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Case Report

Hypopituitarism may be an Additional Feature of *SIM1* and *POU3F2* Containing 6q16 Deletions in Children with Early Onset Obesity

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Abstract

Over the past decades, 6q16 deletions have become recognized as a frequent cause of the Prader-Willi-like syndrome. Involvement of *SIM1* in the deletion has been linked to the development of obesity. Although *SIM1* together with *POU3F2*, which is located close to the *SIM1* locus, are involved in pituitary development and function, pituitary dysfunction has not been reported frequently in cases of 6q16.1q16.3 deletion involving both genes. Here we report on a case of a girl with typical Prader-Willi-like symptoms including early-onset hyperphagic obesity, hypotonia, short hands and feet and neuro-psychomotor development delay. Furthermore, she suffered from central diabetes insipidus, central hypothyroidism and hypocortisolism. Her genetic defect is a 6q16.1q16.3 deletion, including *SIM1* and *POU3F2*. We recommend searching for a 6q16 deletion in children with early onset hyperphagic obesity associated with biological signs of hypopituitarism and/or polyuria-polydipsia syndrome. The finding of a combined *SIM1* and *POU3F2* deletion should prompt monitoring for the development of hypopituitarism, if not already present at diagnosis.

Keywords: 6q16 deletion; *SIM1*; *POU3F2*; Prader-Willi-like syndrome; Hypopituitarism

Introduction

Prader-Willi-Syndrome (PWS), one of the most common genetic causes of early onset obesity, is characterized by neonatal hypotonia and feeding problems, as well as delayed neuro-psychomotor development and early childhood-onset hyperphagic obesity. In the absence of chromosome 15 abnormalities, this phenotype is called Prader-Willi-Like Syndrome (PWLS) and has been observed in deletions of chromosomes 1p, 2p, 3p, 6q, 9q, 10q and 12q and in different X-chromosome abnormalities, such as inversion and Xq deletions [1,2].

Frequently described chromosomal abnormalities in PWLS are 6q16 deletions. Haploinsufficiency of the Single-minded homolog 1 (*SIM1*) gene and the POU Domain, class 3, transcription factor 2 (*POU3F2*), located in respectively the 6q16.3 and 6q16.1 region, have been suggested to play a role in early-onset hyperphagic obesity both through hyperphagia and reduced energy expenditure [3-5]. *POU3F2* and *SIM1* act in a cascade for Arginine-Vasopressin (AVP), Thyrotropin-Releasing Hormone (TRH) and Corticotropin-Releasing Hormone (CRH) neuron differentiation in the supraoptic and paraventricular nuclei [6]. *Sim1* is a basic helix-loop-helix PAS transcription factor, involved in the development of the neurons of the supraoptic, paraventricular and anterior periventricular nuclei of the rodent hypothalamus, which produce the neuro-endocrine peptides oxytocin, AVP, CRH, TRH and somatostatin [6,7]. *Pou3f2* is highly expressed in the hypothalamus and is involved in the vasopressin, oxytocin and gonadadotropin releasing hormone expression in the rodent hypothalamus [8]. Based on their role in hypothalamic development, one would expect the occurrence of central diabetes insipidus and of some specific pituitary hormone deficiencies in children with a combined *SIM1* and *POU3F2* deficiency. We describe the clinical and hormonal findings in a 10 year old female child with a relatively small deletion of 6q16.1q16.3, containing the *SIM1* and *POU3F2* loci, who presented with early-onset hyperphagic obesity, central diabetes insipidus and secondary hypothyroidism and hypocortisolism.

Case Report

A 10 year old girl with early-onset hyperphagic obesity and mental retardation was seen at our endocrine clinic for additional endocrine investigations because of unexplained hypothyroxinemia and hypocortisolism.

Her parents were not consanguineous. Her father was known with persistent enuresis nocturna and his Body Mass Index (BMI) was 35.9 kg/m^2. Her mother had a gastric bypass at the age of 36 years, decreasing her BMI from 53.9 kg/m^2 to 25 kg/m^2. Her only brother and paternal grandparents had severe overweight as well.

She was born at 40 weeks of gestation with a normal birth weight (3.520 kg) and birth length (50.5 cm). Her psychomotor development was slightly delayed (sitting at 8 months and first words at 16 months). She presented with increasing behavioral problems since infancy (mood swings, intolerance to frustration, aggressiveness, emotional liability). Because of learning difficulties, she received special education (type 8 in the Flemish school system). She presented with hyperphagia and increasing body weight from the first year of life (Figure 1). From the age of four years, she had polydipsia (drinking more than 4 liters a day), polyuria and persisting enuresis nocturna.

