Recurrent Achalasia in a Child with Williams-Beuren Syndrome

Pereza, Nina; Barbarić, Irena; Ostojić, Saša; Čače, Neven; Kapović, Miljenko

Source / Izvornik: **Collegium antropologicum, 2011, 35, 941 - 944**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:301634

Coll. Antropol. **35** (2011) 3: 941–944
Case report

Recurrent Achalasia in a Child with Williams-Beuren Syndrome

Nina Pereza[1], Irena Barbarić[2], Saša Ostojić[1], Neven Čače[3] and Miljenko Kapović[1]

[1] University of Rijeka, School of Medicine, Department of Biology and Medical Genetics, Rijeka, Croatia
[2] University of Rijeka, Rijeka University Hospital Centre, Department of Gastroenterology and Nephrology, Clinics for Children's Diseases, Rijeka, Croatia
[3] University of Rijeka, Rijeka University Hospital Centre, Department of Cardiopulmology, Clinics for Children's Diseases, Rijeka, Croatia

A B S T R A C T

Williams-Beuren syndrome is a multysistem genetic disorder caused by the 1.6Mb hemizygous deletion involving the elastin gene in the region q11.23 of chromosome 7. The phenotype of Williams-Beuren syndrome is extremelly variable but the most common findings include cardiovascular disease, distinctive facies, mental retardation, a specific congitive profile, endocrine abnormalities, growth retardation and connective tissue abnormalities. Although gastrointestinal difficulties are one of the most constant and prominent finding of the syndrome, including gastro-esophageal reflux (GER), poor suckling, vomiting, constipation, prolonged colic, rectal prolapse, inguinal, umbilical and hiatal hernia, there have been no reports of achalasia in association with Williams-Beuren syndrome in the literature. We present the case of a boy with Williams-Beuren syndrome, achalasia and recurrent postoperative stenosis of the cardia. After Heller myotomy, the boy developed severe restenosis of the cardia with abundant adhesions which repeated after every treatment, five times in periods shorter than one month. Eventually, he developed GER, errosive gastritis and hiatal hernia which led to severe malnutrition and failure to thrive. Although the genetic defect causing Williams-Beuren syndrome might not be the direct cause of achalasia we suggest that the frequent development of severe restenosis of cardia due to tight adhesions could be the consequence of elastin gene haploinsufficiency and altered structure and function of elastic fibers in esophageal connective tissue. This case highlights the importance of early diagnosis of esophageal motor disorders in childhood which should be included in the differential diagnosis when a child with Williams-Beuren syndrome presents with dysphagia and/or regurgitation.

Key words: *elastin, failure to thrive, genetics, microdeletion*

Introduction

Williams-Beuren syndrome (WBS) is a multisystem disorder caused by the 1.6Mb hemizygous deletion involving the region q11.23 of chromosome 7. It occurs in approximately 1 in 10.000 live births and affects both genders equally[1,2]. The phenotype of WBS is extremelly variable but the most common findings include cardiovascular disease known as elastin arteriopathy (supravalvular aortic stenosis, peripheral pulmonary artery stenosis), distinctive facies, mild to moderate mental retardation, a specific congitive profile, endocrine abnormalities (idiopathic hypercalcemia, hypothyroidism), growth retardation and connective tissue abnormalities[1–4]. Although gastrointestinal difficulties, including gastro-esophageal reflux (GER), poor suckling, vomiting, constipation, inguinal, umbilical and hiatal hernia are a common finding in children, especially infants with WBS[1], to our knowledge, this is the first reported case in the literature of achalasia in association with WBS.

Case Report

A 13-month-old boy presented with a history of regurgitation of feeds after every meal, dysphagia, food rejection and failure to thrive. He is the first child of healthy, non-related parents. Pregnancy and delivery were un-

Received for publication June 7, 2010

eventful. Birth weight was 2880g, birth length 48cm, occipitofrontal circumference 35cm. Based on typical facial appearence and peripheral pulmonary artery stenosis, the patient was previously diagnosed with WBS. The diagnosis was confirmed by karyotype and fluorescent in situ hybridization (46,XY.ish del(7)(q11.23q11.23)(ELN-)).

