Neonatal hypotonia can be a sodium channelopathy- recognition of a new phenotype

Emma Matthews MRCP\textsuperscript{1}, Agnes Guet M.D.\textsuperscript{2}, Michèle Mayer M.D.\textsuperscript{2}, Savine Vicart M.D.\textsuperscript{3,4}, Sally Pemble PhD\textsuperscript{1}, Damien Sternberg PhD\textsuperscript{4,5}, Bertrand Fontaine, PhD\textsuperscript{3,4,5}, Michael G Hanna FRCP.\textsuperscript{1}

\textsuperscript{1}MRC Centre for Neuromuscular Disease, Institute of Neurology, UCL, Queen Square, London.  
\textsuperscript{2}Paediatric Neurology, Hôtel Armand Trousseau, Assistance Publique Hôpitaux de Paris, Paris  
\textsuperscript{3}Centre de Référence des Canalopathies Musculaires, Hôpital Pitié-Salpêtrière, Assistance Publique Hôpitaux de Paris, Paris  
\textsuperscript{4}UMR 546, Université Pierre et Marie Curie and INSERM, Paris  
\textsuperscript{5}Biochemistry and Genetics, Hôpital Pitié-Salpêtrière, Assistance Publique Hôpitaux de Paris, Paris

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Correspondance to: Prof B. Fontaine  
Centre de Référence des Canalopathies Musculaires, Neurologie  
Groupe Hospitalier Pitié-Salpêtrière  
47-83 bd de l’Hôpital  
75651 Paris Cedex 13  
France  
bertrand.fontaine@psl.aphp.fr

Prof. M.G. Hanna,  
Medical Research Council Centre for Neuromuscular Disease,  
Department of Molecular Neuroscience  
Institute of Neurology and National Hospital for Neurology and Neurosurgery  
Queen Square  
London  
WC1N 3BG  
UK  
m.hanna@ion.ucl.ac.uk

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Case History: A 23 year old French woman had an uncomplicated labour producing a male infant by vaginal delivery (case 4-2 in Table 1). The initial APGAR score was 10 but very rapidly he developed generalized hypotonia with impaired sucking. Respiration was initially uncompromised. Full blood count, electrolyte profile, CRP and blood glucose were all within normal limits. Nasogastric feeding was initiated and the infant transferred to the pediatric neurology service.

Examination on the first day found the child to be difficult to wake. Major generalized hypotonia was confirmed with only slight movement of the limbs to stimulation. Reflexes were reduced. Systemic examination was unremarkable. From the second day frequent oxygen desaturations were recorded during sleep and he required nasal oxygen therapy for 5 days. A Chest x-ray was normal. Over the following week gradual spontaneous improvement occurred. On day 8 examination was normal and no further respiratory or nutritional support was required.

The infant’s elder brother born three years earlier also suffered from transient generalized hypotonia with suckling difficulties but with full recovery. At the age of three he began to suffer episodes of muscle paralysis triggered by cold. The mother of the two children had also suffered from cold exacerbated episodes of muscle stiffness [confirmed to be myotonia on EMG] and paralysis from the age of four. Her father, grandmother and great-grandmother experienced similar episodes.

Direct DNA sequencing confirmed the presence of the missense I693T mutation in the IIS5-IIS6 cytoplasmic loop of the alpha-1 subunit of the voltage-gated skeletal muscle sodium channel.
(Nav 1.4) in affected members of this family including both cases with neonatal hypotonia. This mutation has been reported and validated as a paramyotonia congenita mutation.

We have also identified the I693T sodium channel mutation in four additional cases of neonatal hypotonia with or without feeding and respiratory symptoms. These four cases are from two unrelated English families and siblings from one French family (family 3). Table 1 outlines the clinical findings in each case. Earlier generations in families 1, 3 and 4 reported a history of paramyotonia congenita but not of neonatal hypotonia.