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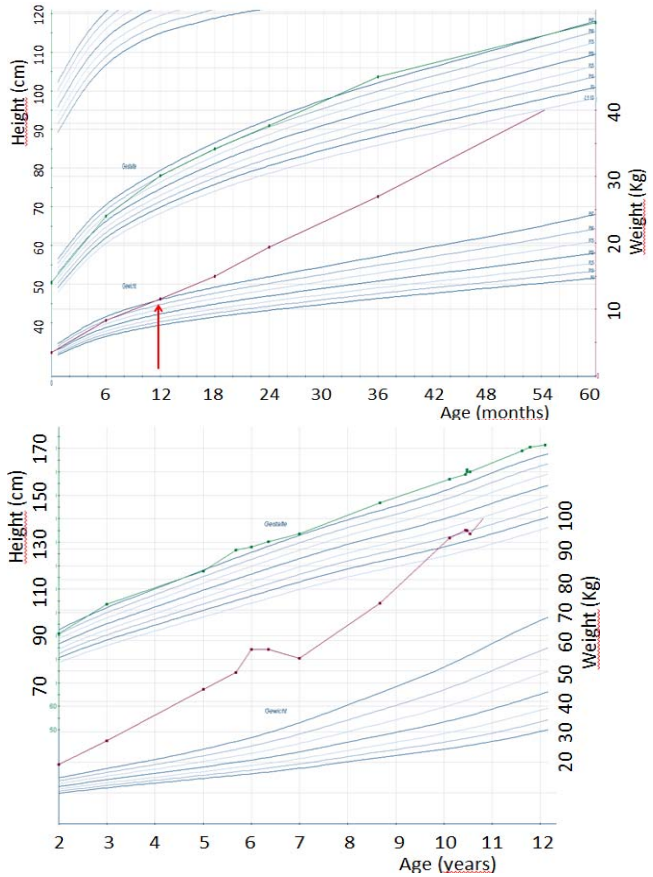

Figure 1: Growth curves showing onset (arrow) of obesity at age 12 months and continuing through childhood. Weight in red and length in green.

Previous hormonal and metabolic investigations between the age of 5 and 9 years showed a partial urinary concentration deficit during a water deprivation test (max urinary osmolality: 529mosm/kg H_2O), a low FT4 concentration of 9.3 pmol/L (reference range 12-22) with a normal TSH concentration, and insulin resistance on oral glucose tolerance testing (peak insulin 210 mIU/L). Previous genetic studies included a negative genetic screening for Prader-Willi Syndrome (PWS) and *MC4R* gene mutations. Brain MRI imaging was normal. Dietary counseling was given, but her overweight increased further. During follow-up, low FT4 (<10 ng/l) and cortisol concentrations (<60 µg/L) were found.

At the age of 10 years, physical presentation showed body weight of 96 kg (+7SD), height of 161 cm (+3SD), head circumference of 56 cm, BMI of 38.0 kg/m^2, blood pressure of 147/96 mmHg, pulse of 75 per minute, and Tanner stage A1P1M1. Vulva and clitoris were normal. Facial dysmorphic features including a flat midface, bilateral epicanthal folds and deep set eyes were noticed. She had hyperlordosis, bilateral genu valgus, short hands with tapering fingers, short feet and global hypotonia (Figure 2).

Bone age was 13 year (Greulich and Pyle method). Biological and hormonal investigations showed an increased uric acid (8.3 mg/L) and confirmed the low FT4 (9.4 pmol/L) and a low morning cortisol (47 µg/L), with a non-compensatory low- normal ACTH (13.8 ng/L) (Table 1). A TRH test showed a high TSH reserve (peak TSH 39.3 mIU/L with prolonged response). A CRH test showed an exaggerated ACTH response (65.8 ng/L). She was treated with oral levothyroxine 100 µg once daily and intranasal desmopressin 10 µg twice daily.

Figure 2: Photographs of the proband showing obesity, facial dysmorphic features (a flat midface, bilateral epicanthal folds and deep set eyes), hyperlordosis, bilateral genu valgus, short hands with tapering fingers and short feet.

