males and 14846 females as depicted in Tables 1 and 2. The complex age-related dynamics were more pronounced in the pre-pubertal group as represented by a significant proportion of samples in this age range.

Figures 1 and 2 illustrate the comparison of our results with RIs established using the direct method as reported by Tahmasebi *et al*[11], Molla *et al*[13] and the current RIs being used for reporting by our laboratory adopted from the Tietz textbook of clinical chemistry and molecular diagnostics.

DISCUSSION

Due to the lack of standardized data formats and experience in dealing with big data analytics, the majority of laboratories in LMIC as well as a few developed countries,

Table 1 Distribution of lower and upper reference intervals of creatinine in Pakistani male children

Age (yr)	*n*	Our study, LRI	Our study, URI	Tahmasebi *et al*[11], LRI	Tahmasebi *et al*[11], URI
< 2	9658	0.15 mg/dL (13 μmol/L)	0.39 mg/dL (34 μmol/L)	0.17 mg/dL (15 μmol/L)	0.52 mg/dL (46 μmol/L)
2- < 5	2964	0.15 mg/dL (13 μmol/L)	0.80 mg/dL (71 μmol/L)	0.18 mg/dL (16 μmol/L)	0.49 mg/dL (43 μmol/L)
5- < 9	2833	0.16 mg/dL (14 μmol/L)	0.69 mg/dL (61 μmol/L)	0.31 mg/dL (27 μmol/L)	0.61 mg/dL (54 μmol/L)
9- < 12	1796	0.27 mg/dL (24 μmol/L)	0.92 mg/dL (81 μmol/L)	0.41 mg/dL (36 μmol/L)	0.68 mg/dL (60 μmol/L)
12- < 15	2291	0.29 mg/dL (26 μmol/L)	1.06 mg/dL (94 μmol/L)	0.43 mg/dL (38 μmol/L)	0.85 mg/dL (75 μmol/L)
15- < 17	2378	0.40 mg/dL (35 μmol/L)	1.26 mg/dL (111 μmol/L)	0.61 mg/dL (54 μmol/L)	1.02 mg/dL (90 μmol/L)

LRI: Lower reference limit, URI: Upper reference limit.

Table 2 Distribution of lower and upper reference intervals of creatinine in Pakistani female children

Age (yr)	*n*	Our study, LRI	Our study, URI	Tahmasebi *et al*[11], LRI	Tahmasebi *et al*[11], URI
< 2	6323	0.12 mg/dL (11 μmol/L)	0.73 mg/dL (65 μmol/L)	0.17 mg/dL (15 μmol/L)	0.52 mg/dL (46 μmol/L)
2- < 5	2012	0.15 mg/dL (13 μmol/L)	0.74 mg/dL (65 μmol/L)	0.18 mg/dL (16 μmol/L)	0.49 mg/dL (43 μmol/L)
5- < 9	1997	0.16 mg/dL (14 μmol/L)	0.68 mg/dL (60 μmol/L)	0.31 mg/dL (27 μmol/L)	0.61 mg/dL (54 μmol/L)
9- < 12	1204	0.26 mg/dL (23 μmol/L)	0.78 mg/dL (69 μmol/L)	0.36 mg/dL (32 μmol/L)	0.63 mg/dL (56 μmol/L)
12- < 15	1573	0.24 mg/dL (21 μmol/L)	0.84 mg/dL (74 μmol/L)	0.40 mg/dL (35 μmol/L)	0.72 mg/dL (64 μmol/L)
15- < 17	1737	0.34 mg/dL (35 μmol/L)	0.93 mg/dL (82 μmol/L)	0.50 mg/dL (44 μmol/L)	0.77 mg/dL (68 μmol/L)

LRI: Lower reference limit; URI: Upper reference limit.

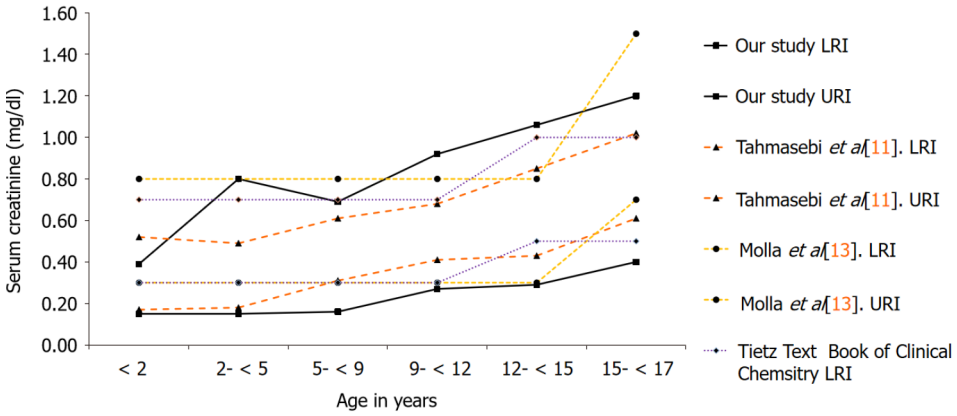

Figure 1 Comparison of serum creatinine reference intervals in males. LRI: Lower reference limit; URI: Upper reference limit.

