CASE REPORT

Clinical and biological phenotype of a patient with familial glucocorticoid deficiency type 2 caused by a mutation of melanocortin 2 receptor accessory protein

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Abstract

Familial glucocorticoid deficiency (FGD) is a rare inherited disorder which may be caused by mutations in the ACTH receptor (melanocortin 2 receptor, MC2R) named FGD type 1 or by mutations in the MC2R accessory protein (MRAP) named FGD type 2. We report the case history of a male patient from birth until adulthood with FGD type 2, confirmed by a mutation of the *MRAP* gene.

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Introduction

Familial glucocorticoid deficiency (FGD, OMIM 202200) is a rare autosomal recessive disorder which comprises two types: type 1 (FGD type 1) caused by mutations in the adrenocorticotropin (ACTH) receptor (melanocortin 2 receptor, MC2R; OMIM 607397) (1–3); and type 2 (FGD type 2) produced by mutations of MC2R accessory protein (MRAP; OMIM 609196) (4). In addition, in some patients no mutations were demonstrated for MC2R or MRAP (5). Experimental evidence suggests that MRAP, previously identified as a protein expressed in differentiating adipocytes (6), is essential for MC2R expression and is critical in either the processing, trafficking, and/or function of MC2R (4). In the human, this protein is expressed in the adrenal cortex, pituitary, brain, testis, ovary, breast, thyroid, lymph node, skin, and fat (4), whereas MC2R is expressed in the adrenal cortex, the pituitary, skin, and fat tissue (7).

FGD is a potentially lethal disorder if not treated promptly. The clinical manifestations are due to glucocorticoid deficiency and are characterized by hypoglycemia (particularly in the neonatal period), jaundice, failure to thrive, hyperpigmentation of the skin, eczema, and increased susceptibility to infection (8). Low levels of plasma cortisol unresponsive to ACTH as well as high plasma ACTH and undetectable adrenal androgens are usually observed in the absence of mineralocorticoid deficiency (3). Glucocorticoid replacement is the recommended treatment. In the present case, we describe for the first time the clinical

and biological phenotypes from birth until young adulthood of a patient with FGD type 2.

Case history

The male patient was born at 39.5 weeks of gestation, to consanguineous parents of Caucasian origin, with a weight of 4.1 kg, a length of 49 cm, and a head circumference of 38 cm. Pregnancy was uncomplicated and APGAR score was 10 at 5 min of life. At 9 h of life, he presented an episode of hypoglycemia (dextrostix 0), apnea, and bradycardia. He was treated with i.v. glucose and was transferred 5 days later to the pediatric intensive care unit (PICU) for suspicion of congenital cardiopathy. Upon admission to PICU, his blood sugar was 34 mg/dl. During his stay in PICU, he acquired *Klebsiella* sepsis that responded successfully to antibiotic therapy and developed severe jaundice that required blood exchange transfusion. At 25 days of life, he was discharged from PICU with hypotonia thought to be due to kernicterus. At 1 month of life, he was again admitted for hypotonia and anemia. After a blood transfusion, he presented with seizures and bradycardia and was then transferred to our hospital for further investigation and management. No etiology of the seizures was found at that time: electroencephalogram, cerebral ultrasound and computed tomography, lumbar puncture as well as visual and auditory evoked potentials were normal. In particular, no electrolyte imbalance or hypoglycemia was identified. However, at day 15 of hospitalization, hypoglycemia (13 mg/dl) occurred again with hypotonia and

hypothermia. During a hypoglycemic challenge test induced by fasting, blood glucose dropped to 23 mg/dl after 3 h with concomitant unmeasurable plasma cortisol (<28 nM, normal range 260–540 nM). An i.v. ACTH challenge test (500 µg/m²) showed no rise in cortisol after 4 h supporting the diagnosis of ACTH resistance. Plasma renin activity was normal (4 ng/ml per h, N: ≤5). In addition, ACTH insensitivity was confirmed by very high morning plasma ACTH concentrations (>730 pg/ml, N: 10–50). Karyotype was 46,XY. The above-mentioned results lead to the presumed diagnosis of an isolated glucocorticoid deficiency secondary to ACTH insensitivity or FGD. Therefore, he was treated with hydrocortisone (25 mg/m² per day). Additional investigations revealed the absence of adrenal autoantibodies, normal levels of very long-chain fatty acids, excluding respectively autoimmune adrenal disease and adrenoleukodystrophy. The presence of tears and the absence of achalasia and neuropathy made triple A or Allgrove syndrome very unlikely.

Clinical follow-up of the patient was remarkable for a steady height growth (close to 1 s.d.) leading to a final height of 0.5 s.d. (178.0 cm), within his sex-corrected target height range (171.8 ± 10 cm; Fig. 1). Until 4 years, his weight remained at the upper limit (21.6 kg, +2.3 s.d.; body mass index (BMI) 19.9 kg/m², +2.8 s.d.). Thereafter, weight and BMI increased steadily reaching at adulthood 102.8 kg (+2.8 s.d.) and 33.7 kg/m² (+2.8 s.d.). Skin hyperpigmentation and eczema were present since early infancy. Puberty onset (Tanner G2) was first documented at 10 years of age, with onset of pubarche at 11.9 years and axillary hair at 13.5 years, while near-adult pubertal status (A3P4G4) was achieved at 13.9 years of age. Bone ages, estimated by one of us (MM) from the Greulich and Pyle atlas, were retarded until chronological age 11.6 years (delayed from 3 to 1.5 years). At 12.5 years, his bone age was only delayed by 6 months.

