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Visceral myopathy causing chronic intestinal pseudoobstruction and intestinal failure in a child with Sanjad-Sakati syndrome

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Abstract Sanjad-Sakati syndrome is a rare autosomal recessive disorder mainly occurring in the Arab Peninsula. This condition is associated with metabolic and septic complications starting in the neonatal period. Chronic intestinal pseudoobstruction owing to visceral myopathy is a rare disabling condition. We report a rare concurrence of Sanjad-Sakati syndrome and chronic intestinal pseudoobstruction in a Saudi child complicated by intestinal failure, sepsis, and early mortality.

Sanjad-Sakati syndrome (SSS), characterized by congenital hypoparathyroidism, growth retardation, seizures, and typical facial dysmorphism, is a rare entity, mostly reported from the Arabic Peninsula. Metabolic derangements and immune deficiency in SSS lead to a morbid course commencing at an early age. However, there have been no reports concerning gastrointestinal manifestations of SSS in the literature. We encountered an instance of chronic intestinal pseudoobstruction (CIPO) owing to primary sporadic visceral myopathy associated with intestinal failure in a child with SSS. Herein we describe the clinical presentation, diagnostic dilemma, and management issues in this child, which is the first report of the rare concurrence of SSS and visceral myopathy leading to a morbid course and eventual fatality.

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1. Case report

A 6-year-old Saudi boy, diagnosed with SSS in the neonatal period, was seen on consultation for frequent episodes of intermittent abdominal distension, bilious vomiting, and constipation of 2 years' duration. History documented multiple admissions to the emergency services with remission of abdominal symptoms on conservative management during all of these prior episodes. The perinatal history revealed that patient was a preterm (34 weeks) infant born by spontaneous vaginal delivery with a birth weight of 1850 g. He was the product of a 25-year-old gravida 3, para 2 Saudi woman in a consanguineous marriage to her first cousin. There was no maternal illness noted during the pregnancy. Additional family history documented early death of their first son at 4 months of age who manifested facial dysmorphism. The parents could not provide any metabolic or genetic studies concerning the deceased child.

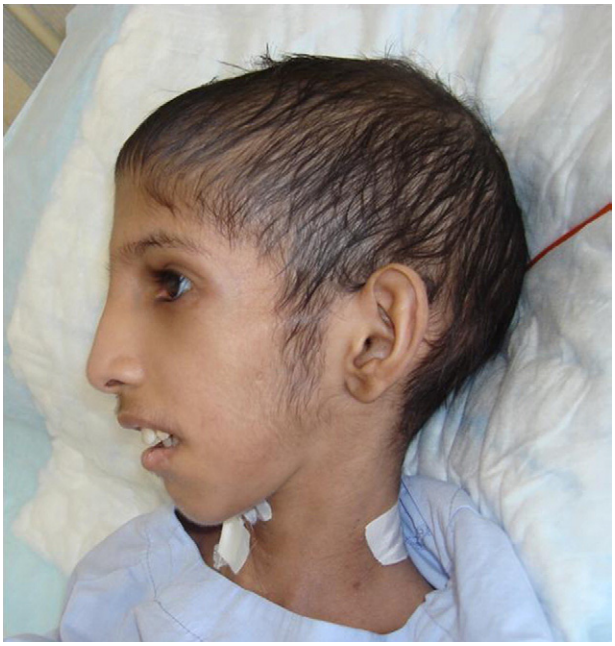

Fig. 1 Typical dysmorphic features of SSS.

There was no history of chronic abdominal complaints in the maternal or paternal side of the family, and the only surviving sibling was a 4-year-old healthy girl.

In the present case, facial dysmorphism, stunted intrauterine growth with short hands and feet, and tonic and clonic seizures were noted in the neonatal period. At that time, serum laboratory studies were obtained and showed hypocalcemia (Ca = 0.7 mmol/L; reference range, 2.19-2.54), hypomagnesemia (Mg = 0.35 mmol/L; reference range, 0.7-1.05), hypoparathyroidism (hypoPTH) (parathyroid hormone = 0.190 pmol/L; reference range, 0.59-6.89), and hyperphosphatemia (phosphate = 3.25 mol/L; reference range, 0.81-1.58). He had a normal thyrotropin, thyroxine, serum ammonia, and alkaline phosphatase level. He was started on calcium, magnesium, and vitamin D supplements. A diagnosis of SSS was considered likely because of the classic dysmorphism, metabolic derangement, growth retardation, and seizures. Chromosomal analysis with homozygosity mapping confirmed a 12–base pair deletion (155-166del) at chromosome 1q42-43, the tubulin-specific chaperone E (TBCE) locus mutation. However, the parents refused to participate in carrier studies.