considerably lag behind in evaluating the transformative potential of the big data they have in store. The methodology employed was based on big data analytics and extraction of data from the laboratory information system of a tertiary care hospital's laboratory that receives specimens from the entire country in order to ensure participation from all the ethnic groups existing in Pakistan.

Compared to the study by Molla *et al*[13] and RIs reported in the Tietz textbook of clinical chemistry and molecular diagnostics, a notable strength of this study is that it demonstrates a strong influence of age on CREA activity with the age-wise partitioning of RIs[12,13]. The differences noted, adds strength to the fact that it is imperative in clinical care to use age- and gender-specific RIs, for adequate comprehension of the dynamics of this widely used renal biomarker[5].

A literature review revealed that most of the reported RIs for CREA, have been established using healthy population-based approaches *i.e.* direct methods. While this approach is undoubtedly considered the gold standard, it has certain limitations

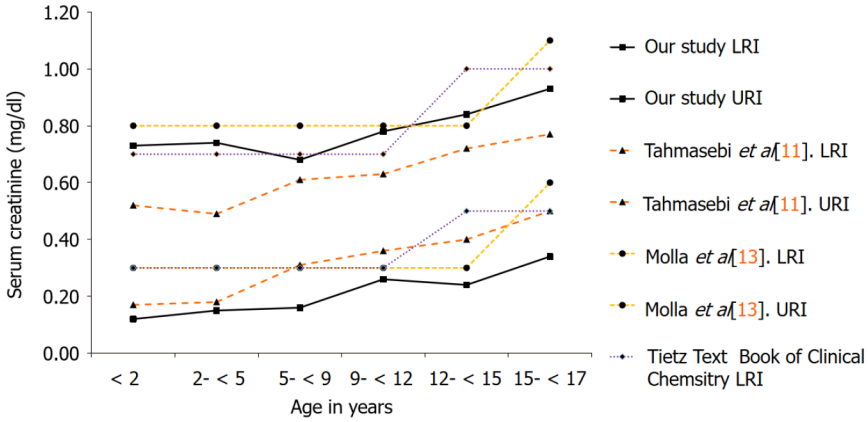

Figure 2 Comparison of serum creatinine reference intervals in females. LRI: Lower reference limit; URI: Upper reference limit.

including those specifically pertaining to expenses for conducting these large-scale prospective studies especially for a LMIC. Additionally, attainment of a minimally acceptable sample size for the different age groups in pediatrics is also a concern. The indirect method not only made it possible to statistically analyze big data (n = 36766), acquired as part of routine care, which further minimized the ethical and practical concerns. However, this approach, requires significant refinement of the specimen selection alongside validated and robust statistical analysis. In this context, we utilized an established algorithm that had already been extensively evaluated and validated by large scale multicenter studies[4,15]. Notably, a literature review revealed that RIs in children established using direct methods do not correctly account for the extensive changes with age as most of them lack age-based partitioning. Moreover, in instances of non-normal distribution, the direct method often generates unacceptably broad confidence intervals (CIs) limiting their widespread adoption[16].

Next to, the RIs reported in the CALIPER cohort, our proposed RIs for CREA seem to differ. In particular, our lower reference limits (LRIs) are considerably lower than the CALIPER cohort, indicating that Pakistanis tend to have a different genetic structure with significantly lower lean tissue mass and a lower GFR compared to the CALIPER cohort. The LRIs and upper reference limits from the CALIPER cohort and the study by Molla *et al*[13] remain continuous up to five years of age, on the contrary, this study demonstrates pronounced age-related fluctuations in this age group for both genders. The maximum values were attained at 12 years in all the studies evaluated, trailed by an incline, having a probable association with the increase in muscle mass with age and attainment of puberty. On gender stratification, our study demonstrated that the peak levels of CREA attained in males *i.e.*, 1.26 mg/dL (111 μmol/L) significantly differed from females *i.e.* 0.93 mg/dL (82 μmol/L). The need for fine grained age- and gender-based RIs for CREA is also supported by another study by Pottel *et al*[17] that has established age- and gender-specific CREA RIs from hospital laboratory data based on different statistical methods, and has shown pronounced age-based fluctuation in CREA for both genders[17]. This phenomenon is in accordance with the dependency of CREA on physical structure, muscle mass, physical activity and protein uptake which differs significantly between the two gen-ders[18,19]. Furthermore, as the utilized method does not allow creation of CIs, equivalence limits were derived according to previously established and validated equations and significant differences between our study RIs and Tahmasebi *et al*[11] were noted as depicted in Tables 1 and 2. It is evident the direct and indirect methods can more often generate overlapping but not identical values[20].

