Clinical and genetic analysis of a family with two rare reflex epilepsies

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ABSTRACT

Purpose: To determine clinical phenotypes, evolution and genetic background of a large family with a combination of two unusual forms of reflex epilepsies.

Method: Phenotyping was performed in eighteen family members (10 F, 8 M) including standardized EEG recordings with intermittent photic stimulation (IPS). Genetic analyses (linkage scans, Whole Exome Sequencing (WES) and Functional studies) were performed using photoparoxysmal EEG responses (PPRs) as affection status.

Results: The proband suffered from speaking induced jaw-jerks and increasing limb jerks evoked by flickering sunlight since about 50 years of age. Three of her family members had the same phenotype. Generalized PPRs were found in seven members (six above 50 years of age) with myoclonus during the PPR.

Evolution was typical: Sensitivity to lights with migraine-like complaints around adolescence, followed by jerks evoked by lights and spontaneously with dropping of objects, and strong increase of light sensitivity and onset of talking induced jaw jerks around 50 years.

Linkage analysis showed suggestive evidence for linkage to four genomic regions. All photosensitive family members shared a heterozygous R129C mutation in the SCNM1 gene that regulates splicing of voltage gated ion channels. Mutation screening of 134 unrelated PPR patients and 95 healthy controls, did not replicate these findings.

Conclusion: This family presents a combination of two rare reflex epilepsies. Genetic analysis favors four genomic regions and points to a shared SCNM1 mutation that was not replicated in a general cohort of photosensitive subjects. Further genetic studies in families with similar combination of features are warranted.

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1. Introduction

Epileptic jaw jerks (orofacial myoclonus) provoked by reading is a rare, but known syndrome [1]. Isolated speaking-induced facial myoclonic jerks without provocation by reading and writing is even more special [1,2]. We describe a family with members who have both speaking induced jerks and reflex photosensitivity still active above 50 years of age; a phenotype that to our knowledge has never been reported.

Clinical photosensitivity and the photoparoxysmal EEG response (PPR), predominantly expressed around adolescence a female predominance. It is more common in patients with myoclonic forms of generalized epilepsies and seen in only 1% of non-epileptic controls [3,4]. A feature of PPR is the autosomal dominant segregation in families. Linkage and candidate gene studies have been performed for PPR but findings indicate that the epilepsy background of families determines which PPR locus is linked [5–8]. We describe an unique family to delineate its clinical expression and part of its genetic background.

2. Material and methods

2.1. Clinical assessments

The Dutch Caucasian family was ascertained through a single patient (II-2). After informed consent, eighteen family members (10 F, 8 M) were investigated, with medical history taking and obtainment of medical record data. Each subject underwent an EEG with standardized intermittent photic stimulation (IPS) using a Grass PS33 stimulator. Flash frequencies were given in trains of 5 s ranging from 2 to 60 Hz with clinical symptoms noted [9]. See Fig. 1 for pedigree.

2.2. Genetic analyses

Family members with PPR were classified as affected. The remaining family members were set as unknown. Linkage analysis, was performed using Merlin 1.1.2 and standard settings. WES of proband and II-1 was done to identify the gene mutation underlying the trait. Furthermore, European and Australian individual PPR–IGE samples and healthy control samples were analyzed for that particular gene mutation. Functional studies were done with a splicing assay based on a minigene construct [10] (see Fig. 3) that was analyzed using qPCR and different expressions were tested using t-test of dCt values of replicates.

3. Results

3.1. Summary (of evolution) of phenotypes (see Table 1)

We ascertained eighteen family members (10 F, 8 M):

Four had speaking evoked jaw jerks, jerks in the limbs provoked by light, and generalized PPRs. Another four had jerks provoked by flickering lights and generalized PPRs. Six of eight family members of above 50 years still showed PPR. Seven of these eight photosensitive members showed myoclonus during the PPR. MRI and background EEGs were normal in nearly all; mostly

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Fig. 1. Pedigree of the family with very rare combination of persistent photosensitivity and speaking induced jaw jerks.
generalised ED were registered, either spontaneous or provoked (slightly by HV, but by far the most by IPS).

3.1.1. Evolution was typical

1. Around adolescence sensitivity to lights with migraine-like complaints, then jerks evoked by lights and spontaneously with dropping of objects;
2. Around age fifty strong increase of light sensitivity and onset of talking induced jaw jerks.

Epileptic manifestations become burdensome especially after age 50 (jerks and even GTCS).