On postnatal follow-up, the child was kept on calcium, vitamin D supplements, and phenobarbitone. The serum calcium and magnesium levels were within the reference range during 3 admissions to our hospital required for symptoms of subacute intestinal obstruction during the past 2 years. There was no correlation observed between the serum calcium and magnesium levels and either the occurrence or remission of abdominal symptoms. In each instance, the symptoms resolved.

During these admissions, the child was found to have dysmorphic features in the form of microcephaly, deep-set eyes, beaked nose, abnormal ears, and micrognathia, (Fig. 1) typical of SSS. Failure to thrive, growth retardation, severe nontender generalized abdominal distension, palpable loops, and a dilated rectum impacted with soft fecal matter were also noted. Biochemically, mild hypocalcemia, hypoPTH, and normal thyroid function were noted and corrected by adjustment of his maintenance dose of calcium and vitamin D. Plain abdominal radiographs and contrast barium swallow with follow-through showed dilated loops of intestine throughout the abdomen beginning at the duodenum (Fig. 2).

Because of increasing abdominal distension, respiratory difficulty, and failure of conservative management, a laparotomy was performed. Dilatation of the entire intestine from the duodenum to rectum was noted without an identifiable structural cause of obstruction. Full-thickness biopsies were obtained from the distal rectum, sigmoid, colon, ileum, and an appendectomy specimen. Antegrade and retrograde decompression of stomach and rectum, respectively, was done; and a provisional diagnosis of CIPO was made. Histopathology studies confirmed the

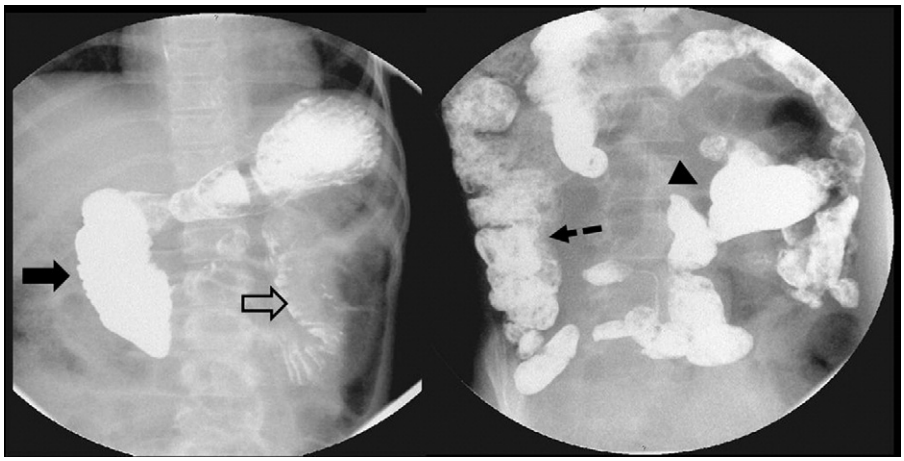

Fig. 2 Dilated duodenum (solid arrow), jejunum (block arrow), ileum (arrow head), and colon (dotted arrow) with extremely slow transit of contrast.

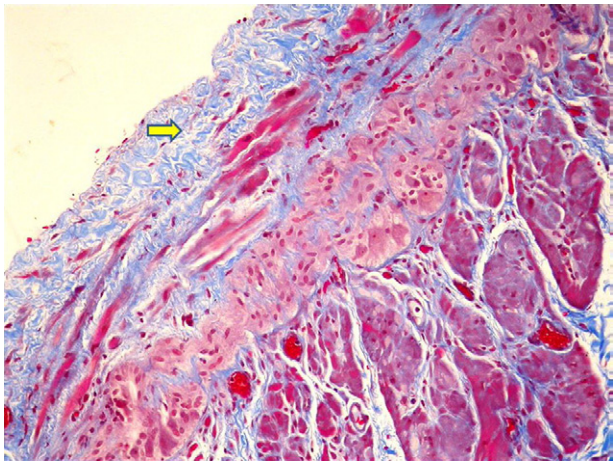

Fig. 3 Section of the muscularis propria of the colon stained with trichrome stain to illustrate the fibrotic changes involving the atrophic outer longitudinal layer with few smooth muscle fibers (arrow) seen surrounded by dense fibrosis (trichrome stain ×200).

presence of ganglion cells with normal neuronal elements in all the sections of the bowel; however, sections of the muscularis propria of the ileum and colon showed fibrotic changes involving the atrophic outer longitudinal smooth muscle layer with few smooth muscle fibers seen surrounded by dense fibrosis (Fig. 3) consistent with a visceral myopathy. Results of stains for C-kit CD117 (Dako, Glostrup, Denmark) were positive, suggesting normal presence of the interstitial cells of Cajal (ICC). There was no evidence of blood vessel inflammation or perivascular collagen deposits suggestive of connective tissue disorder.