Table 1: Hormonal results at the age of 10 years. TSH: Thyroid Stimulating Hormone, LH: Luteinizing Hormone, FSH: Follicle Stimulating Hormone, ADH: Anti-Diuretic Hormone, IGF-1: Insulin-Like Growth Factor 1, IGFBP-3: Insulin-Like Growth Factor Binding Protein 3, ACTH: Adrenocorticotropic Hormone, CBG: Cortisol Binding Globulin, DHEAS: Dehydroepiandrosteron Sulfate, SHBG: Sex Hormone Binding Globulin.

Analyte	Value	Reference range
TSH (mIU/L)	4.34	0.27-4.2
Free T4 (pmol/L)	9.4	12.0-22.0
LH (IU/L)	<0.1	0.10-11.9
FSH (IU/L)	0.9	2.11-11.1
Prolactin (mcg/L)	3.72	1.97-31.44
ADH (ng/L)	<0.4	<2.0
IGF-1 (mcg/L)	78	75-440
IGFBP-3 (mcg/L)	4208	2321-6195
ACTH (ng/L)	13.8	Jun-55
8 am Cortisol (mcg/L)	47.1	62-194
CBG (mg/L)	58.4	31.0-53.4
17-OH progesteron (mcg/L)	<0.1	0.21-1.4
DHEAS (mg/L)	0.3	0.34-2.80
Estradiol (ng/L)	<5	<40.5
Androstenedion (ng/L)	542	<2540
SHBG (mmol/L)	15.1	20.0-99.6

An array comparative genomic hybridization revealed a 6.9 Mb deletion on chromosome 6q (arr [hg 19] 6q16.1q16.3 (96,037,310-102,931,814)x1 dn). The genes with OMIM reference involved in the deletion include: *MANEA, FUT9, UFL1, FHL5, GPR63, NDUFAF4, KLHL32, MMS22L, POU3F2, FBXL4, FAXC, COQ3, PNISR, USP45, CCNC, PRDM13, MCHR2, SIM1, ASCC3 and GRIK2* [9]. Genetic investigation of the parents showed a normal array CGH.

Table 2: Clinical features and additional results of reported cases with a similar deletion (deletion of only 6q16.1q16.3 and including *SIM1* and *POU3F2*).

	Present case	Rosenfeld	Bonaglia	El Khattabi (case 2)	El Khattabi (case 3)	El Khattabi (case 4)	El Khattabi (case 7	El Khattabi (case 10)	El Khattabi (case 11)	El Khattabi (case 12	El Khattabi (case 13)	Wang	Le Caignec	Total	Total %
Sex	F	F	M	F	M	M	M	M	M	M	M	F	F	-	-
Age last evaluation	10y	3y	16y	17y	3,5y	23y	18y	8y	12y	10y	7y	7y	2y	-	-
Hypotonia	+	-	+	-	+	?	-	-	-	?	-	-	+	4/10	40%
Feeding problems	-	?	+	-	-	?	-	-	-	+	+	-	?	3/9	33%
Hyperphagia	+	?	?	+	+	?	?	+	?	?	-	-	-	4/7	57%
Obesity	+	+	overweight	+	+	+	+	+	overweight	overweight	overweight	+	-	8/13	62%
Onset	1y	?	?	?	?	?	?	?	?	?	?	?	-	-	-
Motor delay	+	+	+	+	+	?	+	+	+	+	+	+	+	12/12	100%
Mental retardation	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13	100%
Behavioural problems	+	-	+	+	+	?	+	-	-	?	+	-	+	7/11	64%
Facial dysmorphisms	+	-	+	+	+	+	+	+	+	+	+	+	+	12/13	92%
Round face	+	-	+	+	+	+	+	+	+	?	?	-	+	9/11	82%
Macrocephaly	-	+	-	+	+	-	-	-	-	+	+	+	-	6/13	46%
Bulbous nose	-	-	-	+	+	-	-	-	+	-	+	+	+	6/13	46%
Philtrum	-	-	short	marked	-	-	-	-	marked	-	long	-	prominent	-	-
Other	-	-	-	horizontal eyebrows	-	-	-	synophris	epicanthal folds	-	hyper-telorism	synophris	hyper-telorism	-	-
Acromicria	+	-	-	+	-	-	-	+	+	-	-	-	?	5/12	42%
Brain MRI	normal	small pituitary gland	enlarged third ventricle and hypertrophy of the left choroid plexus	?	?	?	?	normal	normal	ventriculo-megaly	normal	?	normal	-	-
Visus problems	-	-	?	severe myopia	-	-	myopia	astig-matism	hyper-metropia	nystagmus	-	-	strabismus, hyper-metropia	-	-
Pituitary dysfunction	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thyrotropin deficiency	+	+	?	?	?	?	?	?	?	?	?	?	?	-	-
Corticotropin deficiency	+	?	?	?	?	?	?	?	?	?	?	?	?	-	-
Central diabetes insipidus	+	?	? (enuresis +)	?	?	?	?	?	?	?	?	?	?	-	-
GH deficiency	-	?	?	?	?	?	?	?	?	?	?	?	?	-	-
Gonadotropin deficiency	prepubertal	?	?	?	?	?	?	?	hypo-gonadism	?	?	?	?	-	-

