European Journal of Medical Genetics 54 (2011) 209–213

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Original article

Severe lysosomal storage disease of liver in del(1)(p36): A new presentation

Motti Haimi [a,*], Theodore C. Iancu [c,d], Lisa G. Shaffer [e], Aaron Lerner [b,d]

[a] Children's Health Center, Clalit Health Services, ArmonTower, Haifa, Israel
[b] Pediatric Gastroenterology and Nutrition Unit, Carmel Medical Center, Haifa, Israel
[c] Pediatric Research and Electron Microscopy Unit, Israel
[d] Rappaport Faculty of Medicine, Technion, Haifa, Israel
[e] Signature Genomic Laboratories, Spokane, WA, USA

ARTICLE INFO

Article history:
Received 20 April 2010
Accepted 30 November 2010
Available online 9 December 2010

Keywords:
Liver
Monosomy 1p36
Lipolysosomes
Lipid storage disease
Hyperphagia

ABSTRACT

1p36 deletion is the most common terminal deletion syndrome with an estimated occurrence of 1:5000 live births. The deletion is of variable size. It usually involves less than 10 Mb in the 1pter-1p36.23 interval. Variability of the phenotype is partially related to the extent of the deletion. Some children with a 1p36 deletion were reported with obesity and hyperphagia, raising the question of possible phenotypic overlap with Prader–Willi syndrome. Correlation between presence of obesity and the size of the deletion has only been documented in one case. We report a 11-year-old girl with 1p36 deletion and the classical dysmorphological features. In late infancy, she developed an uncontrolled voracious appetite, overweight, truncal obesity and elevated serum transaminases. Liver biopsy disclosed severe steatosis. The hepatocytes contained accumulation of lipofuscins. Lipolysosomes were abnormally numerous and extremely enlarged. These features have not been previously reported in 1p36 deletion. Oligonucleotide-based microarray analysis showed a subtelomeric 2.2 Mb deletion at 1p36.33p36.32. This suggests that this chromosome segment is a critical region for obesity and hyperphagia. The accumulation in the liver with abnormal ultrastructure may be an additional feature of this form of syndromal obesity. 1p36 deletion syndrome should be considered in patients with obesity, hyperphagia and liver fat accumulation.

1. Introduction

1p36 deletion syndrome – or del(1)(p36) – is one of the commonest chromosome deletion syndromes, with an estimated incidence of 1 in 5000 to 10,000 live births [1–3]. The deletion is usually telomeric and smaller than 10 Mb. The proximal breakpoints vary from bands 1p36.13 to 1p36.33. Some patients show interstitial (between 1p36.23 and 1p36.11) which may present with a distinct phenotype [11].

Clinically, the most prevalent phenotypic features of del(1)(p36) are developmental delay [4], variable but often moderate to severe mental retardation, epilepsy, growth retardation, microcephaly, behavioral difficulties and self-injury. Hypotonia and feeding problems with oropharyngeal dyspraxia are frequent [5]. The dysmorphic phenotype includes: large anterior fontanels, microcephaly, brachycephaly, frontal bossing, deep-set eyes, short narrow and slanting palpebral fissures, flat nose and nasal bridge [6–8]. Midface hypoplasia, dysplastic, low-set and small ears, a small mouth with down-turned corners and a pointed chin-also have been noted. Distinguishing findings were a large or late closing anterior fontanel and facial asymmetry [9,5]. Sensorineural or conductive hearing problems [5], heart defects (cardiomyopathy and structural heart defect) [7], ocular abnormalities, hypothyroidism [5], redundant nuchal skinfolds [12], congenital spinal stenosis [12], telangiectatic skin lesion, hyperpigmented macules and polydactyly [14] – were noted in some patients [5]. Some children with a 1p36 deletion or a translocation breakpoint in this chromosome band have developed neuroblastoma [5]. Some cases have been reported with gastrointestinal (GI) complaints including constipation, reflux, and general GI discomfort [7]. Intestinal malrotation and annular pancreas were also noted [15].

Interestingly, the association of obesity and hyperphagia with the 1p deletion syndrome in childhood was reported in a few cases only [13–17]. Their clinical presentation has been suggested to be similar to Prader–Willi syndrome (PWS) [17]. Nevertheless, to the best of our knowledge, the previous cases of obese children associated with del(1p36) did not demonstrate any liver disease and more specifically, severe lysosomal storage disease was never described – or overlooked – in the syndrome.

* Corresponding author. Fax: +972 4 8351650.
E-mail address: mottiha@clalit.org.il (M. Haimi).

1769-7212/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmg.2010.11.012

2. Patient report

2.1. Clinical report

The patient, a girl, was the second child of healthy parents, both born in Israel. The mother is of Kurdish–Tunisian origin, and the father of German–Polish–Moroccan origin. Her older sister and her younger brother were healthy.

During pregnancy, she was noted to be small for gestational age. Delivery occurred after 37 weeks. Birth weight was 2160 g (3rd centile); length was 46 cm (10th centile) and head circumference was 31.5 cm (<3rd centile) (Fig. 1). At the age of 4 months she presented with CMV pneumonitis. Since the age of 6 months she developed mild motor delay and hypotonia. She was wrongly diagnosed as having cerebral palsy (C.P) and was followed in a neurological clinic. Brain CT was normal. Brain MRI at the age of 3 years showed mild dilatation of the frontal subarachnoidal spaces.