On examination the patient was afebrile, malnourished and weighed 8300g ($p<5$). Although he gained weight normally during the first 5 months, difficulties in feeding, including poor suckling, food rejection and vomiting, were present since birth. After mixed food was introduced at the age of 4 months, the boy frequently presented with abdominal colics and refused to chew and eat solid food. Dysphagia and frequent regurgitation commenced when he was 6-months-old and worsened until he was vomiting after each meal. After admission to Clinics for children's diseases at the Clinical hospital centre Rijeka, examination by barium esophagography (BE) showed a long spastic reaction of the cardia with significant antiperistalsis, a prolonged timed barium swallow (>5 minutes) and failure of relaxation of the lower esophageal sphincter (LES) with swallowing. During the following upper gastrointestinal endoscopy (UGE), the LES failed to open spontaneously on air insufflation, but the endoscope passed without resistance. Diagnosis of achalasia was made based on BE and UGE findings and was confirmed using manometric studies. Nifedipine was introduced and the patient's symptoms improved transiently but returned within the following 4 weeks. The patient was operated upon at the age of 16 months using Heller myotomy by laparotomy but only 1 month after surgery he was rehospitalized due to severe vomiting, food rejection and dehidration. Repeat UGE revealed that he had developed a severe stenosis of the cardia with dense adhesions. There were no signs of hypertrophic musculature. The patient was operated upon again using adhesiolysis by laparotomy. The symptoms improved and the boy was released home.

Another month later the boy started to reject food again, refused to swallow, and developed projectile vomiting after every meal. Examination by UGE revealed a severe restenosis and adhesions of the cardia with a baggy dilatation of the distal third of esophagus (2cm above the cardia). This time the stenosis was treated with balloon dilatation and the condition improved. However, the boy presented with the same symptoms, UGE and contrast esophagogram findings 3 times during the following 3 months and was treated with 3 sessions of balloon dilatations during this period. His symptoms had improved after each dilatation but returned soon after.

At the age of 1 year and 8 months the symptoms repeated again. This time BE revealed a dilated esophagus in the middle third with impaired tonic activity, aperistalsis and a mid-size hiatal hernia with delayed barium clearance time. UGE showed that there was no opstruction or stenosis and LES was widely open. Multiple biopsies revealed hypertrophic squamous epithelium, elongation of subepithelial papillae of the lamina propria (60% of the thickness of the mucosa) with mononuclear inflammatory infiltrate and erythrocytes. He was diagnosed with GER and erosive gastritis grade 2. Pantoprasol was included in therapy to which the boy responded well. The boy is now 6-years-old and did not require further hospitalizations but still has difficulties chewing and swallowing solid food.

Discussion

Gastrointestinal difficulties are one of the most constant and prominent features of WBS and can be caused by hypercalcemia, haploinsufficiency of the elastin gene or sensory defensiveness. Infants with WBS have a high frequency of feeding problems, including poor suckling and swallowing, vomiting, prolonged colics, rectal prolapse, inguinal and umbilical hernia and textural aversion leading to failure to thrive[2–5]. There is a considerable sub-cohort of WBS patients whose diagnosis can be difficult because they are not affected by clinically evident cardiovascular disease and are associated with mild facial dysmorphisms. Gastointestinal anomalies and failure to thrive can often be the presenting signs in these children.

The common digestive symptoms of WBS, including frequent vomiting, regurgitation of feeds, dysphagia, prolonged colic and failure to thrive can be the presenting symptoms of achalasia, an uncommon condition characterized by the absence of esophageal peristalsis together with increased resting pressure and failure of relaxation of the LES. Achalasia affects both genders with a prevalence of 1:100.000 and only 4–5% of these are described in children[6,7]. The widely accepted mode of achalasia treatment in children is Heller myotomy with or without a fundoplication using an open or a laparoscopic approach. Complications in the pediatric population treated with Heller myotomy are low and in 90% of patients good to excellent longterm results have been reported while recurrence of symptoms is uncommon[8–12]. Postoperative complications in our case are unique, since the restenosis of the cardia with abundant adhesions repeated five times in periods shorter than one month while the usual mean for recurrence of symptoms is 13 months[8].

