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Unusual presentation of more common disease/injury

A rare genetic disorder causing persistent severe neonatal hypoglycaemia the diagnostic workup

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Summary

We report a case of familial glucocorticoid deficiency (FGD), a rare genetic autosomal-recessive disorder with typical hyperpigmentation of the skin and mucous membranes, severe hypoglycaemia, occasionally leading to seizures and coma, feeding difficulties, failure to thrive and infections. A newborn child was admitted, on his second day of life, to our neonatal intensive care unit because of seizures and respiratory insufficiency. Hyperpigmentation was not evident due to his Senegalese origin. The clinical presentation led us to consider a wide range of diagnostic hypothesis. Laboratory findings brought us to the diagnosis of FGD that was confirmed by molecular analysis showing an MC2R:p.Y254C mutation previously reported as causative of type 1 FGD and two novel heterozygous non-synonymous single-nucleotide polymorphisms in exon 2 and 3 of melanocortin 2 receptor accessory protein-α, whose role in the disease is currently unknown. The importance of an early collection and storage of blood samples during hypoglycaemic event is emphasised.

BACKGROUND

A transient hypoglycaemia is a fairly common condition in newborns. A blood glucose <2 mM/l in the first 24–36 h of life is not a general indication for starting a broader diagnostic workup, but only for prompt correction of hypoglycaemia by infusion therapy to prevent neuroglucopenia and consequent brain damage, followed by blood glucose monitoring over time. When the hypoglycaemia is repeated, as the case reported here, it is mandatory to undertake further investigations, specifically aimed to define the cause of hypoglycaemia. It is also particularly important to obtain a blood sample during the hypoglycaemic event (called the 'critical' blood sample). The case we are describing documents the central role of the 'critical blood sample' which allowed us to discard some causes and, though we were faced with a rare genetic adrenal disease, it suggested the right diagnosis and treatment in a reasonable limited time.

CASE PRESENTATION

CN, born at the term of uncomplicated pregnancy by caesarian section for cardiotocographic changes during labour, is a male infant, first born of Senegalese first-degree healthy cousins. Birth size was normal (weight 3580 g, length 52 cm and head circumference 37 cm) and Apgar score showed good extra uterine adaptation (first minute 8; fifth minute 9). The physical examination at birth was normal. On his second day of life the baby showed poor sucking, moderate axial hypotonia, hyporeactivity and vomiting. During clinical evaluation, a generalised seizure occurred and was followed by desaturation, laboured breathing, generalised hypotonia and lethargy. Blood glucose was <18 mg/dl (<1 mM/l). A blood sample (the critical sample) was drawn and stored at −20°C for further testing. Blood glucose was normalised by dextrose 10% infusion (7.2 mg/kg/min). Blood gases revealed respiratory acidosis (pH 7.13, pCO_2 73 mm Hg, base excess −4.3). The baby was then transferred to the neonatal intensive care unit, intubated and mechanically ventilated for 30 h. Parenteral nutrition (PN) was started and protracted for 10 days because of intolerance to enteral nutrition. Electrolytes, lactic acid, renal and hepatic functions were normal. Urine analysis was negative, and no ketone bodies were detected. Given mild bilateral hilar and interstitial opacities at chest x-ray and moderately elevated white blood count, cultures were taken from blood, cerebrospinal fluid and urine. Sepsis was suspected and systemic antibiotic treatment was started. C-reactive protein (CRP) values turned out to be normal on repeated testing and all cultures were negative. A mild impairing of coagulation tests on day 2, normalised right after vitamin K oral administration.

The baby went through one more episode of severe hypoglycaemia as a result of an accidental interruption of the PN on day 7. Blood gases and electrolytes were normal, and blood glucose normalised after low-rate dextrose infusion. In the following days he showed poor reactivity, axial hypotonia, reduced general movements and a progressive general neurologic impairment until diagnosis was performed and therapy was started.

INVESTIGATIONS

Once excluded that a sepsis could have caused the hypoglycaemia, we initiated investigations to identify the cause of fasting intolerance.

Increase of lactate, pyruvate and 4-OH-fenil-lactic at urinary acid chromatography was found, suggesting for a non-specific hepatopathy. The child was retested 1 week later

Table 1 Glycaemic and lactacidaemic response to Glucagon test (20 μg/kg intramuscular)

Time (min)	Glucose (mg/dl)	Lactate (mM/l)
0	31	1.1
30	42	0.6
60	66	1.1
90	85	1.2

showing a normal chromatographic profile. Ammoniaemia, urinary reducing substances, plasma and urinary amino acid profile, glucose-phosphate-uridiltransferase activity and plasma-free carnitine and acylcarnitines were all normal. Glucagon test (20 μg/kg intramuscular) was performed and resulted in normal glycemic and lactacidaemic response (table 1), which excluded glycogen storage disease type 1.

Hormones involved in glucose homeostasis were measured in the critical sample. Insulin and C-peptide were undetectable, as expected; growth hormone was 6.5 ng/ml, adrenocorticotropic hormone (ACTH) was extremely elevated (1400 μg/ml) with Cortisol undetectable both in plasma and in urines.

ACTH stimulation test (Tetracosactide-Synacthen 0.250 mg intravenous) confirmed the diagnosis of primary adrenal insufficiency (table 2).

Echo scan imaging showed adrenal glands of normal size. Serum electrolytes, plasmatic renin and aldosterone were normal. A familiar glucorticoid deficiency was suspected.

