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13q Deletion in a Girl Contributing to Antenatal Stroke, Insulin Resistance and Lymphedema Praecox: Expanding the Clinical Spectrum

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Abstract

The phenotypic description of 13q deletion syndrome is dependent on the location and size of the deleted segment. The syndrome is divided into three groups based on the location of the deletion relative to chromosomal band 13q32. Groups 1 (proximal to q32) and 2 (including q32) have shown distinctive phenotypes including mental retardation and growth deficiency, whereas group 3 (q33-34 deletion) is defined by the presence of mental retardation but usually the absence of major malformations. 13q deletion has been associated with factor VII and X deficiencies. We report a 10-year-old girl with cytogenetically detectable 13q33.3-34 deletion (group 3) and antenatally detected factor VII deficiency leading to stroke *in utero* and consequently hemiplegia at birth. This is the first report of a 13q deletion associated with factor VII deficiency leading to antenatal stroke. Our patient also developed rapidly progressive obesity and lymphedema praecox which have not been previously reported with 13q deletion.

Keywords: 13q deletion; Neonatal stroke; Obesity; Lymphedema praecox

Introduction

13q deletion is an example of a rare chromosomal deletion syndrome and about 180 cases have been reported in the medical literature. The clinical features associated with 13q deletion include moderate to severe mental and growth retardation, craniofacial dysmorphisms, hand and foot anomalies, brain, heart and kidney defects [1, 2]. A translocation or deletion involving the region 13q33.1-34 results in low concentrations of coagulation factors [3]. Clinically this may or may not be associated with bleeding. Sub-clinical factor VII deficiency associated with a 46, XY, t(13;Y)(q11;q34) translocation and probable deletion of a terminal segment of 13q manifesting as elevated prothrombin time (PTT) has been reported [4].

We report an unusual presentation of 13q deletion. In our child factor VII assays showed a level of less than 3 IU/dL *in utero* resulting in intracranial hemorrhage. However factor VII levels increased spontaneously without treatment and although she continued to have an abnormal clotting profile with a raised PTT, there have been no symptoms of bruising or bleeding in the postnatal period.

Case Report

A baby girl was born at 39 weeks to non-consanguineous parents by emergency section for fetal distress in a good condition with a birth weight of 2.3 kg. The baby was noted to have a paucity of movement of the left side of the body and was diagnosed to have left sided hemiplegia subsequently. Antenatally, an ultrasound scan done at 22 weeks showed right ventriculomegaly with caudothalamic groove atrophy, which was thought to represent earlier hemorrhage. Antibody titers for toxoplasma, rubella, cytomegalovirus and herpes infections were negative. The fetal blood sampling showed a normal platelet count. Maternal platelet counts were normal and there was no history of maternal intake of aspirin, antiplatelet medications, anticoagulants or any other drug ingestion. Functional factor VII assay performed antenatally, demonstrated a factor VII level of less than 3 IU/dL (normal range > 50 IU/dL). Cytogenetic analysis of the amniotic fluid revealed a terminal deletion of chromosome 13 with a breakpoint at 13q33.3 (46XX del (13) (q33.3) ish del (13) (q33.3) (wcp13+, D13S327-)). The genotype was confirmed in the postnatal period. A probe for the subtelomeric region of chromosome 13 (D13S327) demonstrated a small distal long arm deletion in the anomalous chromosome. A cytogenetic analysis performed on both the parents did not reveal any abnormalities.

Functional factor assays performed in the postnatal period

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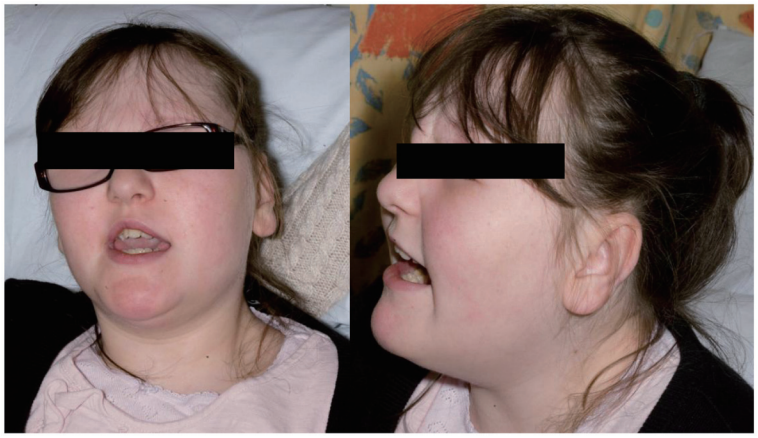

Figure 1. Dysmorphic features include prominent forehead, triangular face, high nasal root, thin upper lip, downturned corners of the mouth, and a small, pointed chin.

showed an increase in the factor VII level to 8 IU/dL from an antenatal assay level of less than 3 IU/dL. At 3 months of age her factor VII levels spontaneously rose to 35 IU/dL. There was no history of bruising epistaxis or bleeding during childhood. The factor X assay was subsequently within the normal range.