Postoperatively, the child was maintained on continuous nasogastric drainage and total parenteral nutrition. For consecutive 6-month periods, short courses of metoclopropamide, erythromycin, and octreotide were administered with a trial of oral feedings; but the child did not tolerate these attempts, and abdominal distension and vomiting ensued. Initially, there was satisfactory weight gain with total parenteral nutrition (TPN) and careful management of the metabolic abnormalities. Subsequently, he developed frequent culture-proven septic episodes and TPN-related cholestasis. He finally died after an episode of sepsis and multiorgan dysfunction at 7½ years of age. Attempts to transfer the patient to centers with facilities for bowel transplantation were unsuccessful because of a long waiting list and lack of donors.

2. Discussion

A consensus working group including pediatric and adult gastroenterologists defined *intestinal pseudoobstruction* as a rare, severe, and disabling disorder characterized by repetitive episodes or continuous symptoms and signs of bowel obstruction including radiographic documentation of dilated bowel with air-fluid levels in the absence of a fixed lumen-occluding lesion [1,2]. If the abdominal radiograph is normal without distension or air-fluid levels and there is delayed intestinal transit or abnormal manometric findings suggesting dysmotility, some clinicians refer to this as a diffuse gastrointestinal motility disorder rather than CIPO [3]. Chronic intestinal pseudoobstruction is an important cause of chronic intestinal failure in both children (15%) and adults (20%) [4-6]. Affected individuals are often unable to maintain normal body weight and/or normal oral nutrition. Chronic intestinal pseudoobstruction is primary in the majority of cases (95%), mainly caused by primary visceral myopathy or primary visceral neuropathy. However, diseases affecting the enteral nervous system, enteric smooth muscles, or both are responsible for secondary cases (5%) and potentially curable causes of CIPO [6]. Secondary causes of CIPO include diseases of central autonomic and enteric nervous systems (eg, stroke, encephalitis, calcification of basal ganglia, orthostatic hypotension, Von Recklinghausen disease, Hirschsprung disease), immune-mediated and collagen diseases (eg, scleroderma, dermatomyositis, amyloidosis, Ehlers-Danlos syndrome), paraneoplastic (eg, central nervous system neoplasms, lung microcytoma, bronchial carcinoid, leiomyosarcomas), iatrogenic (radiation enteritis, clonidine, phenothiazines, antidepressants, antiparkinsonian medications, antineoplastic drugs, bronchodilators, anthraquinones), jejunal diverticulosis, and Chagas disease [7]. Endocrine and metabolic diseases such as hypothyroidism, hypoPTH, pheochromocytoma, and diabetes mellitus have been described as being responsible for some cases of secondary CIPO, even if the underlying mechanism remains undetermined [5].

Sanjad-Sakati syndrome or hypoPTH-retardation-dysmorphism syndrome is a rare autosomal recessive syndrome characterized by congenital hypoPTH, prenatal and postnatal growth retardation, seizures, and a typical facial dysmorphism consisting of prominent forehead, deep-set eyes, abnormal external ears, microcephaly, microphthalmous, thinned upper lip, hooked small nose, micrognathism, and small hands and feet [8]. Metabolically, babies suffer from often severe and fatal hypocalcemia, hypomagnesemia, hyperphosphatemia, and congenital permanent hypoPTH. These metabolic derangements have been responsible for nephrocalcinosis, medullary stenosis of long bones, and convulsions. To date, fewer than 15 reports of patients with SSS have been published. In Saudi Arabia, the estimated incidence varies from 1:40,000 to 1:100,000 live births [9].

However, intestinal dysmotility or pseudoobstruction has not previously been described in association with SSS.