Discussion

A relatively small deletion of 6q16.1q16.3, involving both *SIM1* and *POU3F2*, was documented in a severely obese girl, who presented with the typical clinical features of PWLS, including hyperphagic early-onset obesity, hypotonia, short hands and feet and neuro-psychomotor development delay. Furthermore, she had several features that have been described previously in cases with 6q16 deletions, such as behavioral problems and non-PWS associated facial dysmorphic features, including a flat midface, bilateral epicanthal folds and deep set eyes. In addition, central diabetes insipidus, central hypothyroidism and hypocortisolism were observed.

In similar and other 6q deletions of variable sizes, whereas obesity has been a common finding, hormonal deficiencies have been rarely reported. Hypothyroidism of unclear origin has been described in five cases [10-12], evolving hypopituitarism, but of childhood onset, was documented in one case [13] and GH deficiency in another child [10]. In 2000, Holder and colleagues reported hypocortisolism in a patient with severe early onset obesity and a de novo balanced translocation between chromosomes 1p22.1 and 6q16.2 [3].

In most cases with a deletion of only the 6q16.1q16.3 region, as in our case, hyperphagia and obesity started in general at young age. In cases with only *POU3F2* deletions, hyperphagia was reported to develop after the onset of obesity [5]. Both central hypothyroidism and hypocortisolism was documented in our case. Growth hormone testing was not performed given the regular linear growth above percentile 97 and the normal serum IGF-1 concentration. In addition, *Sim1*-/-or *Pou3f2*-/-mouse do not have GHRH deficiency. Given the age of the patient, hypogonadotropic hypogonadism could not be assessed. Of the 12 cases with a 6q16.1q16.3 deletion including both *SIM1* and *POU3F2* previously reported in the literature [10-12,14,15], only one case had symptoms of hypogonadism [11] and

another case had enuresis nocturna [10], but none had been tested for either gonadotropin or ADH deficiency. None of the above 12 mentioned cases had a formal anterior or posterior pituitary function evaluation (Table 2, with arrayCGH results in supplementary Table S1). We suspect that behavioral problems of these children might have suspended detailed hormonal testing. In addition, increased drinking might have been attributed to their associated aberrant behavior. Furthermore, the pituitary hormones might have only been partially deficient, as was documented in our patient. We wanted to exclude AVP, TRH and CRH deficiency in our patient since, at least in mice, *Pou3f2* and *Sim1* act in a cascade for AVP, TRH and CRH neuron differentiation in the supraoptic and paraventricular nuclei [6,7]. In *Sim1* heterozygous mice, hypothalamic mRNA levels of TRH, AVP and CRH were 42, 41 and 30% respectively [16] and in *Pou3f2* heterozygous mice decreased AVP expression was evidenced [8]. Thus the combination of *POU3F2* and *SIM1* deficiency might explain the central diabetes insipidus, central hypothyroidism and central hypocortisolism in our patient. Based on our findings, it seems that hypopituitarism may be a feature of children with small 6q16 deletions, which might have been underestimated for several reasons up to now.

Based on this case report and review of literature, we recommend searching for a 6q16 deletion in children with early onset hyperphagic obesity associated with biological signs of hypopituitarism and/or polyuria-polydipsia syndrome. We suggest the use of molecular karyotyping with overlapping deletions to delineate critical regions, thereby improving genotype/phenotype correlation. On the other hand, the finding of a combined *SIM1* and *POU3F2* deletion should prompt monitoring for the development of hypopituitarism, if not already present at diagnosis.

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