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Late-Onset Pyloric Stenosis and Intussusception With Final Diagnosis of Food Proteins' Hypersensitivity in Schaaf-Yang Syndrome: A Case Report

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Abstract: Schaaf-Yang syndrome (SYS) is a rare neurodevelopmental disorder whose clinical spectrum includes neurodevelopment delay, dysmorphic features, and gastrointestinal symptoms such as feeding difficulties, gastroesophageal reflux, and chronic constipation. Given the small number of patients diagnosed with this syndrome, our aim is to describe novel clinical features that have not yet been reported. The patient we are describing is a 14-year-old male affected by a severe form of SYS. Initial clinical presentation included respiratory distress at birth, feeding difficulties, and neurodevelopmental delay. Since the age of 8 months, he had been tube fed with a semi-elemental formula, and this was well tolerated. At 9 years of age, the pathological mutation (variant *p.Val701fs* in *MAGEL2* gene) associated with SYS was diagnosed. At 13 years of age, he presented severe gastrointestinal symptoms associated to progressive feeding difficulties. He also suffered from recurrent pancreatitis, late-onset pyloric stenosis and intussusception. Histology showed duodenal villous atrophy with a negative serology for celiac disease. Food protein's hypersensitivity was diagnosed and symptoms resolved after starting an elemental formula.

Key Words: food allergy, gastrointestinal disease, pediatrics, rare disease

INTRODUCTION

Schaaf-Yang syndrome (SYS) is a rare neurodevelopmental disorder, caused by a paternally derived mutation in MAGEL2 gene on chromosome 15, initially described by Dr Schaaf in 2013 (1) as a variant of the genetically related Prader-Willi syndrome (PWS). Subsequently, as the number of cases grew, the differences between the 2 syndromes became more evident, and, to highlight these phenotypic differences, SYS was considered as a separate entity. As of today, 250 cases have been described globally.

Received February 28, 2022;accepted March 28, 2022.

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The patient's parents gave their consent for clinical information to be reported in the journal. The patient's parents understand that the patient's name will not be published. Informed consent for publication of this case report was obtained.

The authors report no conflicts of interest.

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JPGN Reports (2022) 3:2(e202)
ISSN: 2691-171X
DOI: 10.1097/PG9.0000000000000202

The clinical phenotype of SYS largely overlaps with PWS's phenotype. Prenatal signs of SYS may be present in the most severe forms and include reduced fetal movements, polyhydramnios, and arthrogryposis. At birth, the first clinical sign of SYS is variable degree of muscular hypotonia, present in almost every newborn affected by SYS. Feeding difficulties and respiratory distress in the neonatal period are common consequences of hypotonia. SYS is also associated to mild-to-severe neurodevelopment delay, cognitive impairment, dysmorphic features including a pointed chin, low-set ears, and frontal bossing. Gastrointestinal (GI) symptoms classically associated to SYS are feeding/swallowing difficulties, chronic constipation, and gastroesophageal reflux (GERD). Feeding difficulties may resolve in the first year of life in up to 50% of affected patients, but inadequate oral intake often leads to gastrostomy tube placement. Less frequent findings, compared with PWS, are hyperphagia and obesity, whose incidence increases especially in adult age (2,3) (Table 1).

We report the case of a 14-year-old boy with SYS, focusing on his peculiar GI symptoms associated with feeding difficulties.

CASE REPORT

The patient is the first born of healthy, unrelated parents. He was born at term from a pregnancy complicated by polyhydramnios. He presented respiratory distress at birth and developed severe feeding difficulties and GERD since the first months of his life, complicated by 2 episodes of aspiration pneumonia.

He also suffered from marked neurodevelopmental delay with cognitive and motorial impairment.

At the age of 8 months, he underwent a percutaneous endoscopic gastro-jejunostomy (PEG-J) placement intervention, and he had been tube fed with a semi-elemental formula (1 kcal/mL) since then.

A long diagnostic pathway was required to identify SYS in the patient, and the pathological mutation (variant *p.Val701fs* in *MAGEL2* gene) was identified at 9 years of age. This variant had not been previously described in literature.

The patient well tolerated enteral feeding during infancy and childhood. At 11 years of age, he had an ileal-jejunal intussusception on the distal end of the PEG-J tube. After the intussusception, he underwent a Nissen fundoplication intervention, and the PEG-J was converted to percutaneous endoscopic gastrostomy. When the patient was 11 years old, he suffered from a first episode of pancreatitis, and, after few days of fasting, parenteral feeding was administered in the recovery phase. The patient presented urticaria during infusion of lipidic emulsion for parenteral feeding containing soya and egg yolk lecithin.