Discussion: Paramyotonia congenita is a skeletal muscle disorder caused by impaired inactivation of the voltage gated sodium channel Nav1.4. The inactivation defect results in a hyper-excitable muscle fibre membrane such that a single nerve impulse produces a sequential train of action potentials. This is reflected clinically as myotonia (delayed muscle relaxation following forceful contraction), which usually presents in the first decade and is exacerbated by cold and exercise. Most commonly the muscles of the face and upper limbs are affected but there are reports of respiratory compromise. Patients also commonly experience episodic muscle weakness that can last for hours or even days. Neonatal paramyotonia congenita often presents with myotonic phenomenon when the infant cries or is washed, especially with cool water. Recently, a rare lethal neonatal paramyotonia case with extreme sensitivity to cold was reported and attributed to another mutation (N1297K). However, neonatal hypotonia, has not previously been reported as a clinical manifestation of muscle sodium channel dysfunction. Our observations in these six individuals from four unrelated French and English families indicate that neonatal hypotonia can be a manifestation of muscle sodium channel dysfunction. The systematic collection of genetic and clinical information in databases at our two centres allowed us to retrospectively identify
neonatal hypotonia as a phenotype that was common to individuals with the I693T sodium channel mutation.

Pathological muscle hypotonia is an important neonatal presentation and can be a sign of either a peripheral or central abnormality. Careful diagnostic assessment and often multiple investigations are required. Recognition of a sodium channel mutation as a cause of neonatal hypotonia may prevent unnecessary and invasive investigations. For example a muscle biopsy is very unlikely to be contributory. EMG assessment has been shown to be beneficial in adults if performed according to specific protocols but these are not easily applicable in neonates. Treatment in our cases was supportive as symptoms are self-limiting but it is important to recognise that symptoms may be cold-triggered and temperature-dependent. Therefore, a constant warm ambient temperature is essential in such cases.

We conclude that sodium channel gene mutations can cause neonatal hypotonia and that women harbouring such mutations should be considered at risk for having neonates with such hypotonia. In addition where the father is known to be affected these pregnancies should also be considered at risk. The data we present suggest that a sodium channelopathy should enter the differential diagnosis in unexplained neonatal hypotonia, since a positive family history may not always be evident in muscle channelopathies.

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Reference List

Table 1

Features of hypotonia and motor development in six neonates carrying the Nav 1.4 I693T mutation (the case reported in detail in this case report is 4-2). Following recovery, episodes of cold exacerbated myotonia +/-or paralysis subsequently began in all children before the age of five except case 4-2 who has not yet manifest any such symptoms but is currently only one year of age.

<table>
<thead>
<tr>
<th>Family</th>
<th>Sex</th>
<th>APGAR at birth</th>
<th>Onset of Hypotonia</th>
<th>Impairment of sucking-swallowing</th>
<th>Desaturation</th>
<th>Kalemia (mmol/l)</th>
<th>Motor Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (English)</td>
<td>Female</td>
<td>1-1</td>
<td>NA</td>
<td>Birth</td>
<td>Day1 - bottle fed, unable to breast feed</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>2 (English)</td>
<td>Female</td>
<td>2-1</td>
<td>NA</td>
<td>Birth</td>
<td>No (hypotonia limited to limbs)</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>3 (French)</td>
<td>Female</td>
<td>3-1</td>
<td>10</td>
<td>Day1, some hours after birth</td>
<td>Day1-3, some hours after birth, nasogastric tube</td>
<td>Day1, some hours after birth (cyanosis); no reported treatment</td>
<td>5.1 then normal</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>3-2</td>
<td>10</td>
<td>Day1, some hours after birth when bathed</td>
<td>Day1-3 onset in bath</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>4 (French)</td>
<td>Male</td>
<td>4-1</td>
<td>NA</td>
<td>Day1</td>
<td>Day1-3 no treatment reported</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>4-2</td>
<td>10</td>
<td>Day1, some hours after birth</td>
<td>Day1-6, some hours after birth nasogastric tube</td>
<td>Day2-6, nasal oxygen required</td>
<td>Normal</td>
</tr>
</tbody>
</table>

NA - NOT AVAILABLE