The dysmorphic features comprised of prominent forehead, triangular face, almond shaped eyes with upslanting palpable fissures, mild ptosis, high nasal root, hypoplastic alae nasi with prominent columella, thin upper lip, downturned corners of the mouth, and a small pointed chin (Fig. 1). She also developed swelling of both lower limbs, which progressively increased with time. A series of abdominal ultrasounds showed no evidence for obstruction of the inferior vena cava. A clinical diagnosis of lymphedema praecox was made.

She was noted to be failing to thrive due to severe gastroesophageal reflux. Nissen's fundoplication was performed at 8 years of age. The surgical procedure was not associated with abnormal bleeding. She was subsequently noted to gain excessive weight. At 10 years of age, the patient's body mass index (BMI) was 29.5 (+3.07 standard deviation score) with microcephaly (below 0.4th centile).

Endocrine investigations to identify the cause of obesity including a 24-h glucose and cortisol profile, urinary steroid profile, adrenal androgens, thyroid function tests, and baseline pituitary function tests were within normal limits. An oral glucose tolerance test showed evidence of insulin insensitivity (Table 1) with the peak plasma insulin level of 170 mU/L at 30 min and peak plasma glucose of 124 mg/dL. She was commenced on metformin at a dose of 500 mg twice daily and follow-up of 12 months did not reveal any significant benefit.

Discussion

Partial deletions in chromosome 13q lead to variable phenotypes based on the size and position of the deleted region [5]. While distal deletions are closely associated with severe phenotypes, proximal deletions tend to cause fewer major anomalies, with the exception of retinoblastoma [6].

In our patient, the deletion occurred before the coding region for factor VII, with the break point occurring at 13q33.3 (Table 2). This possibly led to antenatally detected very low levels of factor VII leading to intracranial hemorrhage. This is the first case report of 13q deletion associated with factor VII deficiency leading to antenatal stroke. Interestingly the factor VII levels improved spontaneously in the postnatal period. The reason for this fluctuation in the factor VII levels remains unclear. In addition to factor VII deficiency, the deletion of COL4A1 (OMIM 120130) and COL4A2 (OMIM 120090) genes, which have been mapped to chromosome 13q33.3-34 (Table 2) could have contributed to the hemorrhagic stroke in the antenatal period [7].

The human insulin receptor substrate 2 (IRS2) (OMIM 600797) is localized on chromosome 13q34 (Table 2). This gene encodes the IRS2, a cytoplasmic signaling molecule that mediates effects of insulin, insulin-like growth factor 1, and other cytokines [8]. Homozygous deletion of IRS2 in mice is known to generate insulin resistance which is particularly pronounced in liver [9]. Mice lacking IRS2 develop diabetes due to peripheral insulin resistance, failed hypothalamic regulation of appetite and β-cell insufficiency [10]. Our patient had a heterozygous deletion of IRS2 gene (Table 2) which we postulate

Table 1. Oral Glucose Tolerance Test (OGTT)

	-30 min	0 min	30 min	60 min	90 min	120 min	150 min	180 min
Glucose (mg/dL)	82	79	154	80	106	99	70	68
Insulin (mU/L)	13.7	14.6	170	59.5	92.9	72.6	30.7	14.7

Homeostasis model of assessment-insulin resistance (HOMA-IR): 2.8.

Table 2. Genes Mapping to Chromosome 13q33.3-34 (Ensembl/Biomart)