The etiology of achalasia, as a primary esophageal motor disorder, is still unknown although infectious, autoimmune and genetic factors have been implicated in its pathogenesis[13]. Esophageal achalasia has been previously described in other genetic syndromes, such as Down syndrome where its high prevalence is attributed to the aforementioned factors, including increased susceptibility to infections, organ-specific autoimmunity and possible genetic predisposition to alterations in the enteric nervous system[14]. However, none of these factors can adequatly explain the occurence of achalasia and its recurrence in our WBS patient since they are not a common characteristic of the syndrome.

The WBS critical region on chromosome 7 includes the elastin gene which contributes to the well defined connective tissue abnormalities[15]. Although elastic fibers

are important constituents of many tissues where they serve as a network responsible for the physiological elasticity of the organs, little is known about their phenotype in patients with WBS. Histopathological features of elastin structure are well defined only for the arterial tree and have not been determined for most other tissues. It has been shown that the hemizygosity of the elastin gene leads to reduced deposition of elastin in elastic fibers and an altered elastic fiber ultrastructure in dermal layers of the skin[16]. It might be possible that there might be an altered organization of elastic system components in esophageal tissue and that the connective tissue abnormalities due to elastin haploinsufficiency might be the link between recurrent development of abundant adhesions and restenoses of the cardia in our case. Other gastrointestinal disorders in children with WBS, such as hernias and diverticulosis, are postulated to be due to defects in the elastin gene and encoded protein, resulting in reduced elasticity of the bowel wall, which is normally required to withstand the intraluminal colonic pressures exerted by stools and peristalsis[17].

The effect of elastin deficiency on postoperative wound healing is also not defined in WBS syndrome. It might be possible that a genetic susceptibility to altered postoperative wound healing in this well defined connective tissue disorder could explain severe restenoses after esophageal surgeries and balloon dilatations in our case. However, it is also possible that achalasia in our case could be the consequence of another, unrelated genetic defect aside from 7q11.23 microdeletion.

Our case points to the importance of further studies on the role of elastin in postoperative wound healing in WBS and altered organization of elastic system components in various organs.

Conclusion

To our knowledge, we report the first patient with WBS whose clinical course was complicated by recurrent achalasia cardia. The genetic defect causing WBS might not be the direct cause of achalasia, because this is the first known reported case of esphageal achalasia occurring in association with WBS. However, we suggest that the frequent development of severe restenosis of the cardia due to tight adhesions could be the consequence of elastin gene haploinsufficiency and disturbed structure and function of elastin in esophageal connective tissue. Our case points to the importance of further studies on the effect of elastin in postoperative wound healing in WBS as well as altered organization of elastic system components in various organs. This case also highlights the importance of early diagnosis of esophageal motor disorders which should be included in the differential diagnosis when a child with WBS presents with dysphagia and/or regurgitation. The proper and timely diagnosis is extremely important to prevent complications which could increase the risk for operative and postoperative complications.

