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ScienceDirect

Neuromuscular Disorders 27 (2017) 294–297

www.elsevier.com/locate/nmd

Case report

Intrafamilial phenotypic variability in Andersen–Tawil syndrome: A diagnostic challenge in a potentially treatable condition

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Received 9 March 2016; accepted 12 November 2016

Abstract

Andersen–Tawil syndrome (ATS) is a rare autosomal dominant channelopathy characterized by periodic paralysis, cardiac dysrhythmias, and distinct facial and skeletal characteristics, that may be variably present in the affected members. Mutations in the *KCNJ2* and *KCNJ5* gene have been associated with this disorder. We describe a family in which several members presented with different ATS phenotypes. The proband, a 4-year-old boy, presented with recurrent episodes of muscle weakness from an early age; two siblings suffered cardiac arrhythmia but had never experienced episodes of paralysis; their mother reported occasional muscle pain after exercise and unspecified cardiac arrhythmias. The analysis of *KCNJ2* gene in the proband disclosed the presence of a pathogenic mutation (p.R218W), that was subsequently confirmed in the other affected subjects. Our results underline the possible intrafamilial phenotypic variability, ranging from full clinical triad to exclusive cardiac or muscular involvement, representing a diagnostic challenge that may also delay adequate management. There are still limited data on the treatment of ATS; in our patient there was clinical improvement with dichlorphenamide.

Keywords: Andersen–Tawil syndrome; Periodic paralysis; Cardiac dysrhythmias; *KCNJ2*; Dichlorphenamide

1. Introduction

Andersen–Tawil syndrome (ATS) is a rare autosomal dominant channelopathy, with an estimated prevalence of 1/500,000, accounting for less than 10% of all periodic paralysis [1]. It is characterized by the clinical triad of periodic paralysis, cardiac dysrhythmias, and distinctive facio-skeletal features. Muscle involvement usually occurs early in the disease resulting in episodic attacks of muscle weakness which may involve all four limbs, may be associated with hypo-, normo- or hyperkalemia, and may last from a few hours to a couple of days. If the episodes of muscle weakness affect only one limb and are short-lasting they may be underestimated by the patients themselves and can remain undiagnosed. Cardiac involvement may be asymptomatic and the occurrence of long QT intervals or ventricular arrhythmias can be an occasional finding during cardiac screening for other causes. Even when arrhythmias are symptomatic, the absence of muscle symptoms may mislead the correct diagnostic investigations. Moreover, the most common dysmorphic features, including facial (hypertelorisms, broad nose, short neck, low-set ears, micrognathia) dental and skeletal abnormalities, are usually present, but may be very mild and not always easily recognized as part of the syndrome [2,3]. The diagnosis of ATS is therefore challenging. To date about 80% of ATS patients present a genetically-defined diagnosis, mostly linked to *KCNJ2* gene, that are *de novo* in 30% of cases [4–7]. *KCNJ2* encodes the inward rectifier K+ channel Kir2.1 protein, expressed in skeletal and cardiac muscle [8]. Recently, a second gene causing ATS has been identified, *KCNJ5*, which encodes the G-protein activated inwardly rectifying K+ channel Kir3.4; mutant Kir3.4 has an inhibitory effect on Kir2.1 [9]. Kir2.1 channels are essential for maintaining the highly negative resting membrane potential of muscle fibers and accelerating the repolarization phase of the cardiac action potential. The loss of function in Kir2.1 affects the excitability of both cardiac and skeletal muscles. The molecular mechanism underlying facial and skeletal abnormalities remains at present not fully understood. A recent study demonstrated a possible mechanism for craniofacial dysmorphogenesis: *KCNJ2* mutations change the normal pattern of membrane voltage potential

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http://dx.doi.org/10.1016/j.nmd.2016.11.006
0960-8966/

regionalization in the developing face, disrupts expression of craniofacial patterning genes, revealing the endogenous control of craniofacial patterning by bioelectric cell states [10].

We describe a family carrying mutations in *KCNJ2* gene in whom the classic clinical triad of ATS was not clearly evident in all subjects, leading to a challenging diagnosis because of intrafamilial phenotypic variability.

