Is genetic aetiology an absolute contraindication for epilepsy surgery? Description of two patients with focal genetic epilepsy who underwent presurgical study

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Abstract

In an era in which genetic panels are widely available, a growing number of lesional focal epilepsy cases, classically considered acquired, have been proven to have a genetic aetiology. Surgical anecdotal cases of focal genetic epilepsy have been reported but the prognostic value of a genetic aetiology is still uncertain, due to the lack of long follow-up data. From preliminary studies it seems that SCN1A epilepsy is associated with a bad surgical outcome, while DEPDC5 related epilepsy could be improved by a surgical approach. We reported the cases of two patients with focal epilepsy due to SCN1A and DEPDC5 mutations who underwent pre-surgical evaluation. Patient 1, despite suffering from SCN1A-related epilepsy, had a good surgical outcome, while patient 2 with DEPDC5-related focal epilepsy was unsuitable for surgery. In our opinion genetic aetiology may not be an absolute contraindication for surgery; phenotypic expression and a personalized pre-surgical workup could help to select which patients could benefit from surgery.

KEY WORDS: genetic epilepsy surgery, SCN1A, DEPDC5, focal cortical dysplasia, hippocampus sclerosis.

Introduction

A monogenetic Mendelian aetiology was long supposed in epilepsy, overall for idiopathic generalized epilepsy. However, the first gene to be identified in epilepsy was CHRNA4, implicated in a rare form of focal epilepsy recently renamed Sleep related Hypermotor Epilepsy (ADSHE) (1, 2). Since 1995 a growing number of mutations have been reported in gene coding for ion-channel or protein associated with ion channels, such as CHRNA4, CHRNA2, KCNT1, LGI1, RELN, SCN1A, SCN1B (3); they have been proved to cause both familial and sporadic focal epilepsy, with an autosomal-dominant inheritance or with a less obviously Mendelian inheritance (3, 4). In particular, the discovery of SCN1A mutations has been very important, since it has become over time the most frequent causative gene in epilepsy (5). The SCN1A related epilepsy disclosed two interesting features, indeed the same mutation, in different members of the same family, could cause both generalized epilepsy and focal epilepsy; moreover, some forms of focal epilepsies were found to be associated with well-known epileptogenic lesions such as hippocampus sclerosis or focal cortical dysplasia (6, 7).

Lastly mutations in Dishevelled, Egl-10 and Pleckstrin Domain-Containing protein 5 (DEPDC5) have been proven to be the aetiology of a wide variety of familial focal epilepsies ranging from Sleep-Related Hypermotor Epilepsy (SHE) to focal epilepsy due to malformation of cortical development such as focal cortical dysplasia (8). Surprisingly, DEPDC5 protein is not connected to the ion-channel function, but its mutations hyper-activate the mammalian target of rapamycin complex 1 (mTORc1), which is an important regulator of cell proliferation, migration and plasticity (9, 10). The mTORc1 dysregulation is an interesting epileptogenic model since on the one hand it is able to provoke neuronal hyperexcitability, and on the
other it could impair neuronal proliferation/differentiation leading to MCV (11). Even if some de novo pathogenic variants have been reported, DEPDC5-related epilepsy is mainly inherited in an autosomal dominant manner (8). Similarly to SCN1A family, DEPDC5 family showed high phenotypic variability, with members affected by different types focal epilepsy (i.e. FFEVF) associated or not with MCV (8).

In clinical practice, in the presence of a focal lesion in an epileptic drug-resistant patient with a known genetic mutation that is thought to have affected all neurons, it is reasonable to consider whether the surgical resection of a focal area is sufficient to achieve seizure-freedom. In literature some anecdotal surgical series of patients with genetic focal epilepsy associated or not with a visible lesion have been reported (12-19, Table 1), but the right management of genetic focal epilepsy and long follow-up data are still lacking. From preliminary studies it seems that focal epilepsy related to mTORc1 dysregulation (DEPDC5, NPRL3 and NPRL2) is associated with epileptogenic lesions, mainly focal cortical dysplasia, and that they could benefit from surgery; while SCN1 (A and B) mutations are mostly connected to aspecific lesions and seem to have a bad surgical outcome (12-19, Table 1). We report the cases of two patients who suffered from focal epilepsy due to genetic mutation that underwent pre-surgical study.

