Case Report

Hypokalaemia and dysmorphia, is there a link?

Stéphane Burtey1, Damien Sternberg2, Karine Nguyen3, Nicole Philip3, Yvon Berland1 and Bertrand Dussol1

1Centre de Néphrologie et Transplantation Rénale, AP-HM, Université de la Méditerranée, Marseille, 2Biochemistry and Genetics, Hôpital Pitié-Salpêtrière, Assistance Publique Hôpitaux de Paris, Université Pierre et Marie Curie and INSERM, Paris and 3Service de Génétique médicale, Hopital de la Timone, AP-HM, Université de la Méditerranée, Marseille, France

Abstract

A 15-year-old boy with quadriplegia and facial dysmorphia was referred to the emergency room. This was his first episode of tetraplegia. One maternal uncle had exhibited the same manifestation 20 years before. Blood test revealed severe hypokalaemia and mild hypocalcaemia. The clinical diagnosis revealed an Andersen–Tawil syndrome. Moleculartools allowed us to make the diagnosis of familial hypokalaemic periodic paralysis type 1 associated with a de novo 22q11.2 microdeletion syndrome. Our case report emphasizes the importance of molecular diagnosis in genetic diseases.

Keywords: 22q11 microdeletion syndrome; familial hypokalaemic periodic paralysis type 1; hypocalcaemia; hypokalaemia

Background

Hypokalaemia with paralysis (HP) is a medical emergency. The number of entities responsible for hypokalaemia and paralysis is limited [1]. HP can be divided into hypokalaemic periodic paralysis (HPP), due to a short-term shift of potassium into cells (transfer hypokalaemia), and non-HPP, due to a large potassium deficit (renal losses are the main cause). The differential diagnosis is based on urinary sample analysis and calculation of a trans-tubular potassium gradient (TTKG) and potassium–creatinine ratio. A TTKG <3 or potassium–creatinine ratio <2.5 mmol/mmol is associated with HPP [1]. The distinction between HPP and non-HPP is important. In HPP, potassium chloride supplements should be minimal and associated with close kalaemia follow-up, to prevent rebound hyperkalaemia [2]. Rebound hyperkalaemia can lead to abnormalities in heart conduction.

Case report

In July 2005, a 15-year-old boy was hospitalized in the emergency room for tetraplegia. Tetraparesis began in the legs during the afternoon after an intense physical exercise and ingestion of numerous sweets and was complete in 6 h. Physical examination revealed a flask tetraplegia. Blood pressure, pulse rate and temperature were normal. EKG identified a long QT without extrasystoles. A blood sample revealed profound hypokalaemia: 1.6 mmol/l. In urine, the kaliuresis was 17 mmol/l, the TTKG was 3.85 and the potassium/creatinine ratio was 0.85 mmol/mmol. The only other abnormality was hypocalcaemia (2.16 mmol/l), which spontaneously resolved. The patient was transferred to the nephrology ICU, and 8 g of potassium chloride was perfused in 8 h. The tetraplegia resolved in 5 h, and a kalaemia check revealed an overshoot response (5.4 mmol/l). Clinical examination showed mild dysmorphia associating small mouth, a broad nose and low implantation of ears (Figure 1). He had nasal speech. He did not take any drugs, and the thyroidal hormone levels (measured twice) were normal. His personal antecedents were a neonatal
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Fig. 1. Facial dysmorphia. The mouth is small, the ears have low implantation and the nose ridge is broad.

Fig. 2. (A) Arg528His mutation of the CACNA1S gene. Mutation responsible for familial hypokalemic periodic paralysis. Sequence analysis of the CACNA1S gene (exon 11) by the SeqscapeR software (Applied Biosystems, Foster City, CA, USA) showing the c.1583 G>A p.Arg528His mutation in our proband. (B) FISH analysis of the 22q11 deletion. The green dots mark the 22 chromosome. The red dot (tuple) marks the microdeleated region in the 22q11 deletion syndrome. The hybridization is missing on one chromosome, confirming the deletion.

hypocalcaemia and surgical correction of a transmission hypoacusia. His twin maternal uncles had exhibited the same manifestations 20 years before, and a cousin had hypokalaemia attributed to a Gitelman syndrome without identification of mutation in SLC12A3. His mother never had any manifestation of hypokalaemia, and her kalaemia was normal.