3.2. Detailed phenotypic evaluations of family members with epilepsy

3.2.1. II-1 (proband)

At age 12, she experienced nausea and vomiting when exposed to flickering sunlight or artificial lights (fluorescent lighting) and to black and white striped patterns. Later in adolescence she developed myoclonic jerks in her limbs mostly on the right side evoked by visual stimuli and tiredness. Since her mother and sisters had similar complaints, the signs and symptoms were not considered as abnormal and no investigations have been done. Only, when in her fifties, she asked for a neurological consultation, because she noticed that her photosensitivity became stronger with more violent jerks in arms and shoulder, with in addition jaw-jerks induced by speaking. Jerks can occur at any time during day and night. What bothered her most however, were jaw-jerks provoked by talking, making her work as a teacher impossible.

Physical examination, was normal except for jaw jerks to the right side during talking. EEG recording at age 52 (no medication) confirmed a very strong sensitivity to IPS (generalized epileptiform discharges between 3 and 60 Hz) with generalized myoclonic jerks and an unpleasant sensation during these photic induced EEG discharges. No spontaneous epileptiform discharges were recorded, or spontaneous jerks. Visual Evoked Potentials were normal; Magnetic Resonance Imaging was refused due to claustrophobia.

VPA 600 mg was prescribed, suppressing most of her spontaneous and photic induced myoclonic jerks, but not her sensations when exposed to flickering lights. EEG registration at age 53 (VPA

![Fig. 2. The figure shows the four identified linkage peaks on chromosomes 1, 5, 13, and 19. Linkage was performed under a dominant model (chromosomes 1, 13, and 19) and for a recessive model for chromosome 5 using an affected only approach.](image-url)
Table 1
Clinical and EEG data from the proband (II-1) and her family members.

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age (year)</th>
<th>Onset M provoked by flickering lights</th>
<th>Onset M spontaneous</th>
<th>Onset jaw jerks (year) provoked by talking</th>
<th>Sz other than M</th>
<th>Age (year) at EEG (AED)</th>
<th>EEG background</th>
<th>Interictal epileptiform discharges</th>
<th>PPR range (Hz)</th>
<th>Clinical symptoms during PPR</th>
<th>Complaints during PPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-1</td>
<td>F</td>
<td>61</td>
<td>12 year</td>
<td>12 year</td>
<td>51</td>
<td>–</td>
<td>53 (VPA 600 mg)</td>
<td>N</td>
<td>–</td>
<td>5–50 gen</td>
<td>M arms</td>
<td>Unpleasant feeling</td>
</tr>
<tr>
<td>II-5</td>
<td>F</td>
<td>64</td>
<td>Adol.</td>
<td>50 year</td>
<td>44 year</td>
<td>45</td>
<td>GTCS; occipital sz?</td>
<td>58 (VPA 1000 mg)</td>
<td>N</td>
<td>–</td>
<td>13–25 gen</td>
<td>Electric shock</td>
</tr>
<tr>
<td>II-6</td>
<td>F</td>
<td>63</td>
<td>Adol.</td>
<td>55 year</td>
<td>55</td>
<td>–</td>
<td>56</td>
<td>N</td>
<td>–</td>
<td>16–18 gen</td>
<td>M body</td>
<td>Anxious feeling</td>
</tr>
<tr>
<td>II-9</td>
<td>F</td>
<td>58</td>
<td>50 year</td>
<td>50 year</td>
<td>?</td>
<td>?</td>
<td>51</td>
<td>N</td>
<td>Gen ir. Spike-and Waves</td>
<td>5–30 gen</td>
<td>M body</td>
<td>Anxious feeling</td>
</tr>
<tr>
<td>II-3</td>
<td>M</td>
<td>65</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>58</td>
<td>N</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>II-11</td>
<td>F</td>
<td>61</td>
<td>Adol.</td>
<td>Adol.</td>
<td>50</td>
<td>–</td>
<td>50</td>
<td>Irr.</td>
<td>–</td>
<td>15–60 gen</td>
<td>M body</td>
<td>Loss of control</td>
</tr>
<tr>
<td>I-2</td>
<td>F</td>
<td>89</td>
<td>Adol.</td>
<td>Adol.</td>
<td>?</td>
<td>?</td>
<td>ND</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>III-4</td>
<td>F</td>
<td>31</td>
<td>13 year</td>
<td>13 year</td>
<td>?</td>
<td>A</td>
<td>24</td>
<td>N</td>
<td>Gen ir. Spike-and Waves; Occ Sharp Waves</td>
<td>25–30 gen</td>
<td>15; 20 occ</td>
<td>EMA</td>
</tr>
<tr>
<td>II-8</td>
<td>F</td>
<td>58</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>53</td>
<td>N</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>III-10</td>
<td>F</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>15</td>
<td>Irr.</td>
<td>–</td>
<td>10–25 occ</td>
<td>–</td>
<td>Loss of control</td>
</tr>
<tr>
<td>III-1,2,3, 6,7,8,9</td>
<td>2F, 5 M</td>
<td>29–35</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>24–30</td>
<td>N</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