Despite the physiologic supplementation of hydrocortisone, measured plasma ACTH levels were elevated, while plasma levels of androstenedione and DHEA-S remained low (1.3 nM (N: 2.5–7.5) and 1 µM (N: 2.5–12) respectively) at 21 years of age. Plasma testosterone was 13.9 nM (N: 13–35) with FSH: 1.8 mIU/l (N: 1.4–9.9) and LH: 2.9 mIU/l (N: 1.7–12.1). Thyroid function tests were also normal (free thyroxine: 1.3 ng % and thyrotropin: 1.98 µU/ml).

DNA sequencing had originally shown this patient to have a normal MC2R sequence. However, recent genetic testing identified a frameshift mutation (deletion of one of the three G residues between 128–130 bp 130delG) causing a premature termination (V44X) in exon 4 of the MRAP gene (Fig. 2) (4), responsible for his isolated glucocorticoid and adrenal androgen deficiency. His parents were heterozygotes for the same mutation, as were two of his three sisters. The weights and BMI of the heterozygotes were 80.0 kg and 26.9 kg/m² respectively for the father, 104.5 kg and 41.6 kg/m² for the mother, 111.8 kg,

Figure 1 Growth curves for height (A) and weight (B). Squares represent the bone ages estimated by the Greulich and Pyle method. G indicates Tanner stages of genitalia. TH, sex-corrected target height.

39.2 kg/m² for one of the sister and for the other sister 102.0 kg and 34.4 kg/m², while the only non-affected sister had a BMI of 24.4 kg/m² and a weight of 70.5 kg.

Discussion

ACTH insensitivity syndromes are a group of rare diseases that may be lethal if not recognized. We report a case of FGD type 2 that presented during the neonatal period with hypoglycemia and jaundice and laboratory findings characteristic of an ACTH insensitivity syndrome: elevated plasma ACTH in the presence of unmeasurable plasma cortisol levels in the presence of a preserved renin–aldosterone axis. A homozygous frameshift mutation leading to a premature termination in exon 4 of the MRAP gene (V44X) and hence a truncated protein was found in

Figure 2 Partial sequence of exon 4 showing the 130 delG mutant. (A) wild-type and (B) mutant sequences. The position of the deleted G is indicated by an arrow, this results in a frameshift and introduction of a premature stop codon (V44X).

our patient. To date, this is the only mutation reported in exon 4 of this gene – all other mutations affect exon 3. In accordance with the autosomal recessive mode of inheritance, his two sisters and the parents were heterozygous for this mutation.

Very recently, the case history of a 19-month-old Ethiopian male infant with a novel mutation of MRAP has been reported (9). The infant presented with severe psychomotor retardation, spastic quadriplegia, and microcephaly due to severe symptomatic and recurrent hypoglycemia. The authors speculated that this particular severe phenotype could be due to this novel MRAP mutation. Since our patient had normal psychomotor development despite episodes of neonatal hypoglycemia, we believe that the neurological sequelae of this young infant with FGD are more likely due to the delayed diagnosis and treatment of the hypoglycemia, rather than the nature of the MRAP mutation.

Frequent minor infections or a single major infectious episode are additional modes of presentation of FGD as in our patient, who presented with sepsis during the neonatal period. Excessive pigmentation of the skin is often seen in these patients and was present in our patient since early infancy.

While patients with FGD type 1 and 2 share many common clinical features, Clark and Weber reported that patients with the ACTH receptor mutations have a mean height that is about 2 s.d.s greater than normal, whereas patients with FGD type 2 have heights that fall within the normal distribution (3). In line with these findings is the adult height of our patient, which was appropriate for his target. In contrast to the advanced

bone ages reported in some patients with FGD type 1 (10, 11), the bone ages of our patient were always retarded until 12.5 years of age, 2.5 years after onset of gonadarche. Whether the difference in skeletal maturation between the two types of FGD is real or spurious will require further observations.

ACTH is required for normal adrenal androgen secretion, which triggers adrenarche at around 7 years of age. Patients with FGD have no adrenarche and often have undetectable levels of adrenal androgens as measured in our patient, in whom androstenedione and DHEA-S were very low even at an adult age. These findings underline the importance of ACTH, MC2R, and MRAP in stimulating secretions of androgens by the adrenals. Although he did not develop adrenarche, his gonadarche occurred at a normal age. Despite the lack of expression of MRAP in the testis, puberty occurred at a normal age and progressed normally in our patient.

His ACTH remained elevated despite physiological cortisol substitution. This incomplete ACTH suppression may be explained by the ineffective MC2R-dependent short feedback loop of ACTH on the pituitary or the hypothalamus (10).

It is well known that the hypothalamic melanocortin system in humans plays an important role in energy balance (11). α -melanocyte-stimulating hormone, a pro-opiomelanocortin (POMC) cleavage product, is an anorectic peptide acting as an agonist of MC4R in the hypothalamic arcuate nucleus leading to an increase in energy expenditure and a decrease in food intake. Patients with defects in the synthesis and processing of POMC or mutations of the MC4R gene have early onset obesity. Whether the MRAP mutation described in our patient played a role in his obesity is, at this point, purely speculative. Indeed, MRAP is expressed in the pituitary and the brain and might be essential for the proper functioning of the hypothalamic melanocortin system (12). By analogy with patients with gene mutations who develop severe obesity in early infancy, it is tempting to hypothesize that the MRAP mutation observed in our patient could be responsible for his obesity if MRAP were essential for the expression and activation of other melanocortin receptors. Only scientific evidence and clinical observation will clarify this hypothesis.

In summary, we describe for the first time the long-term clinical and biological follow-up of a young male patient affected with FGD type 2 due to a rare mutation of MRAP. While some clinical and hormonal features are shared with FGD type 1, others such as height and skeletal maturation may be different.

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