Kalureis, potassium/creatinine ratio and the rapid correction of small amounts of potassium after perfusion orientated us towards a shift hypokalaemia. The familial history of hypokalaemia oriented us towards a genetic disease. The association of familial hypokalaemic paralysis with dysmorphia suggested the clinical diagnosis of an ATS (MIM#170390). The first molecular investigation did not detect any mutation in KCNJ2 gene coding regions. KCNJ2 is the gene mutated in an ATS. A systematic search for mutations responsible for other forms of hypokalaemic channelopathy revealed the heterozygous R528H missense mutation (Figure 2A) in the CACNA1S gene. The transfer hypokalaemia was secondary to HOKPP (MIM#170400), which is related to missense mutations of the S4 segments of Cav 1.1. We confirmed the presence of the mutation in all affected members of the maternal branch of the family tree and in the asymptomatic mother.

The dysmorphia was still not explained. Because of the neonatal hypocalcaemia and mild hypocalcaemia observed during this episode, we performed a parathormone and vitamin D assay on the initial serum. The parathormone level was inappropriately low (<7 pg/ml normal values: 10–55 pg/ml) in view of the hypocalcaemia (2.16 mmol/l). The vitamin D level and 1,25(OH)2 vitamin D level were normal. Because of the hypoparathyroidism and the dysmorphia, we suspected a 22q11 microdeletion syndrome (MIM#188400). A 22q11 microdeletion syndrome was detected (Figure 2B). It was a de novo deletion. His mother and his father did not present the microdeletion.

The final diagnosis was the infrequent association of a 22q11 microdeletion syndrome with familial hypokalaemic periodic paralysis type 1. Hypokalaemia occurred twice without tetraparesis, but with weakness in the extremities. The identification of the mutation in the CACNA1S gene and not in the SCN4A gene led us to add acetazolamide to the potassium supplementation. Hypokalaemia and paralysis never recurred after addition of acetazolamide. Advice for the anaesthesia management was given to the carriers of the CACNA1S mutation.

Discussion

The association of dysmorphia or a permanent long QT evokes an ATS. An ATS is a rare autosomal dominant genetic disease secondary to missense mutations in the KCNJ2 gene, which encodes the inward-rectifying potassium channel known as Kir2.1 [5]. An ATS is a multisystemic channelopathy characterized by the triad of periodic paralysis, ventricular arrhythmias and distinctive dysmorphic facial or skeletal features [6]. This diagnosis was the initial clinical diagnosis in our patient. Genetic testing dismissed the clinical diagnosis of ATS and allowed us to establish the right diagnosis for his genetic HPP.

HOKPP is a rare genetic autosomal dominant disease (1/100 000) with a variable penetrance (females can be asymptomatic like the mother of our patient) [7]. The episodic hypokalaemia is profound and associated with episodes of paraplegia or tetraplegia. The mechanism of episodic hypokalaemia is still not understood, although triggering factors such as carbohydrate-rich meals and sustained physical effort have been identified [7]. Molecular diagnosis is available and may help in the adaptation of treatment. Two genes may be mutated, CACNA1S or SCN4A [8,9]. In some SCN4A mutation carriers, acetazolamide may increase the frequency of paralysis onset [9]. Identifying non-symptomatic mutation carriers (like the mother of the propositus) is important to avoid complications of anaesthesia [10]. The patients with HOKPP are prone to presenting malignant hyperthermia [11] or paralysis and need specific management during anaesthesia.
The 22q11 microdeletion syndrome is the most frequent microdeletion (1/5000) syndrome [12]. The main manifestations of the syndrome include palatal anomalies such as cleft palate or velopharyngeal insufficiency, conotruncal heart defects, hypocalcaemia, immune disorders and minor facial anomalies. Learning disabilities are frequent, and 15% of patients are prone to developing psychiatric disorders. The phenotypic expression of the 22q11 microdeletion is highly variable and ranges from severe life-threatening DiGeorge syndromes to nearly asymptomatic individuals [13]. The mode of inheritance is autosomal dominant, with 95% of cases being sporadic, due to de novo mutations. The condition is probably underdiagnosed [13]. Dysmorphia is one of the most common signs of a 22q11 microdeletion syndrome [12]. In most patients hypoparathyroidism is frequently (70%) latent, and symptomatic hypocalcaemia is uncommon (10%) but can occur during stress (surgery or infection) [14]. Hypocalcaemia is common during the neonatal period and resolves spontaneously during the first year of life. Renal malformations are frequent in the 22q11 microdeletion syndrome and can be associated with end-stage renal failure. Thirty-six percent of the patients have abnormal kidneys and the frequency of renal failure is 10% in adults [12]. Our patient presented typical dysmorphia with mild hypoparathyroidism, his cognitive function was normal and no cardiac malformations or renal dysfunction was identified.