Clinical cases description

**Case 1**
A 27-year-old man with normal development had a known missense mutation in p.Glu1881Lys of SCN1A inherited from his healthy mother. The mutation was discovered in his family during the diagnostic process of his younger sister, a 22-year-old girl affected by an epileptic Dravet-like encephalopathy. The older 28-year-old sister had two isolated tonic-clonic seizures at the age of 6 months and 8 years, one during fever. She had a child with neonatal seizures under diagnostic investigation. The patient had a first unprovoked tonic-clonic seizure at the age of 20 years. One year later he had the first episode of impaired consciousness associated with a fixed standing position lasting few seconds; the episodes continued as multiple per years and could be followed by a secondary generalization. After trying numerous anti-epileptic drugs (AED), generalized seizures decreased in frequency, but minor episodes of impaired consciousness occurred on a monthly frequency. These episodes were characterized by oral automatism, drooling, stiffness of the right arm, right hemibody jerks and autonomic activation. He was therefore hospitalized to undergo pre-surgical study. Video-EEG monitoring documented frequent inter-ictal epileptiform spikes over the left temporal region. We recorded one habitual episode characterized by unresponsiveness status, oral automatism and left eyes orientation. The ictal EEG showed a recruited theta activity arising from the left temporal region that remained confined to the left hemisphere. The 3T MRI disclosed left mesial temporal sclerosis (Fig. 1). Due to high concordant anatomo-clinical correlation, the patient underwent left temporal lobectomy and today have been seizure-free for 1 year.

**Case 2**
A 55-year-old woman, born by a forceps delivery followed by normal development, started to experience seizures in wakefulness at the age of 10. During the episode she turned around herself and laughed because of a funny subjective dizziness. The first EEG showed a right fronto-temporal epileptic focus and so antiepileptic therapy with carbamazepine and phenytoin was introduced. At the age of 15 years nocturnal hypermotor seizures appeared. During the episodes

<table>
<thead>
<tr>
<th>Genes</th>
<th>No. of cases</th>
<th>Phenotype</th>
<th>Imaging</th>
<th>Histology</th>
<th>Outcome</th>
<th>Reference</th>
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<tbody>
<tr>
<td>DEPDC5</td>
<td>8</td>
<td>ADSHE</td>
<td>6</td>
<td>4 FCD IIA</td>
<td>63% SF</td>
<td>12-14</td>
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<td></td>
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<td>NPRL-2</td>
<td>1</td>
<td>FFEVF</td>
<td>-</td>
<td>FCD Ia</td>
<td>50% reduction</td>
<td>15</td>
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<td>NPRL-3</td>
<td>5</td>
<td>FFEVF</td>
<td>5</td>
<td>5 FCD IIA</td>
<td>3 SF</td>
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<td>2 rare seizures</td>
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<td>SCN1A</td>
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<td>Dravet</td>
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<td>CPS</td>
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Table 1 - Patients with focal epilepsy due to mTORc1 and SCN mutation that underwent surgical treatment. ADSHE, Autosomal Dominant Sleep Related Hypermotor Seizures; FFEVF, Familial Focal Epilepsy with Variant Foci; GEFS+, Generalized Epilepsy Febrile Seizures plus; CPS, Complex Partial Seizures; n.c, not conclusive; FCD, Focal Cortical Dysplasia; SF, Seizure Free; HS, Hippocampus Sclerosis; MTS, Mesio-Temporal Sclerosis.
she showed a wide variety of sleep-related movements ranging from purposeless flex-extension movements of the limb to epileptic wandering during which she could go out of home and walk naked around the neighbourhood; the same sensation as the daytime events sometimes preceded the nocturnal episodes. Seizures in daytime, characterized by a sensation of instability, of “being on the edge of an abyss”, fear-induced tachycardia and automatism of the left arm, were rare in frequency. Despite trying numerous AED the nocturnal episodes continued at high frequency, while the diurnal attacks occasionally occurred mainly during therapy changes. At the age of 37 she started diagnostic and pre-surgical workup.

The EEG monitoring showed rare epileptiform activity over both fronto-central-parietal regions, with left prevalence. She underwent nocturnal video-polysomnographic monitoring, during which we recorded 7 seizures from 2N-REM sleep, one during REM sleep and one during wakefulness. The episodes consisted in purposeless flex-extension movement of all four limbs, wider in right leg; the left arm appeared fixed, sometimes stiff, while the right arm was brought up and flexed behind the head. Sometimes a right orientation of the head was noted during the episodes. In wakefulness the patient described, as first ictal symptom, a sensation of heat in the whole body, then because of fear to fall she clung to bed. We performed a 1.5 T MRI that did not disclose abnormalities.