REFERENCES

1. DONNAI D, KARMILOFF-SMITH A, Am J Med Genet, 97 (2000) 164. — 2. POBER BR, N Engl J Med, 362 (2010) 239. — 3. AMERICAN ACADEMY OF PEDIATRICS, COMMITTEE ON GENETICS, Pediatrics, 107 (2001) 1192. — 4. MORRIS CA, DEMSEY SA, LEONARD CO, DILTS C, BLACKBURN BL, J Pediatr, 113 (1988) 318. — 5. POBER BR, MORRIS CA, Am J Med Genet C Semin Med Genet, 145C (2007) 280. — 6. MAYBERRY JF, Gastrointest Endosc Clin N Am, 11 (2001) 235. — 7. OLSEN AM, HARRINGTON SW, MOERSCH HJ, ANDERSEN HA, J Thorac Surg, 22 (1951) 164. — 8. ASKEGARD-GIESMANN JR, GRAMS JM, HANNA AM, IQBAL CW, TEH S, MOIR CR, J Pediatr Surg, 44 (2009) 909. — 9. VAOS G, DEMETRIOU L, VELAORAS C, SKONDRAS C, Pediatr Surg, 43 (2008) 1262. — 10. KARNAK I, SENOCAK ME, TANYEL FC, BÜYÜKPAMUKÇU N, Eur J Pediatr Surg, 11 (2001) 223. — 11. MORRIS-STIFF G, KHAN R, FOSTER ME, LARI J, Ann R Coll Surg Engl, 79 (1997) 432. — 12. LELLI JL JR, DRONGOWSKI RA, CORAN AG, J Pediatr Surg, 32 (1997) 338. — 13. PARK W, VAEZI MF, Am J Gastroenterol, 100 (2005) 1404. — 14. ZÁRATE N, MEARIN F, HIDALGO A, MALAGELADA JR, Am J Gastroenterol, 96 (2001) 1718. — 15. EWART AK, MORRIS CA, ATKINSON D, JIN W, STERNES K, SPALLONE P, STOCK AD, LEPPERT M, KEATING MT, Nat Genet, 5 (1993) 11. — 16. URBÁN Z, PEYROL S, PLAUCHU H, ZABOT MT, LEBWOHL M, SCHILLING K, GREEN M, BOYD CD, CSISZÁR K, Pediatr Dermatol, 17 (2000) 12. — 17. GARCIA MA, KLING KM, NEWBURY RO, HUANG JS, J Pediatr Gastroenterol Nutr, 48 (2009) 233.

N. Pereza

University of Rijeka, School of Medicine, Department of Biology and Medical Genetics, B. Branchetta 20, 51000 Rijeka, Croatia
e-mail: nina.pereza@xnet.hr

AHALAZIJA U DJETETA SA WILLIAMS-BEUREN SINDROMOM

S A Ž E T A K

Williams-Beuren sindrom je multisistemski genetički poremećaj koji nastaje zbog hemizigotne delecije regije q11.23 kromosoma 7 veličine 1,6Mb koja uključuje gen za elastin. Fenotip Williams-Beuren sindroma iznimno je varijabilan, ali najčešća klinička obilježja uključuju kardiovaskularne poremećaje, specifičnu dismorfiju lica, mentalnu retardaciju, specifični kognitivni profil, abnormalnosti endokrinog sustava, zaostajanje u rastu i abnormalnosti vezivnog tkiva. Iako su gastrointestinalni poremećaji jedan od najčešćih i najizraženijih kliničkih obilježja Williams-Beuren sindroma, uključujući gastroezofagealni refluks (GER), nenapredovanje na težini, opstipaciju, abdominalne kolike, prolaps rektuma i hernije, u literaturi nije opisana povezanost između ahalazije i Williams-Beuren sindroma. U ovom prikazu slučaja opisali smo dječaka sa Williams-Beuren sindromom, ahalazijom i učestalom postoperativnom stenozom kardije. Nakon Hellerove miotomije, pacijent je razvio tešku stenozu kardije sa obilnim čvrstim priraslicama koje su se ponavljale nakon svake terapije, sveukupno 5 puta u razdobljima kraćim od mjesec dana. Pacijent je konačno razvio GER, erozivni gastritis i hijatalnu herniju koji su doveli do daljnje malnutricije i nenapredovanja na težini. Iako genetički poremećaj koji uzrokuje Williams-Beuren sindrom možda nije izravni uzrok ahalazije, moguće je da je učestali razvoj restenoza kardije zbog obilnih priraslica posljedica haploinsuficijencije gena za elastin i promjenjene strukture i funkcije elastičnih vlakana u vezivnom tkivu jednjaka. Ovaj prikaz slučaja ukazuje na važnost rane dijagnoze motornih poremećaja jednjaka u djetinjstvu koji moraju biti uključeni u diferencijalnu dijagnozu u djece sa Williams-Beuren sindromom koji imaju simptome disfagije i/ili regurgitacije.