Our case emphasizes the importance of molecular diagnosis of orphan genetic diseases to firmly confirm, or sometimes rectify, clinical diagnosis and thereby ensure the proper care of patients and their families. In our patient, the correct diagnosis, permitted only by mutation identification and FISH analysis, permitted us to avoid the cardiac follow-up needed in Andersen disease [15], to guide the treatment and to avoid the recurrence of life-threatening HPP. The firm diagnosis through systematic analysis of the electrolyte abnormalities and molecular tools permitted us to propose a follow-up and advice to the affected members of the family and to reassure the others.

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Conflict of interest statement. The authors declare no competing of interest. S.B., Y.B. and B.D. contributed to the clinical care, D.S. contributed to the molecular diagnosis of hypokalaemic paralysis, and K.N. and N.P. contributed to the diagnosis of the 22q11 microdeletion syndrome. S.B. wrote the manuscript and all the authors reviewed it.

References

1. Lin SH, Lin YF, Chen DT et al. Laboratory tests to determine the cause of hypokalemia and paralysis. Arch Intern Med 2004; 164: 1561–1566
2. Manoukian MA, Foote JA, Crapo LM. Clinical and metabolic features of thyrotrophic periodic paralysis in 24 episodes. Arch Intern Med 1999; 159: 601–606
3. Alazami M, Lin SH, Cheng CJ et al. Unusual causes of hypokalemia and paralysis. Q J Med 2006; 99: 181–192
4. Ko GT, Chow CC, Yeung VT et al. Thyrotrophic periodic paralysis in a Chinese population. Q J Med 1996; 89: 463–468
5. Plaster NM, Tawil R, Tristani-Firouzi M et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen’s syndrome. Cell 2001; 105: 511–519
6. Tawil R, Ptacek LJ, Pavakis SG et al. Andersen’s syndrome: potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. Ann Neurol 1994; 35: 326–330
7. Venance SL, Cannon SC, Fialho D et al. The primary periodic paralyses: diagnosis, pathogenesis and treatment. Brain 2006; 129(Pt 1): 8–17
8. Sternberg D, Maisonobe T, Jurkat-Rott K et al. Hypokalemic periodic paralysis type 2 caused by mutations at codon 672 in the muscle sodium channel gene SCN4A. Brain 2001; 124(Pt 6): 1091–1099
9. Bendahhou S, Cummins TR, Griggs RC et al. Sodium channel inactivation defects are associated with acetazolamide-exacerbated hypokalemic periodic paralysis. Ann Neurol 2001; 50: 417–420
10. Caciotti A, Morrone A, Domenici R et al. Severe prognosis in a large family with hypokalemic periodic paralysis. Muscle Nerve 2003; 27: 165–169
11. Rajabally YA, El Lahawi M. Hypokalemic periodic paralysis associated with malignant hyperthermia. Muscle Nerve 2002; 25: 453–455
12. Kobylnski LJ, Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. Lancet 2007; 370: 1443–1452
13. Scambler PJ. The 22q11 deletion syndromes. Hum Mol Genet 2000; 9: 2421–2426
14. Al-Jenaidi F, Makite O, Grunebaum E et al. Parathyroid gland dysfunction in 22q11.2 deletion syndrome. Horm Res 2007; 67: 117–122
15. Sansone V, Tawil R. Management and treatment of Andersen–Tawil syndrome (ATS). Neurotherapeutics 2007; 4: 233–237

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