Due to the uncertain epileptogenic zone she underwent stereo-EEG study (SEEG). The SEEG examination was based on the prevalence of left epileptiform activity on interictal EEG and some lateralizing semiological features; bilateral limbic exploration extended to inferior lobe was therefore scheduled. During s-EEG monitoring numerous typical nocturnal episodes were recorded; inter-ictal activity was diffuse prevailing on the right medial cingulate cortex (Fig. 1). Ictal s-EEG was characterized by an epileptiform activity highly suggestive of focal cortical dysplasia (20), arising, synchronously/asynchronously, from both anterior cingulate regions, sometimes prevailing on the right central-anterior mesial cortex (H electrode) (Fig. 2). Multiple 1.5 T MRI examinations, including spectroscopy and resting-state fMRI studies, were repeated over time without evidence of brain lesions. Due to the lack of a clear epileptogenic zone the surgical approach was contraindicated. A whole
exome sequencing identified a likely genetic cause of her epileptic disorder nine years later: a frameshift mutation in DEPDC5 (c.492delTCGTT; p.Arg165 Tyrfs*14), inherited from the healthy mother [details in (21), family 18]. Recently we have performed a PET study that showed a small hypo-metabolic area in left frontal anterior dorsolateral cortex and a 3T MRI study that disclosed a suspected blurring gyrus within the same area (Fig. 2). To date the patient still has weekly nocturnal seizures but due to old age she refused surgery.

Discussion

We reported the cases of two patients with focal epilepsy, due to genetic aetiology, that exemplify the possible scenario that epilepsy surgery might have to face in the next years. Case 1 had a well-known epileptogenic lesion, good anatomo-electro-clinical correlation and despite an SCN1A mutation and a sister affected by Dravet syndrome, he had a favourable surgical outcome. Moreover, case 1 confirms that HS should be included in SCN1A clinical spectrum, regardless of any history of febrile infantile seizures (22). Even if the first surgical series reported bad surgical outcome in SCN1A patients, mainly affected by Dravet syndromes or GEFS+ (17, 18), our case suggests that genetic aetiology should not be an absolute contraindication, but it could be taken into account in the pre-surgical evaluation, which has to be personalized in each patient. If during the evaluation a clear lesion is concordant with clinical and neurophysiological study, surgery could be effective even in genetic cases. Anecdotal surgical series of epilepsy due to mTORc1 mutations seem to confirm the good surgical outcome of some forms of genetic focal epilepsy. Most of the reported cases were connected to FCD and had concordant anatomo-electro-clinical correlation; also, in some MRI negative cases it is possible to speculate the presence of a focal unrecognized lesion, due to lower sensitivity of 1.5 MRI scan and PET evidence of focal hypometabolic area in some cases (12, 15, 16). Case 2 may reflect this intermediate scenario in which...
Surgery in focal genetic epilepsy

some electro-clinical data point to a focal epilepto-genic area, but MRI fails to disclose a visible lesion. The SEEG study, usually considered the gold standard in EZ localization, showed a diffuse epileptiform activity, highly suggestive of FCD (20), without evidence of a focal onset and so the patient was discarded by surgery. SEEG result could be explained partly by a wide EZ, often observed in FCD-related epilepsy, but also by an incomplete left frontal exploration that did not allow EZ definition. Years later we found a hypometabolic area in left fronto-polar region that addressed the 3T MRI examination to look for subtle focal alterations. We believe that advanced MRI studies could be diriment in this intermediate scenario, indeed due to higher spatial resolution, they could guide SEEG examination and help to select the patients who can benefit from surgery. The last possible scenario of focal genetic epilepsy consists in an MRI negative patient with focal seizures and uncertain electro-clinical correlation; in these cases we believe that SEEG examination and surgery should be contraindicated unless some advanced MRI evidence pointed to a presumed focal lesion.

To conclude, genetic etiology does not seem an absolute contraindication for epilepsy surgery. The phenotypic expression and personalized anatomoelectro-clinical correlation have a leading role in assessing which patients could benefit from surgery. Even if genetic etiology could have a prognostic value, this is still uncertain, in fact the surgical outcome of the patients we presented disagreed with those reported in literature. More data of long follow-up are needed to clarify the prognostic value of mutation in focal epilepsy. We hope that our cases could add two more pieces in this complex puzzle.

References

