Severe infantile hyperkalaemic periodic paralysis and paramyotonia congenita: broadening the clinical spectrum associated with the T704M mutation in SCN4A

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The authors describe an Italian kindred with nine individuals affected by hyperkalaemic periodic paralysis associated with paramyotonia congenita (hyperPP/PMC). Periodic paralysis was particularly severe, with several episodes a day lasting for hours. The onset of episodes was unusually early, beginning in the first year of life and persisting into adult life. The paralytic episodes were refractory to treatment. Patients described minimal paramyotonia, mainly of the eyelids and hands. All affected family members carried the threonine to methionine substitution at codon 704 (T704M) in exon 13 of the skeletal muscle voltage gated sodium channel gene (SCN4A). The association between T704M and the hyperPP/PMC phenotype has been only recently revealed. Nevertheless, such a severe phenotype has never been reported so far in families with either hyperPP or hyperPP/PMC. These data further broaden the clinical spectrum of T704M and support the evidence that this mutation is a common cause of hyperPP/PMC.

Hyperkalaemic periodic paralysis (hyperPP) and paramyotonia congenita (PMC) are autosomal dominant allelic diseases caused by mutations in the skeletal muscle voltage gated sodium channel gene (SCN4A) on chromosome 17q23. HyperPP is characterised by transient and recurrent episodes of paralysis lasting minutes to hours, triggered by fasting or rest after exercise and accompanied by increased serum potassium concentrations. The episodes usually start in the first decade of life occurring on a weekly to monthly basis and tend to decrease in severity and frequency in adult life. A progressive proximal weakness may become apparent in some people. The hallmarks of PMC are cold induced myotonic stiffness and weakness generally involving the face and hand muscles, and paradoxical myotonia. Onset of paramyotonia is usually at birth.

HyperPP/PMC shows characteristics of both hyperPP and PMC with varying degrees of overlap and has been reported in association with eight mutations in SCN4A gene (I693T, T704M, A1156T, T1313M, M1360V, M1370V, R1448C, M1592V). While T704M is an important cause of isolated hyperPP, this mutation has been only recently described in a single hyperPP/PMC family. As with other SCN4A mutations, there can be marked intrafamilial and interfamilial variability in paralytic attack frequency and severity in patients harbouring T704M. We report an Italian kindred, in which all patients presented with an unusually severe and homogeneous hyperPP/PMC phenotype associated with the T704M.

CASE REPORT

The VV family is a three generation kindred with nine members affected by a remarkably severe, homogeneous hyperPP/PMC phenotype (fig 1). Autosomal dominant inheritance was observed with no apparent lack of penetrance. A summary of the clinical data for each affected member is presented in table 1.

The onset of paralytic episodes was around six to nine months of age in all patients. During infancy and childhood, the episodes were frequent (up to two to three a week), lasting 10 minutes to two hours and were usually accompanied by muscle stiffness, mainly at the lower limbs. Nocturnal, potentially life threatening episodes of complete paralysis with respiratory difficulties were experienced in the first years of life. During adolescence, episodes were always related to a precipitating factor (that is, rest after exercise, exposure to cold, alcohol intake, fasting), and carbohydrate intake sometimes alleviated the paralysis. The frequency and severity of episodes insidiously worsened over the years. In adulthood, the attacks occurred with daily frequency and arose spontaneously or with minimal provocation (for example, sitting down for a