Considering the scarcity of literature on fine grained age group-based pediatric RIs for CREA in Pakistan, one of the highly densely populated countries reportedly with a high burden of kidney disease, the data mining approach can serve as the missing link [21,22]. Furthermore, the deployment of indirect approaches using "big data" solutions are barely utilized in LMIC and this study highlights the utility of this approach at no additional cost. Several LMIC lack a medical insurance system with universal coverage; thus, in most instances, the expenditure has to be self-born by the subjects [23]. Adequate interpretation based on population specific RIs can prevent unnecessary further investigations and medical interventions[24]. This study is in line with good laboratory practices that advocate the need for RIs establishment alongside the attainment of the quality improvement of the post analytical phase, aimed at appro-

priate report interpretation.

In addition to the merits of this real-world big-data approach in laboratory medicine, there is a notable limitation of this indirect algorithm, that any potential differences cannot be analyzed between the groups formulated; hence, individual results have to been complemented with clinical judgement and correlation. Moreover, the CIs with the established RIs were not calculated, as the used algorithm does not contain a provision for CI generation.

CONCLUSION

Good laboratory practices advocate the necessity for generation of population specific RIs, which is widely lacking, particularly in LMIC owing to the various challenges of the conventional direct method. This study has highlighted and further substantiated the utility of an alternative validated indirect algorithm by data mining in a clinical laboratory in Pakistan. This approach can be easily adopted by laboratories in resource constrained regions and the RIs generated will provide more accurate comprehension of laboratory reports in order to facilitate clinical care.

ARTICLE HIGHLIGHTS

Research background

Population specific reference intervals (RIs) are pivotal for laboratory results interpretation.

Research motivation

The indirect methods of RIs establishment based on big data analytics overcome the challenges and the cost associated with the conventional direct approach.

Research objectives

To establish RIs for serum creatinine (CREA) levels in Pakistani children using an indirect data mining approach.

Research methods

RIs were calculated using a previously validated indirect algorithm developed by the German Society of Clinical Chemistry and Laboratory Medicine's Working Group on Guide Limits.

Research results

The lower and upper RIs were calculated based on 36766 CREA results obtained from 21920 males and 14846 females.

Research conclusions

These RIs generated for serum CREA demonstrate the complex age- and gender-related dynamics occurring with physiological development.

Research perspectives

This indirect approach can be easily adopted by laboratories in resource constrained regions and the RIs generated will provide more accurate comprehension of laboratory reports in order to facilitate clinical care.

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CASE REPORT

Glans ischemia after circumcision in children: Two case reports

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Author contributions: Codrich D, Boscarelli A and Cerrina A collected the data, conceptualized the report and drafted the initial manuscript; Scarpa MG, Iaquinto M and Olenik D contributed to the collection of iconographic material and revised the manuscript; Guida E and Schleef J contributed to critically review the manuscript for important intellectual content and language editing.

Informed consent statement: Consent to publish the case report not obtained. The report does not contain any personal information that could lead to identification of the patient.

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Abstract

BACKGROUND

Circumcision refers to the removal of the skin covering the tip of the penis and is one of the most common surgical procedures performed in childhood. Even though circumcision is a well-standardized operation, several minor and major complications may be experienced by paediatric surgeons. Glans ischemia (GI) has been widely reported in the paediatric literature as a complication following circumcision. Nonetheless, etiopathogenesis of GI is not well defined and management guidelines are lacking.

CASE SUMMARY

We describe our experience with this rare and scary complication using subcutaneous enoxaparin alone or in association with a topical vasodilator.

CONCLUSION

Hypothetical causes and different management strategies are discussed.

Key Words: Circumcision; Children; Complications; Glans penis; Ischemia; Case report

Core Tip: Glans ischemia (GI) after circumcision is a rare complication, which has been widely described by paediatric surgeons in the modern literature. To date, etiopathogenesis of GI is not well defined and management guidelines are lacking. In order to achieve a prompt diagnosis and to start appropriate treatment, an accurate postoperative medical assessment and parental education are crucial before hospital discharge for children undergoing circumcision.