M, myoclonus or jerk; Sz, seizure; PPR, photoparoxysmal EEG response on IPS; Adol, adolescence; GTCS, generalized tonic-clonic seizure; A, Absence; EMA = eyelid myoclonia with absences; VPA = valproate; N = normal; Irr. = irregular; gen = generalized; occ = occipital; ND = not done.
600 mg) showed a diminished more occipital response to 2 and 60 Hz flashing lights, but still rather strong reactions to IPS (generalized PPRs between 5 and 50 Hz, evoking arm myoclonic jerks). She appeared to be also sensitive to black and white vertical patterns and a 50 Hz TV screen (occipital epileptiform discharges). Generalized epileptiform discharges could be evoked by the provocative program Pokémon cartoon with red/blue 15 Hz flashing images, at both a 50 and 100 Hz TV screen.

No spontaneous epileptiform discharges were recorded, or spontaneous jerks.

3.2.2. II-5 – older sister of II-1

Similar to her sister she started complaining of flashing sunlight in adolescence. She noticed spontaneous myoclonic jerks in arms and legs (L > R) since the age of 44. A year later she experienced jerks on the L side of her body accompanied by stuttering and swallowing movements. Jaw jerks were provoked by talking. EEG (no medication) showed frequent spontaneous generalized spike and waves with frontal maximum; photic stimulation was not performed.

When traveling by train at age 48 flickering sunlight through the trees evoked a GTCS; the seizure started with “an electric shock” in her left arm and leg, then shivering and subsequent loss of consciousness.

EEG recording at age 58 (VPA 1000 mg) showed a normal background with epileptiform activity exclusively during photic stimulation (13–25 Hz). During these PPRs the patient had myoclonic jerks in her arms.

Treatment with VPA 1000 mg suppressed the seizures adequately.

LEV was added after two 15 min episodes of blurred vision and black circling dots – it was unclear if these were migrainous or occipital seizures, and she became completely free of attacks. MRI was normal.

3.2.3. II-6 – older sister of II-1

After a head injury at age 12, she was treated with phenobarbione and phenytoin. Sensitivity for light started around that time, but spontaneous and talking-induced jerks became more prominent after her fifties. Headache with photophobia, nausea and vomiting became more pronounced. EEG at age 56 (no medication) showed high voltage occipital alpha and generalised PPR at 16 Hz. After the PPR at 18 Hz with panic and body jerks the IPS procedure was stopped.

3.2.4. II-9 – younger sister of II-1

After an uneventful period, she started at age 50 experiencing “jerks”, mainly felt in her head when confronted with sunlight shining through the trees. Similar experiences were noticed during flashing TV programs.

EEG at age 51 (no medication) showed normal background with sharp and slow waves over the temporal regions (independently R/L) increasing during HV and generalized PPR with occipital maximum (5–30 Hz). Body jerks were seen during most of the PPRs.

3.2.5. II-11 – youngest sister of II-1

Since adolescence she experienced jerks in her body with short periods of loss of consciousness when driving in a car with sunlight flickering through the trees. Spontaneous jerks with dropping objects were present as well. In her fifties she noticed jaw jerks when talking.

EEG at age 50 (no medication) showed irregular sharp background activity that increased during HV. IPS evoked occipital PPRs at 5, 10 and 30 Hz and generalized PPRs between 15 and 60 Hz with slight body jerks.

3.2.6. III-4 – daughter of II-1

As a child she regularly complained about headache and abdominal pain. At age 13 she experienced an episode of blurred vision, dropped chewing gum, was numb in her L arm and had nausea. Myoclonic jerks began at age 15, especially when she was tired, stressed, or used alcohol. The jerks affected her arms more than her legs with dropping of objects that could happen up to 3 times daily. Like in her aunt (proband II-1) the jerks could disturb her sleep. After a myoclonic jerk she was usually disoriented for a while. Absences without myoclonic jerks were also noted, similar to her mother as she remarked. Being an architect, above described seizure manifestations disturbed her career. She complained in addition about having a strong sensitivity to discotheque lighting, computer screens and flickering sunlight.

EEG at age 24 showed a normal background with spontaneous fronto-parietal irregular epileptiform activity. Hyperventilation increased the frequency of this. IPS between 25 and 30 Hz provoked generalization of these complexes with concomitant eyelid myoclonia and absences. Pattern sensitivity was not found, but Pokémon red and blue flickering frequencies evoked diffuse epileptiform activity at both the 50 and 100 Hz TV. MRI was normal.

3.2.7. I-2 – grandmother

Proband II-1 and other children reported that mother had exactly the same combination of jerks leading to dropping objects.
Whole genome linkage analysis revealed suggestive linkage to four locations: chromosome 1p12-q22, 13q31.1-q32.1, 19p13.3, and 5q11.2-q13.1 (see Fig. 2).