Table 1 Clinical characteristics of the affected individuals

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex (age)</th>
<th>Age at onset of paralytic attacks</th>
<th>Frequency of paralytic attacks</th>
<th>HyperPP during attacks</th>
<th>Duration of episodes</th>
<th>Precipitant factors</th>
<th>Cardiac arrhythmia</th>
<th>Response to drugs</th>
<th>Site of paramyotonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>II:2</td>
<td>F (81)</td>
<td>&lt;1 y</td>
<td>1/day</td>
<td>no</td>
<td>1–15 min</td>
<td>fasting, CTH</td>
<td>no</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>II:3</td>
<td>F (79)</td>
<td>&lt;1 y</td>
<td>1–3/day</td>
<td>20 min</td>
<td>RAE, CTH, stress</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>II:4</td>
<td>F (76)</td>
<td>&lt;1 y</td>
<td>1–3/day</td>
<td>10 min</td>
<td>fasting, CTH</td>
<td>yes</td>
<td>no (ACZ)</td>
<td>hand</td>
<td>–</td>
</tr>
<tr>
<td>II:6</td>
<td>M (73)</td>
<td>&lt;1 y</td>
<td>1/day</td>
<td>yes</td>
<td>fasting, carrots</td>
<td>no (ACZ)</td>
<td>eyes</td>
<td>hand</td>
<td>–</td>
</tr>
<tr>
<td>II:1</td>
<td>M (63)</td>
<td>6–7 months</td>
<td>1–2/day</td>
<td>10 min–2 h</td>
<td>RAE, fasting, CTH, alcohol</td>
<td>no (ACZ)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>III:3</td>
<td>M (45)</td>
<td>8 months</td>
<td>1–2/day</td>
<td>no</td>
<td>1 h</td>
<td>RAE, CTH</td>
<td>no (ACZ, SLB)</td>
<td>eyes</td>
<td>–</td>
</tr>
<tr>
<td>III:5</td>
<td>M (38)</td>
<td>9 months</td>
<td>2–3/day</td>
<td>no</td>
<td>1–20 min</td>
<td>RAE, CTH</td>
<td>no (ACZ)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>IV:1</td>
<td>M (18)</td>
<td>6 months</td>
<td>1–2/week</td>
<td>yes</td>
<td>20 min</td>
<td>RAE, CTH</td>
<td>–</td>
<td>eyes</td>
<td>–</td>
</tr>
<tr>
<td>IV:2</td>
<td>M (16)</td>
<td>8 months</td>
<td>1–2/week</td>
<td>20 min</td>
<td>RAE, CTH</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

RAE, rest after exercise; CTH, cold temperature and humidity; ACZ, acetazolamide; CT, chlorothiazide; SLB, salbutamol.
short time to have lunch or a short drive), becoming very debilitating and interfering with most daily activities. The main episodes lasted up to several hours, but focal weakness in a muscle or group of muscles (for example, “floppy foot”) could persist for days. Diffuse inter-episode weakness, mainly in the proximal muscles, invariably developed around the fourth to fifth decade and was slowly progressive, with difficulty in climbing stairs and carrying shopping. Since the neonatal age, lid-lag phenomenon and profuse sweating were typical prodromal signs of an episode. Acetazolamide (up to 1000 mg daily), chlorothiazide (500 mg daily), and salbutamol (either orally 2 mg thrice daily or inhaled 200 µg nasally) were completely ineffective in preventing or aborting the episodes of paralysis. Two patients (II:4 and II:6) developed a cardiac arrhythmia in their 60s, and one of them (II:6) required a pacemaker implantation.

Neurological examination showed calf hypertrophy in all affected individuals. Paradoxical myotonia was usually confined to eyelid closure and grip, and worsened with cooling; there was no percussion myotonia. Mild proximal muscle weakness was evident in adult family members without obvious muscle wasting. Serum potassium concentrations (measured during episodes in all but individuals II:3, II:4, and IV:2) were either increased or at the upper limit of the normal range. Electromyography (EMG), performed in patients III:3 and III:5, revealed profuse myotonic discharges and myopathic changes, consisting of low amplitude, early recruitment pattern with decreased mean duration of motor unit potentials, and high percentage of polyphasic potentials. A McManis long exercise test (performed in individual III:3) revealed a decrement between 40% and 90% in compound muscle action potential (CMAP) amplitude, suggesting an underlying channelopathy. Cold immersion EMG to 20 degrees (performed in patients III:3 and III:5) also showed marked CMAP amplitude decrement, consistent with PMC. A muscle biopsy (performed in patient II:6 at age 37) showed a vacuolar myopathy with single large or multiple smaller vacuoles with no histochemical staining. Fibres varied in size with occasional degeneration and without tubular aggregates. Fibrosis was also observed with no inflammatory cells.