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INTRODUCTION

Circumcision refers to the surgical removal of the foreskin covering the glans and is one of the most common paediatric procedures. The complication rate after circumcision in childhood varies between 0% and 16%[1]. Minor complications include penile shaft swelling, bleeding, meatal stenosis, recurrent preputial stenosis and unsatisfactory cosmetic appearance. Major complications reported in the literature are glans or penile amputation, septicaemia, and urethrocutaneous fistulas[1,2]. Glans ischemia (GI) after circumcision is an extremely rare but scary complication in children[3]. We describe our experience with two cases of GI after circumcision in males aged 8 and 10 years old. Hypothetical causes and different treatment strategies are debated.

CASE PRESENTATION

Chief complaints

Case 1: An 8-year-old boy underwent circumcision at our paediatric surgery department for a true phimosis. The child's medical history was uneventful. Surgery was performed under general anaesthesia with a dorsal nerve penile block using mepivacaine. During surgery, a monopolar electrocautery was used to excise the excessive foreskin and to execute the frenulotomy. The coronal suture was performed with 5-0 interrupted absorbable sutures. No excessive bleeding was noted neither during intervention nor in the immediate post-operative course. No compressive bandaging was used.

Case 2: A 10-year-old boy presented to our paediatric outpatient clinic for a true phimosis. Personal history was unremarkable, except for childhood vitiligo. Circumcision was performed under general sedation with spinal anaesthesia. Bipolar electrocautery was used and coronal suture was performed with 5-0 interrupted absorbable stitches. No compressive bandaging was applied. No excessive bleeding was noted neither during intervention nor in the immediate postoperative course. Minimum glans swelling was reported two hours after surgery.

History of present illness

Phimosis.

History of past illness

Case 1: Uneventful.

Case 2: Unremarkable, except for childhood vitiligo.

Personal and family history

Unremarkable.

FINAL DIAGNOSIS

Case 1

At the clinical examination 6 h after surgery, an ischemic appearance of the glans was documented, without pain or difficulty to urinate. A colour doppler imaging (CDI) showed normal flow in the dorsal penile artery.

Case 2

Four hours after surgery, an ischemic appearance of the glans was documented (Figure 1A). Whole blood count and blood clotting were checked and found to be within normal ranges.

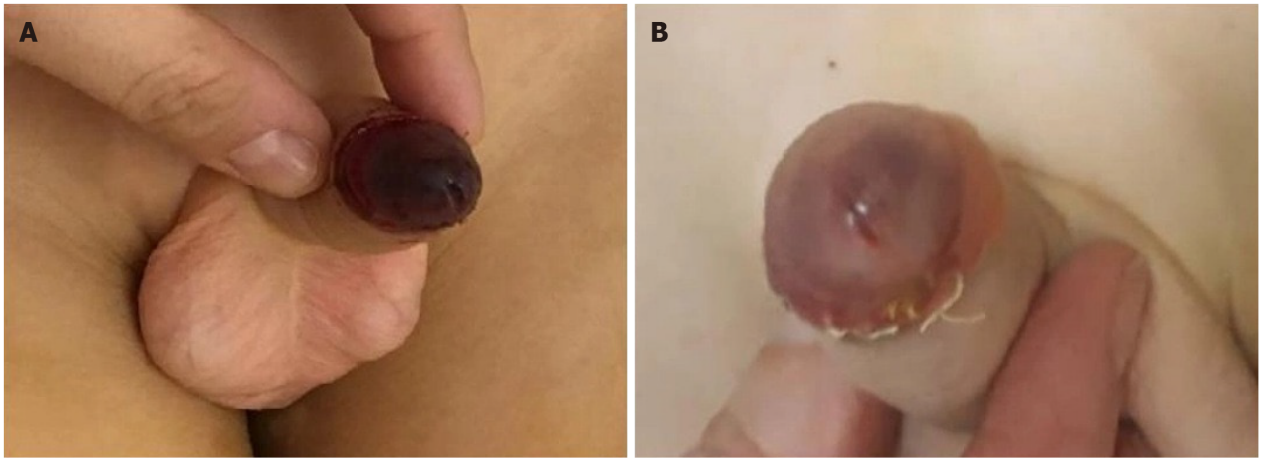

Figure 1 Close up view of circumcision procedure. A: Close up view of a glans ischemia four hours after the circumcision procedure; B: Glans appearance few days after starting therapy with subcutaneous enoxaparin injections.