Genetic studies on proband confirmed the diagnosis showing homozygous A to G substitution in ACTH-R (MC2R: p.Y254C), a missense mutation already reported as responsible for FDG type 1.[1–3] Both the parents were heterozygous for the same mutation. Interestingly, in the proband we also found two novel heterozygous non-synonymous single-nucleotide polymorphisms (SNPs) in exons 2 and 3 of melanocortin 2 receptor accessory protein (MRAP)-α (exon 2 p.V50M from the mother, and exon 3 p.T130I from the father) whose role in the disease is currently unknown. Both the parents had normal cortisol and ACTH levels.

DIFFERENTIAL DIAGNOSIS

In the present case the differential diagnosis included sepsis, hyperinsulinism, defects of enzymes involved in glycogen storage, gluconeogenesis and/or fatty acid oxidation pathways and defects in hyperglycaemic hormones such as glucagon, adrenalin, growth hormone and cortisol. Normal CRP excluded sepsis. An enzyme defect was excluded by appropriate metabolic tests. A normal penis size made hypopituitarism unlikely. Measurement of insulin, C-peptide and cortisol in the 'critical sample' were the most useful test to achieve the right diagnosis and treatment. Among glucocorticoid deficiency, differential diagnosis included adrenoleukodystrophy, excluded because the clinical onset is usually after the age of 10, triple A syndrome, also excluded because the baby had normal oesophageal patency and tearing and familial deficiency of glucocorticoid (FDG) type 1[4] (mostly due to missense mutation of MC2R gene) type 2,[4] with clinical earlier and more severe onset (mostly due to nonsense or splice site mutation of MRAP, MC2R accessory protein) and type 3[5] (due to 'non–classical' Star mutation).

Table 2 Cortisol response to ACTH stimulation test (Tetracosactide-Synacthen® 0.250 mg intravenous)

Time (min)	Cortisol (ng/ml)
−90	<7
−30	<7
0	<7
30	<7
60	<7

TREATMENT

Replacement treatment with hydrocortisone (10 mg/m^2/day), started as a soon as diagnosis of glucocorticoid deficiency was made, successfully prevented further hypoglycaemic events.

OUTCOME AND FOLLOW-UP

The baby growth curve in the first 18 months of life followed the twenty-fifth percentile for length and weight. The neurodevelopmental follow-up showed a mild neurologic motor delay. The child has presented two further episodes of hypoglycaemia during acute gastrointestinal illness that required temporary parenteral route of hydrocortisone administration.

DISCUSSION

Recurrent hypoglycaemia, even associated with seizures and respiratory insufficiency, can be a sign of a wide spectrum of diseases in a newborn, ranging from common clinical conditions to rare congenital diseases. The hyperpigmentation of the skin often suggests the diagnosis of familial glucocorticoid deficiency (FGD), but in our case the African ethnicity masked the sign. Early storage of diagnostic samples when hypoglycaemia occurs can accelerate the diagnosis. Correctly identifying the investigations required to tackle the diagnostic path is mandatory.

Furthermore, parents' consanguinity is frequent among migrants from Africa to Europe leading to increased incidence of rare genetic diseases such as FGD.

To our knowledge there are, within the last decade, at least eight new case reports that were published on this topic. However, none of them reports the findings of two heterozygous non-synonymous SNPs in exons 2 and 3 of MRAP-α, whose role is yet to be defined.

The double heterozygosity for MRAP and MC2R did not result in any clinical or biochemical phenotype in the parents whose baseline blood levels of ACTH and cortisol were normal, thus indicating that the combined haploinsufficiency of these two genes is unlikely to create a detectable adrenal resistance to ACTH action. However, the double heterozigosity in MRAP might have contributed to the severe ACTH refractoriness with a dramatic neonatal presentation of FGD in this patient closer to type 2 than to type 1 FDG.

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Learning points

- In the case of recurrent hypoglycaemia in a newborn child, rare genetic diseases must be thoroughly carried out, especially in the presence of consanguinity of the parents.
- Storing diagnostic samples in the acute phase can lead to early diagnosis and treatment.
- Parents of children affected by familial glucocorticoid deficiency (FGD) must be alerted of never discontinuing treatment and switching to parental route administration of hydrocortisone in the case of gastrointestinal acute disease.
- Double heterozigosity for melanocortin 2 receptor accessory protein in a child with FGD can contribute to severity of the disease causing a dramatic neonatal presentation.

Competing interest None.

Patient consent Obtained.

REFERENCES

1. **Tsigos C,** Arai K, Latronico AC, *et al*. A novel mutation of the adrenocorticotropin receptor (ACTH-R) gene in a family with the syndrome of isolated glucocorticoid deficiency, but no ACTH-R abnormalities in two families with the triple A syndrome. *J Clin Endocrinol Metab* 1995;**80**:2186–9.
2. **Flück CE,** Martens JW, Conte FA, *et al*. Clinical, genetic, and functional characterization of adrenocorticotropin receptor mutations using a novel receptor assay. *J Clin Endocrinol Metab* 2002;**87**:4318–23.
3. **Clark AJ,** Chan LF, Chung TT, *et al*. The genetics of familial glucocorticoid deficiency. *Best Pract Res Clin Endocrinol Metab* 2009;**23**:159–65. Review
4. **Chung TT,** Chan LF, Metherell LA, *et al*. Phenotypic characteristics of familial glucocorticoid deficiency (FGD) type 1 and 2. *Clin Endocrinol (Oxf)* 2010;**72**:589–94.
5. **Metherell LA,** Naville D, Halaby G, *et al*. Nonclassic lipoid congenital adrenal hyperplasia masquerading as familial glucocorticoid deficiency. *J Clin Endocrinol Metab* 2009;**94**:3865–71.