2. Case report

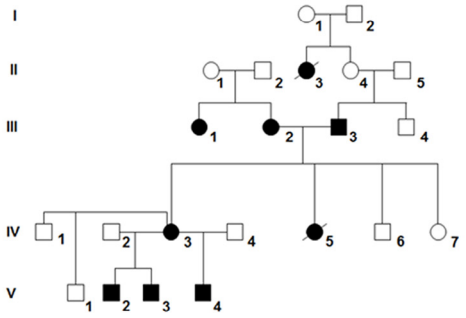
The proband is a 4-year-old boy, born from unrelated parents; pregnancy, delivery and psychomotor development were referred normal. At 16 months of age, he experienced the first episode of acute muscle pain, cramps and generalized weakness following intense physical exercise. Muscle enzymes during the episode were mildly elevated: CK: 346 IU/L (nv 24–195), LDH 546 IU/L (nv 230–480), aldolase 17.4 IU/L (nv 0–7.6). Serum potassium levels were only mildly reduced (3.5 mEq/l, nv 3.8–5); ECG was normal. He underwent a muscle biopsy, that showed normal histological pictures, including immunohistochemical studies for dystrophin, sarcoglycan, caveolin 3 and laminin α2. He fully recovered after 1 week with the diagnosis of "myositis". Subsequently he suffered from additional recurrent episodes of muscle pain and weakness involving both upper and mostly lower limbs, lasting for several hours or days (10 days maximum); muscle strength and motor performances were initially normal between attacks, but as the episodes increased in severity and frequency with age to progressive gait impairment was noticed. Serum electrolytes were never evaluated during the acute attacks, and no triggers were associated with the episodes.

Major episodes occurred once or twice per month and rated on average as grade 7 on a scale from 0 to 9 (0 = no attack; 9 = complete paralysis), while milder episodes occurred daily, and rated on average as grade 2 or 3. The most severe ones were sometimes associated with slurred speech.

The boy was first seen at our Institute at 4 years of age after a further additional episode characterized by acute muscle pain and severe generalized muscle weakness. General examination revealed dysmorphic features: broad forehead, hypoplastic mandible, low-set ears, low height and weight (25th centile). Neurological interictal evaluation showed normal tone and strength, mild hypertrophy of quadriceps and calf muscles, positive Gowers sign and clumsy running. No involuntary muscle activity was detected. Interictal serum potassium levels were mildly raised (5.2 mEq/l, nv 3.8–5). Blood routinary exams, including muscle enzymes, thyroid hormones, carnitine and lactate levels, were normal. Nerve conduction studies and routine electromyography were normal. ECG showed sinustachycardia and QTc was normal. Twenty-four hour Holter monitoring showed sporadic and asymptomatic ventricular ectopic beats.

Possible periodic paralysis was suspected and the family history was revised. The proband's mother proved to have similar dysmorphic features and occasionally reported muscle pain after exercise and sporadic unspecified irregular heart beats. Moreover, in her 20s she reported an episode of sudden muscle weakness involving the lower limbs which she reported


(a)



II-3: episodes of muscle stiffness, sudden death at 14 years
III-1: episodes of muscle stiffness
III-2: cardiac arrhythmias
III-3: episodes of muscle stiffness, cardiac arrhythmias
IV-3: occasional ventricular arrhythmias, muscle pain
IV-5: hypokalemic periodic paralysis, cardiac arrhythmias, sudden death at 14 years
V-2 and V-3: LQT syndrome, ventricular extrasystoles
V-4: proband

Fig. 1. (a) Facial features in reported cases (from right to left: subjects IV3-V2-V4-V3): broad forehead, hypoplastic mandible, low-set ears. (b) Pedigree.

was diagnosed as "Guillain-Barrè-Strohl disease" yet with negative CSF and EMG studies. She had 3 other children from two previous marriages: two of them, with typical ATS facial features (Fig. 1a), had a cardiac history of ventricular tachycardia and long QT syndrome, and were treated with metoprolol. Moreover, a positive history for unspecified cardiac arrhythmias, sudden deaths and episodic muscle weakness were reported in the maternal family (Fig. 1b).

The analysis of *KCNJ2* gene in the proband disclosed the presence of a pathogenic heterozygous mutation c.652C>T (p.R218W) (Fig. 2), and the same mutation was confirmed in the mother (IV-3) and in the two brothers (V-2 and V-3). Further evaluation of the mother by 24 hr Holter monitoring after molecular diagnosis revealed sporadic and asymptomatic ventricular ectopic beats.

Treatment with dichlorphenamide (DCP) 25 mg bid was started in the proband with good control on the frequency and severity of the attacks of weakness and pain. He had been on DCP for 2 years and no major episodes of paralysis occurred since the boy was started on DCP. Milder episodes, rated as grade 2, occurred once or twice a week and resolved after 1–2