Gene name	Description	Band
EFNB2	ephrin-B2 (Source: HGNC Symbol; Acc:3227)	13q33.3
ARGLU1	arginine and glutamate rich 1 (Source: HGNC Symbol; Acc:25482)	13q33.3
FAM155A	family with sequence similarity 155, member A (Source: HGNC Symbol; Acc:33877)	13q33.3
LIG4	ligase IV, DNA, ATP-dependent (Source: HGNC Symbol; Acc: 6601)	13q33.3
ABHD13	abhydrolase domain containing 13 (Source: HGNC Symbol; Acc: 20293)	13q33.3
TNFSF13B	tumor necrosis factor (ligand) superfamily, member 13b (Source: HGNC Symbol; Acc: 11929)	13q33.3
MYO16	myosin XVI (Source: HGNC Symbol; Acc: 29822)	13q33.3
IRS2	insulin receptor substrate 2 (Source: HGNC Symbol; Acc: 6126)	13q34
COL4A1	collagen, type IV, alpha 1 (Source: HGNC Symbol; Acc: 2202)	13q34
COL4A2	collagen, type IV, alpha 2 (Source: HGNC Symbol; Acc: 2203)	13q34
RAB20	RAB20, member RAS oncogene family (Source: HGNC Symbol; Acc: 18260)	13q34
CARKD	carbohydrate kinase domain containing (Source: HGNC Symbol; Acc: 25576)	13q34
CARS2	cysteinyl-tRNA synthetase 2, mitochondrial (putative) (Source: HGNC Symbol; Acc: 25695)	13q34
ING1	inhibitor of growth family, member 1 (Source: HGNC Symbol; Acc: 6062)	13q34
LINC00346	long intergenic non-protein coding RNA 346 (Source: HGNC Symbol; Acc: 27492)	13q34
ANKRD10	ankyrin repeat domain 10 (Source: HGNC Symbol; Acc: 20265)	13q34
ARHGEF7	Rho guanine nucleotide exchange factor (GEF) 7 (Source: HGNC Symbol; Acc: 15607)	13q34
TEX29	testis expressed 29 (Source: HGNC Symbol; Acc: 20370)	13q34
RP11-65D24.2	HCG2045795; Uncharacterized protein (Source: UniProtKB/TrEMBL; Acc: Q5T400)	13q34
SOX1	SRY (sex determining region Y)-box 1 (Source: HGNC Symbol; Acc: 11189)	13q34
SPACA7	sperm acrosome associated 7 (Source: HGNC Symbol; Acc: 29575)	13q34
TUBGCP3	tubulin, gamma complex associated protein 3 (Source: HGNC Symbol; Acc: 18598)	13q34
ATP11A	ATPase, class VI, type 11A (Source: HGNC Symbol; Acc: 13552)	13q34
MCF2L	MCF.2 cell line derived transforming sequence-like (Source: HGNC Symbol; Acc: 14576)	13q34
F7	coagulation factor VII (serum prothrombin conversion accelerator) (Source: HGNC Symbol; Acc: 3544)	13q34
F10	coagulation factor X (Source: HGNC Symbol; Acc: 3528)	13q34
PROZ	protein Z, vitamin K-dependent plasma glycoprotein (Source: HGNC Symbol; Acc: 9460)	13q34
PCID2	PCI domain containing 2 (Source: HGNC Symbol; Acc: 25653)	13q34
CUL4A	cullin 4A (Source: HGNC Symbol; Acc: 2554)	13q34
LAMP1	lysosomal-associated membrane protein 1 (Source: HGNC Symbol; Acc: 6499)	13q34
GRTP1	growth hormone regulated TBC protein 1 (Source: HGNC Symbol; Acc: 20310)	13q34
ADPRHL1	ADP-ribosylhydrolase like 1 (Source: HGNC Symbol; Acc: 21303)	13q34
DCUN1D2	DCN1, defective in cullin neddylation 1, domain containing 2 (Source: HGNC Symbol; Acc: 20328)	13q34
TMCO3	transmembrane and coiled-coil domains 3 (Source: HGNC Symbol; Acc: 20329)	13q34
TFDP1	transcription factor Dp-1 (Source: HGNC Symbol; Acc: 11749)	13q34
ATP4B	ATPase, H+/K+ exchanging, beta polypeptide (Source: HGNC Symbol; Acc: 820)	13q34
GRK1	G protein-coupled receptor kinase 1 (Source: HGNC Symbol; Acc: 10013)	13q34
TMEM255B	transmembrane protein 255B (Source: HGNC Symbol; Acc: 28297)	13q34
GAS6	growth arrest-specific 6 (Source: HGNC Symbol; Acc: 4168)	13q34
RASA3	RAS p21 protein activator 3 (Source: HGNC Symbol; Acc: 20331)	13q34
CDC16	cell division cycle 16 (Source: HGNC Symbol; Acc: 1720)	13q34
UPF3A	UPF3 regulator of nonsense transcripts homolog A (yeast) (Source: HGNC Symbol; Acc: 20332)	13q34
CHAMP1	chromosome alignment maintaining phosphoprotein 1 (Source: HGNC Symbol; Acc: 20311)	13q34

to be the cause of insulin resistance. Our patient has mobility issues that reduce the calorie expenditure in addition to the behavioral difficulties that make calorie restriction very difficult. These factors in association with the genetic predisposition for insulin resistance due to IRS2 deletion possibly act together in contributing to the obesity.

Primary lymphedema (lymphedema praecox), a disorder causing persistent swelling in an extremity, is rare in childhood [11]. The influences of estrogen and inflammation are thought to be important etiologic factors in primary lymphedema [12]. This is the first case report of lymphedema praecox in association with 13q deletion. She did not have any other cause like trauma, illness, pelvic mass or surgery that could have contributed to the lymphedema. No genetic etiology for lymphedema praecox has been identified so far; hence the exact genetic link between 13q deletion and lymphedema is not clear.

Conclusion

While 13q deletion syndromes are well recognized, this is the first reported case report of antenatal, hemorrhagic stroke secondary to factor VII deficiency. In the index case, the deletion has occurred just before the coding region for factor VII leading to intracranial hemorrhage antenatally. A combination of genetic (deletion of IRS2) and environmental factors (diet and exercise) possibly contributes to the obesity and insulin resistance. This is the also first case report of lymphedema praecox in association with 13q deletion.

Competing Interests

None.

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