In our case, the insidious onset, intermittent symptoms of intestinal obstruction with remission on conservative management, and coexisting hypoPTH of SSS with a possibility of secondary CIPO presented a diagnostic dilemma. However, the serum calcium and magnesium levels were normal on maintenance therapy and did not correlate with the abdominal symptoms. Subsequently, persistent unremitting

obstructive symptoms led to surgical exploration resulting in acquisition of full-thickness biopsies of the bowel and histologic confirmation of a visceral myopathy.

Histologic features of CIPO include neuropathic, mesenchymopathic, and myopathic forms based on abnormalities affecting the integrity of nerve pathways supplying the intestine (either intrinsic or extrinsic), ICC, and smooth muscle cells, respectively. Neuropathic, mesenchymopathic, and myopathic changes may contribute to intestinal dysmotility either individually or in combination (eg, neuromyopathies or neuro-ICC alterations [7]).

In our case, intact extrinsic and intrinsic neuronal structures, presence of normal ICC, and atrophic and fibrotic muscularis propria of small and large intestine were consistent with a diagnosis of primary visceral myopathy with total intestinal involvement. The child was maintained on TPN for intestinal failure for nearly 12 months and subsequently experienced complications with frequent culture-proven episodes of sepsis, probably related to the inherent propensity for infection in patients with SSS [10,11]. Maintenance of calcium homeostasis was a challenge in this child. Intestinal transplantation is an option for CIPO with intestinal failure; however, issues related to recurrent infections and metabolic derangements that occur in SSS may be a concern when considering multivisceral or intestinal transplantation and posttransplant immunosuppressive therapy. Attempts to refer our patient to a transplant facility were met with the usual obstacles of a long waiting list and lack of appropriate donor.

Genetically, SSS has been mapped to the long arm of chromosome 1 (1q42-q43). Mutations in the gene coding for TBCE have been identified as the cause of the disease in Arabs and the increased propensity for frequent infections [10]. In series from the Arab world, the genetic abnormality documented in cases with SSS include deletion at TBCE locus in chromosome 1q42-43 [12-14], possibility of microdeletion at chromosome 22 [15], and without TBCE mutation in 1 study [10].

Tubulin-specific chaperone E is required for the normal development and function of neuromuscular synapses and promotes microtubule (MT) formation in vivo by facilitating the folding of the α-tubulin component of MT [16,17]. Both loss-of-function mutations and overexpression of TBCE disrupt the MT network in mammalian systems [16]. Although mechanistic relation between TBCE, MT, and neuromuscular transmission is contemplated in some studies [16,17], the exact mechanism by which TBCE and other MT regulators affect neurotransmission is unknown. Furthermore, elucidation of the role of TBCE and MT in intestinal motility and CIPO might clarify the link between SSS and CIPO as occurred in our case.

Chronic intestinal pseudoobstruction is generally sporadic, but familial forms have also been described with autosomal dominant, autosomal recessive, and X-linked transmission [7]. Some genes and loci have been identified in syndromic forms of CIPO, including the transcription factor *SOX10* on chromosome 22 (22p12), the DNA polymerase γ gene (*POLG*) on chromosome 21 (21q17), and a locus on chromosome 8 [7,18,19]. In terms of X-linked transmission, recently, Gargiulo et al [20] have identified a 2–base pair deletion in exon 2 of the filamin A gene (encoding for a large cytoskeletal protein involved in the modulation of the cellular response to chemical and mechanical environmental factors) that is present at the heterozygous state in the carrier females of a family with syndromic CIPO. Familial cases are more frequent in mitochondrial neurogastrointestinal encephalomyopathy, which is characterized by subocclusive episodes and lactic acidosis, skeletal muscle abnormalities (ie, "ragged red fiber"), and specific mitochondrial changes at the ultrastructural level [21]. In the present case, the child had neither lactic acidosis nor a skeletal muscle abnormality suggestive of mitochondrial neurogastrointestinal encephalomyopathy.

There is a possibility that the consanguineous parents of this child might be harboring identical recessive alleles at more than 1 locus. Although TBCE mutational analysis was positive in our case, further genomic hybridization array analysis would be able to detect any contiguous gene deletion affecting those responsible for CIPO.

Children with SSS manifest failure to thrive, stunted growth, and septic and metabolic derangements starting in the neonatal period. Gastrointestinal symptoms including subacute intestinal obstruction have not been previously described in association with SSS. Visceral myopathy as a sporadic or familial condition may present as chronic intestinal pseudoobstruction in children. A careful search for underlying pathology including full-thickness intestinal biopsy will aid in achieving a diagnosis. The rare concurrence of CIPO and SSS compounds the risk of increased morbidity related to intestinal failure, TPN cholestasis, recurring septic episodes, and metabolic complications, leading to multiorgan dysfunction and early mortality.