Case 1

Subcutaneous enoxaparin 2000 UI injection was started and continued once a day for 5 d. Moreover, a galenic preparation of nitric oxide ointment was applied on the glans once a day for a week.

Case 2

Anticoagulant therapy was started with subcutaneous enoxaparin 3000 UI once a day for 5 d.

OUTCOME AND FOLLOW-UP

Case 1

The child was discharged home on postoperative day 6 when an improvement of the GI was noted. Complete restitution integrum was achieved one month after surgery.

Case 2

The colour of the glans rapidly improved to reddish (Figure 1B), and the patient was discharged home on postoperative day 4. At one-month follow-up, the penis and glans were found to be in a normal status.

DISCUSSION

Circumcision is a common paediatric surgical procedure; approximately 0.5% of patients require a repeat surgery. The most frequent complication reported in patients undergoing circumcision is haemorrhage (0.8%), with more than 60% of cases requiring surgical revision[2].

GI after circumcision has been widely reported in the paediatric literature. However, the etiopathogenesis of GI is not well known. The most commonly reported cause for GI is dorsal nerve block using local anaesthetics with or without vasoconstrictor agents[3]. Compression dressing, tight sutures, and excessive use of monopolar electrocautery are other potential reasons for GI after circumcision[3,4]. In our first case, anaesthesia was achieved by a dorsal penile nerve block; during surgery, a monopolar electrocautery device was used. In the second case, a spinal block and bipolar electrocautery were used. After surgery, we routinely use a combination of antibiotic and corticosteroid ointment on the coronal suture and the penis is gently covered with gauze but without any tight circumferential bandage. Notably, in a similar case, Efe *et al*[5] reported an elevated D-dimer level, with restoration to normal level after five days of enoxaparin treatment, suggesting a penile vascular thrombosis even though CDI showed normal penile and glandular blood flow. Conversely, both Karaguzel *et al*[4] and Gnatzy *et al*[6] reported their experiences, describing two cases of acute GI after circumcision with a normal level of D-dimer and good penile blood

flow at CDI. Regarding our cases, the first one showed normal blood flow at CDI but D-dimer value was not checked. In the second case, the D-dimer level was normal but CDI was not performed. Many authors have reported normal penile blood flow at CDI [5-8], and only one case in the paediatric literature described reduced penile blood flow[9]. Therefore, it is questionable whether a thrombosis may be responsible for GI after circumcision, as suggested by Efe *et al*[5], or whether a transient vasospasm of the dorsal artery may be to blame. Moreover, doubt persists regarding whether the use of monopolar electrocautery in our first case could have played a role in the development of GI.

To date, several treatment options for GI are reported in the literature, but a defined protocol or guidelines are still lacking. Some authors reported a successful outcome with endovenous or oral administration of pentoxifylline (PTX), alone or in association with other therapeutic stratagems. PTX is a hemorheological agent which improves the viscosity of blood and is used in peripheral vascular and cerebrovascular insufficiency [4,9,10]. Comparatively, caudal block reduces sympathetic tone, improves arterial supply and venous drainage, and has been proposed as the sole therapeutic strategy [7], or in association with intracavernous injection of glycerol trinitrate, to improve postarteriolar smooth muscle relaxation[11]. Furthermore, Aminsharifi *et al*[11] reported the use of topical testosterone, which has been shown to improve the vascular density of foreskin *in vitro*, in two cases of delayed GI after circumcision, which resulted in complete healing after one month. Selective angiography with intra-arterial injection of a vasodilator agent has been reported by Gnatzy *et al*[6] in association with oral sildenafil and infusion of L-arginine hydrochloride and unfractionated heparin. Lastly, as previously reported, anticoagulant therapy using enoxaparin has been effective in case of GI after circumcision[5]. In both our cases, we administered subcutaneous enoxaparin injection once a day for 5 d with complete resolution of GI. Notably, in the first case, a topical vasodilator was added and the complete resolution required additional days compared with the second case.

CONCLUSION

In conclusion, although a unique causative factor for GI after circumcision cannot be identified, a favourable outcome has been reported in nearly all cases. The unfavourable outcomes reported in literature are due to delayed discovery of the ischemic condition or late presentation of the patients back to the hospital. Consequently, we strongly recommend that discharge home should be preceded by an accurate medical assessment and should not be scheduled until at least 6 h postoperatively. Additionally, parents and patients should be well instructed in evaluating any possible signs of complication in the postoperative course. Lastly, we recommend rigorously following-up patients experiencing GI after circumcision for at least the first month after surgery.

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