The child's development was delayed: She lifted her head at the age of 1.5 months, and was not able to put weight on her arms before 4.5 months. At 8 months she showed a clear developmental delay corresponding to a developmental age of 3–4 months. She was able to turn from back to side only at age of one year and nine months. She started walking only at 4 years of age. At the age of 2 years, dysmorphologic features were noted including flat occiput, mild hypoplasia of the midface, deep-set eyes, downslanting palpebral fissures, short philtrum, small ears, and short 4th toes. There was mild strabismus and the eyebrows were low-set, flat and straight. There were neither vision nor hearing impairments. She had mild to moderate mental retardation. Metabolic evaluation was normal. Bone x-rays were also unremarkable. Standard karyotype of the girl appeared normal (46,XX).

Since the age of 4 years she became over-weighted (Figs. 2 and 3). At the age of 9 years she developed premature puberty and hirsutism. Her first menstruation appeared at age 11 years. Endocrinological evaluation was normal. During the last 9 months she developed an uncontrolled voracious appetite and overweight, mainly in the abdominal area (Fig. 4a and b). She demonstrated behavioral problems – mainly involving food craves. At the age of 9 years – her weight was 40 kg, height – 134.5 cm (BMI: 22.3); at the age of 10 years – weight was 45 kg, height – 138 cm (BMI : 23.6), and at the age of 11 years – her maximal weight was 54 kg (+5 SD), height – 143 cm (+0.5 SD), BMI: 26.4. Liver size was normal. Biochemical evaluation revealed elevated liver enzymes (SGOT-272 U/L; SGPT-269 U/L; GGT-181 U/L; LDH-968 U/L; ALK. PHOS-318 U/L). Albumin was 2.94 g/dl, PT-17.9 s (60%), APTT-1.22, fibrinogen was normal. Lipid profile included normal cholesterol levels (125 mg/dl) and normal triglycerides (111 mg/dl). Echocardiogram was normal. An extensive laboratory workup for hepatitis was normal. The girl was treated by special low-fat diet. The response was lowering of the weight, although eating craves were still a problem. She reached a weight of 47 kg (BMI-24) nine months after the beginning of the diet.

2.2. Pathological investigations

Liver biopsy disclosed a severe fat storage disease of the liver with micro and macrovesicular steatosis, without abnormalities in

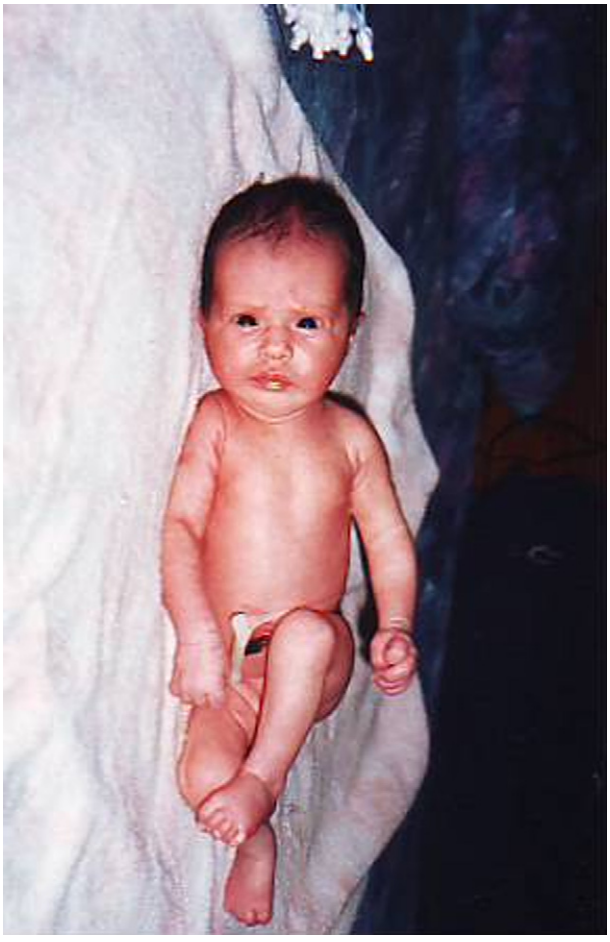

Fig. 1. The girl at birth.

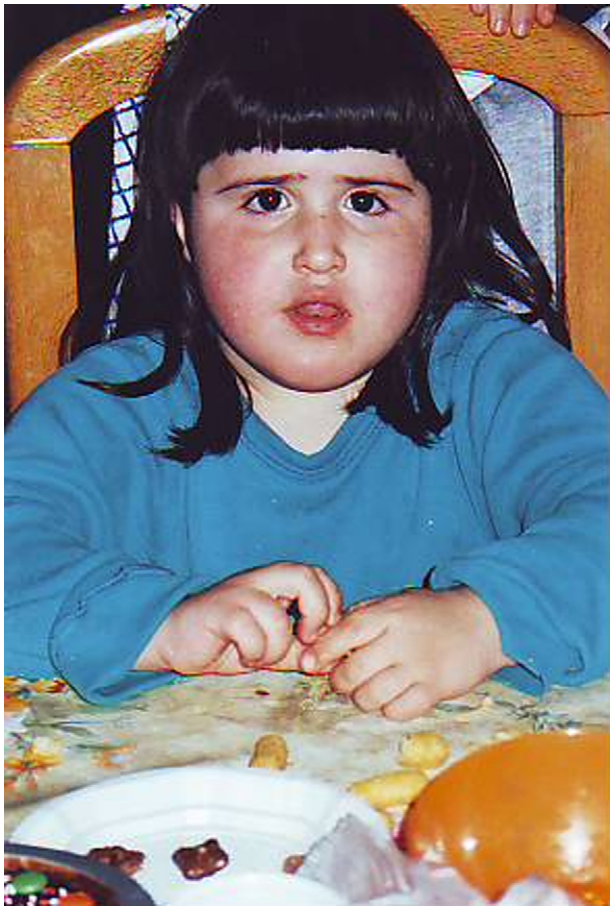

Fig. 2. The girl at age of 4 years.