His feeding difficulties exacerbated at 13 years of age, when he started presenting progressive and worsening, diarrhea, vomiting, and abdominal pain. Abdominal ultrasound and first-level blood tests were

TABLE 1. Clinical presentation of Schaaf-Yang syndrome at various age

Age of presentation	Signs and symptoms
Prenatal findings	Reduced fetal movements
	Polyhydramnios
	Distal joint contractures
At birth	Muscular hypotonia
	Distal joint contractures
	Respiratory distress
	Nonspecific dysmorphic facial features (pointed chin, frontal bossing, low-set ears)
From infancy	
Gastrointestinal	Feeding problems with failure to thrive
	Chronic constipation
	Gastrointestinal reflux disease
	Hyperphagia (adulthood)
Neurologic disorders and behavioral problems	Neurodevelopmental delay of variable degree
	Intellectual disability
	Autism spectrum disorder
	Seizures
Endocrinopathy	Hypogonadism
	GH deficiency and short stature
Musculoskeletal	Scoliosis
	Decreased bone mineral density
	Distal joint contractures
Eye abnormality	Esotropia, myopia, strabismus
	Nystagmus

GH = growth hormone.

unremarkable, with no sign of hypereosinophilia. Variation into enteral feeding volumes or flow rate did not improve the tolerance, and a therapeutic trial with cholestyramine did not reduce the symptoms. Three months after the onset of symptoms, he was hospitalized for a second episode of acute pancreatitis and pyloric stenosis, which required endoscopic balloon dilation and resolved after fasting and infusion therapy.

Recurrence of diarrhea and vomiting led him to another hospital admission few weeks later.

Upper GI tract radiography was unremarkable. Screening for celiac disease (CD) was negative. Fecal occult blood test, fecal culture, and *Clostridioides difficile* glutamate dehydrogenase antigen test were negative. Fecal elastase was normal. Blood tests showed increased levels of total IgE, as well as positivity of specific IgE for egg yolk (3 kU/L), egg white (0.24 kU/L), cow's milk (1.47 kU/L), and cow's milk proteins (alpha-lactalbumin 1.28 kU/L; beta-lactoglobulin 0.42 kU/L; casein 0.6 kU/L).

Upper endoscopy's biopsies found duodenal villous atrophy, mimicking CD, plus chronic inflammatory cell in the lamina propria, and chronic gastritis with 22 eosinophils/ high power field (HPF) in the gastric antrum. Eosinophilic infiltration, below the diagnostic threshold for eosinophilic colitis, was documented in all the districts of the lower GI tract (22/HPF, 11/HPF, 2/HPF, and 6/HPF in cecum, colon, sigma, and rectum, respectively).

Enteral feeding was gradually reintroduced with an aminoacidic formula, with relief of symptoms. Vomiting and abdominal pain quickly resolved, and stool frequency progressively reduced until normalization. As of today, the patient is asymptomatic with good tolerance to enteral nutrition.

DISCUSSION

Rare diseases always constitute a challenge for clinicians dealing with them. The onset of symptoms not previously associated to a syndrome may cause delay in the diagnostic pathway. SYS's clinical spectrum, with only 250 cases described so far, remains largely unknown.

GI symptoms like feeding/swallowing difficulties, chronic constipation, and GERD are well known in SYS.

To our knowledge, chronic diarrhea, recurrent pancreatitis, and mechanical complications, such as late-onset pyloric stenosis and intussusceptions, have not been previously reported in these patients.

Update, few anecdotical cases of recurrent intussusceptions and food allergy (FA) have been reported (4,5). Furthermore, food-induced pancreatitis have been also described (6), although the exact underlying pathogenetic mechanism remains unknown.

To our knowledge, this is the first reported case of SYS and concomitant FA, for example, cow's milk allergy, responsive to an aminoacid-based formula. We speculate that GI tract inflammation, secondary to FA, may have caused chronic diarrhea, recurrent pancreatitis, and also mechanical complications (pyloric stenosis and recurrent intussusceptions) as a result of altered intestinal motility.

Food hypersensitivity may explain the patient's broad GI symptoms/signs and histological features both. In fact, food-induced chronic enteropathy is part of differential diagnosis of duodenal villous atrophy without serologic makers for CD (7). The resolution of symptoms after starting an aminoacidic formula supports this hypothesis.

The extent of hydrolysis is a key point to consider for the choice of the right formula in children with neurological impairment and GI symptoms, that may be due to the neuropathy itself, but also to a concomitant food hypersensitivity.

Actually, many existing formulas intended for enteral nutrition are composed of partially hydrolyzed cow's milk proteins to support impaired motility and digestive functions in children with neurologic impairment (8). However, as partially hydrolyzed peptides can elicit an allergic reaction, semi-elemental formulas are not suitable for children with cow's milk allergy.

Diagnostic test for FA, based on a detailed clinical history, may be considered in the diagnostic work-up of children with neuropathy and persistent GI symptoms. In case of high-suspicious of FA, as in our case, an exclusion diet should be considered to relief symptoms.

Our case suggests considering food allergies in the presence of feeding difficulties, accompanied to other GI symptoms, as in our case, and/or in the presence of atypical and more rare GI manifestations, not settling for previous knowledge, especially when dealing with rare diseases as SYS. On the other side, sharing acquired knowledge about rare diseases and expanding current knowledge represents a valid aid for patients, families, and clinicians treating them.

ACKNOWLEDGMENTS

We would like to thank our patient and his family for allowing us to share his medical story.

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