WES of the proband and II-1 detected 4201 non-synonymous variants. Of these, 209 variants were underlying our linkage peaks. Finally, only 16 variants were either novel or rare (MAF < 0.001) and predicted to affect normal protein function. Of these 16 variants, three were fully cosegregating with disease in the family. These variants are SPAG17 (c.118609491 C>T, p.C806F) on chromosome 1, ABC4 (c.95727686 C>G, p.E889Q; rs148067777, frequency 7/8593 in European population) on chromosome 13, and SCNM1 (c.151139877 C>T, p.R129C; rs144369082, frequency 4/8596 in European population) on chromosome 1. The SCNM1 variant remained the most likely candidate based on its function and expression in brain. However, the R129C variant was not present in 474 PPR cases with generalized epilepsy and 95 Dutch control subjects, suggesting that the R129C is a rare mutation and specific for our family.

We hypothesized that the SCNM1 mutation could act by modulating the amount of alternative splicing of a voltage-gated ion channel splice-variant. We tested splicing of this variant in the context of the splice variant SCN1A (IVS5N + 5 G > A), which was also present in eight of the nine affected family members (see Fig. 4).

The results show increased expression of exon 5N in the SCN1A IVS5N + 5 G/G variant as compared to SCN1A IVS5N + 5 A/A in cells with wildtype SCNM1 (p = 0.004, Fig. 4). Presence of either SCNM1 R187X or R129C mutants reduced exon 5N expression in SCN1A IVS5N + 5 G/G as compared to SCN1A IVS5N + 5 G/G wildtype SCNM1 (p = 0.005 for R187X and p = 0.03 for R129C), indicating aberrant exon splicing. Furthermore, exon 5N expression is increased in SCN1A IVS5N + 5 A/A with R187X SCNM1 mutation as compared to SCN1A IVS5N + 5 A/A wildtype SCNM1 (p = 0.046 for R187X).

Fig. 4. This figure shows the relative expression of exon 5N for the different SCN1A IVS5N constructs that were co-transfected with the different SCNM1 constructs. Relative expression was measured using qPCR with primers specific for the 5A or 5N exon, and different expressions were tested using t-test of 4CI values of replicates. The “*” indicates significant different relative expression, AAR129C, AAR187X and GGwt were compared to AA-wt; GGR129C and GGR187X were compared to GGwt.

4. Discussion

The family members with PPR, light evoked limb or body jerks, and speaking induced-jaw jerks can be classified as Idiopathic Generalized, based on myoclonus and GTCS with normal intelligence, imaging (MRI) and EEG background. The subtype Juvenile Myoclonic epilepsy (JME) does not really fit, because of loss of awareness during the jerks and occurrence at any time [11]. There is only slight resemblance with a French family presenting with jerks in jaw and arms and speaking induced stuttering, yet this family did not present photosensitivity [2].

Remarkably, our family members were still photosensitive at age fifty to sixty. Some members complained even about a strong increase after age forty, which is very unusual [12,13]. It might be that the younger generation, when older, will develop the same clinical symptoms.

Genetic analysis showed evidence for linkage of four regions to the photosensitive phenotype of this family. Nevertheless, we detected a single putative disease variant in SCNM1, as defined as a predicted damaging rare coding variant. Putative disease variants under the remaining three peaks might be non-coding variations with a regulatory function, or were undetected due to limitations of WES. SCNM1 has a role in splicing and modifies disease severity in a mouse model of ataxia caused by primary consensus splice-site mutation in SCN8a. SCN8A is a recently discovered epilepsy gene linked to epileptic encephalopathies [14,15].

Our splicing assay showed that the SCNM1 mutation affects splicing of the SCN1A 5N neonatal exon that is influenced by the IVS5N + 5 G > A SCN1A splice variant present in 8 out of 9 affected family members. As the SCN1A splice variant is not linked to PPR, we can only tentatively hypothesize that SCNM1 mutation can lead to increased susceptibility to PPR and epilepsy, through differential splicing of a yet unobserved ion channel splice variant in this family.

We did not detect additional SCNM1 mutations in other photosensitive individuals. However, none of these subjects resembled the complex phenotype of the family members presented here. These data show that SCNM1 mutations do not play a major role in epilepsy or PPR in general and further screening
may uncover a PPR variant that underlies the photosensitivity in this family.

5. Conclusion

This family presents a combination of two rare reflex epilepsies: one is speaking induced myoclonus, the other is photosensitivity. Remarkable is the increase of light sensitivity and onset of talking induced jaw jerks around the age of 50. Genetic analysis favors four genomic regions and points to a shared SCN1 mutation that was not replicated in a general cohort of photosensitive subjects. Further genetic studies in families with similar combination of features are warranted.

Conflict of interest statement

None of the authors has any conflict of interest to disclose. This study is not industry sponsored.

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