**Molecular Analysis**

After informed consent, blood was obtained from three patients (II:6, III:3, and IV:1), three unaffected family members (II:7, III:4, and III:6) and one spouse (III:2). Each patient was screened for the two common mutations resulting in hyperPP (M1592V, T704M), by means of PCR amplification of the segment containing the mutation and digestion with restriction enzymes TaqI and NsiI respectively. All tested affected members were negative for the M1592V mutation but all harboured the T704M mutation in exon 13 as confirmed by sequence analysis. None of the three unaffected individuals carried the T704M mutation.

**Discussion**

We have investigated an Italian family with hyperPP/PMC carrying the T704M mutation in the SCN4A gene. This severe phenotype has never been reported in patients harbouring T704M. In addition, differently from the commonly observed wide intrafamilial variability, the nine affected individuals showed a homogeneous phenotype. The association between T704M and hyperPP/PMC has been previously reported only in a Korean family by Kim and coworkers. Clinical comparison between the Korean family and the present family disclosed several common features, including similar precipitating factors, mild myotonia, calf hypertrophy, and fixed proximal weakness in affected adults. However, a number of important phenotypic differences between these two families can be distinguished. The onset of paralytic attacks in VV family was in the first months of life in all affected individuals. Conversely, only two of seven affected members of the Korean family had onset in infancy, while the other five patients had a more typical onset towards the end of the first decade. Most striking was the difference in frequency of the episodes. In fact, in family VV the episodes of paralysis could occur several times a day with frequency and severity increasing with age. In addition, a number of family members reported spontaneous attacks (that is, without triggering factors). In family VV acetazolamide, hydrochlorothiazide, and salbutamol (inhaled or oral) were ineffective in preventing or aborting the episodes, in contrast with patients harbouring T704M, which often respond favourably to these treatments.

A muscle biopsy revealed a vacuolar myopathy in one individual of the VV family, in agreement with other studies in families with the T704M mutation. Five of six affected individuals in VV family had normal serum potassium concentrations during episodes (see table 1). This confirms previous suggestions that normokalaemic periodic paralysis represents a variant of hyperPP and is associated with mutations in SCN4A.
It is interesting to speculate whether mutations in SCN4A could give rise to cardiac conduction defects in view of the arrhythmias observed in individuals II-4 and II-6 in family VV. Although this could be related to a different disorder, McClatchey et al reported cardiac arrhythmia requiring pacemaker insertion in a 30 year old patients with paramyotonia congenital harbouring an S804F mutation in SCN4A. This is further supported by the fact that mutations in a closely related channel gene, SCN5A, cause long QT syndrome (LQT3) and that recent murine studies have demonstrated SCN4A expression in cardiac muscle. In contrast with original northern blot analysis, SCN4A expression in human cardiac muscle has recently been confirmed.

This report expands the phenotypic variability of the T704M, further confirming the lack of genotype-phenotype correlation in SCN4A mutations. Functional analysis has not so far offered an explanation for the wide phenotypic variability observed in the sodium channel disorders. Although modifying genetic factors are probable, it is not clear whether these may be in the form of SCN4A polymorphisms or even mutations in other channel genes. A potassium channel gene such as KCNE3, in which mutations are a rare cause of hypokalaemic or hyperkalaemic periodic paralysis, is an example of a possible modifying gene.

In conclusion, we have identified a family with hyperPP/PMC caused by the T704M mutation in SCN4A. This mutation has been previously described and has been confirmed as pathogenic in functional studies. The affected individuals had a remarkably severe phenotype of hyperPP that was refractory to treatment, in association with mild paramyotonia congenita. T704M can be considered a common cause of hyperPP/PMC and patients with this phenotype should be screened for this mutation in the first instance.

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