References

[1] Rudolph CD, et al. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of consensus workshop. J Pediatr Gastroenterol Nutr 1997;24:102-12.

[2] Smith SD. Diagnosis and treatment of chronic gastroparesis and chronic intestinal pseudo-obstruction. Gastroenterol Clin North Am 2003;32:619-58.

[3] Coulie B. Intestinal pseudo-obstruction. Annu Rev Med 1999;50: 37-55.

[4] Cogliandro RF, De Giorgio R, Barbara G, et al. Chronic intestinal pseudo-obstruction. Best Pract Res Clin Gastroenterol 2007;21: 657-69.

[5] Stanghellini V, Cogliandro RF, de Giorgio R, et al. Chronic intestinal pseudoobstruction: manifestations, natural history and management. Neurogastroenterol Motil 2007;19:440-52.

[6] Stanghellini V, Cogliandro RF, De Giorgio R, et al. Natural history of chronic idiopathic intestinal pseudo-obstruction in adults: a single center study. Clin Gastroenterol Hepatol 2005;3:449-58.

[7] De Giorgio R, Sarnelli G, Corinaldesi R, Stanghellini V. Advances in our understanding of the pathology of chronic intestinal pseudo-obstruction. Gut 2004;53:1549-52.
[8] Sanjad SA, Sakati NA, Abu-Osba YK, et al. A new syndrome of congenital hypoparathyroidism, severe growth failure and dysmorphic features. Arch Dis Child 1991;66:193-6.
[9] OMIM: online mendelian inheritance in man. Baltimore, Johns Hopkins University. accessed 21 Sept 2009).
[10] Courtens W, Wuyts W, Poot M, et al. Hypoparathyroidism retardation-dysmorphism syndrome in a girl: a new variant not caused by a TBCE mutation clinical report and review. Am J Med Genet A 2006;140(6): 611-7.
[11] Hershkovitz E, Rozin I, Limony Y, et al. Hypoparathyroidism, retardation, and dysmorphism syndrome: impaired early growth and increased susceptibility to severe infections due to hyposplenism and polymorphonuclear cell functions. Pediatr Res 2007;62(4):505-9.
[12] Parvari R, Hershkovitz E, Kanis A, et al. Homozygosity and linkage-disequilibrium mapping of the syndrome of congenital hypoparathyroidism, growth and mental retardation, and dysmorphism to a 1-cM interval on chromosome 1q42-43. Am J Hum Genet 1998;63:163-9.
[13] Gelb BD, Khan KTS, Diaz GA. The autosomal recessive Kenny-Caffey syndrome locus maps to chromosome 1q42-43. Am J Hum Genet Suppl 1998;63:A290.
[14] Diaz GA, Gelb BD, Ali F, et al. Sanjad-Sakati and autosomal recessive Kenny-Caffey syndromes are allelic: evidence for an ancestral founder mutation and locus refinement. Am J Med Genet 1999;85:48-52.
[15] Teebi AS. Introduction. In: Teebi AS, Farag TI, editors. Genetic disorders among Arab populations. Oxford: Oxford University Press; 1997. p. 1-26.
[16] Jin S, Pan L, Liu Z, et al. *Drosophila* tubulin-specific chaperone E functions at neuromuscular synapses and is required for microtubule network formation. Development 2009;136:1571-81.
[17] Tian G, Huang Y, Rommelaere H, et al. Pathway leading to correctly folded beta-tubulin. Cell 1996;86:287-96.
[18] De Giorgio R, Seri M, Cogliandro R, et al. Analysis of candidate genes for intrinsic neuropathy in a family with chronic idiopathic intestinal pseudo-obstruction. Clin Genet 2001;59:131-3.
[19] Deglincerti A, De Giorgio R, Cefle K, et al. A novel locus for syndromic chronic idiopathic intestinal pseudo-obstruction maps to chromosome 8q23-q24. Eur J Hum Genet 2007;15:889-97.
[20] Gargiulo A, Auricchio R, Barone MV, et al. Filamin A is mutated in X-linked chronic idiopathic intestinal pseudoobstruction with central nervous system involvement. Am J Hum Genet 2007;80: 751-8.
[21] Finsterer J. Mitochondriopathies. Eur J Neurol 2004;11:163-86.