Severe Epilepsy in An Adult with Partial Trisomy 18q

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Epilepsy is one of the most common presentations associated with chromosome aberrations. Detailed descriptions of some aberration-specific epileptic and electroencephalographic (EEG) phenotypes have been reported (i.e., Angelman syndrome, ring 20 etc.). However there is limited and mixed information about the characteristics of epilepsy related to trisomy 18. Thus a common seizure phenotype has not been characterized yet. Here we describe in detail a patient with refractory epilepsy and partial 18q trisomy.

INTRODUCTION

The trisomy 18 syndrome, also known as Edwards syndrome, is a common autosomal chromosomal disorder with an overall prevalence of 1/2,500–1/2,600 and a live born estimated prevalence of only 1/6,000–1/8,000; approximately 50% of babies live longer than one week [Cereda and Carey, 2012]. Of these, only 5–10% live longer than one year because of the high incidence of congenital malformations mainly affecting the heart, genitourinary, gastrointestinal and central nervous system. Minor anomalies involve face, eyes, and limbs. The distinctive phenotype results from full (about 94% of cases), mosaic (5% of cases) or partial trisomy 18q (1% of cases) [Cereda and Carey, 2012]. The incidence of epilepsy is estimated to be about 25–50% [Carey, 2010] but recently Kumada et al. reported a prevalence of 64% [Kumada et al., 2012]. Although Edwards syndrome is the second most common trisomy after Down syndrome, and epilepsy is not rare in this condition, there are only few detailed descriptions about epilepsy associated with Edwards syndrome. We report on an adult with partial 18q trisomy and severe refractory epilepsy.

CLINICAL REPORT

This 30-year-old man is the second child of healthy unrelated parents. Family history is negative for epilepsy and any other neurological condition. Pregnancy was complicated by bleeding during the second trimester and a reduction of fetal movements was noted at that time. He was born at term; the delivery was uneventful. At birth his head circumference was 32 cm (3rd–5th centile), weight was 2,700 g (5th–10th centile) and length was 45 cm (<3rd centile). Feeding problems and delayed psychomotor development were soon noted. During the first evaluation at 17 months of age, many dysmorphic features were present including flat face, strabismus, hypertelorism, anteverted nostrils, long philtrum, thin upper lip vermilion, 2–3 toe syndactyly of both feet (Fig. 1a and b show the dysmorphism of the patient at present, as an adult). Cardiac and abdominal ultrasounds were unremarkable. A metabolic screening test was negative. A brain MRI scan performed at the age of seven years showed only mild cerebral atrophy.

He presented with his first seizure at six years old. This was a generalized tonic-clonic (GTC) convulsion occurring during a febrile illness. Soon after, the patient developed spasms that occurred daily upon awakening and tonic asymmetric seizures occurring during sleep and upon awakening. At that time the interictal electroencephalographic (EEG) showed multiple focal discharges over the posterior regions (see Fig. 1c); sleep worsened these abnormalities (see Fig. 1d); valproic acid (VPA) did not improve the seizures’ severity and frequency. From age 12, the spasms disappeared but GTC seizures continued; drop-attacks appeared with a daily frequency. None of the antiepileptic drugs (AEDs) administered (carbamazepine, clobazam, phelbamate, and vigabatrin) improved the frequency or severity of seizures.

He was referred to our department at the age of 30. Neurological examination showed severe intellectual disability, a lack of sphinct-
FIG. 1. (a) facial and (b) foot dysmorphism of the patient as an adult; (c) interictal EEG recorded at six years old showing multiple focal discharges over the posterior regions with worsening during sleep (d); (e) interictal electroencephalographic (EEG) recorded at the age of 30 showing generalized and focal paroxysmal activity mainly over the left temporal and posterior regions; (f) ictal EEG recorded at 30 years old showing spike/polyspike-slow wave complexes clinically related to a head drop; (g) Schematic of the duplication affecting the long arm of the chromosome 18. The red box indicates the duplication of the present case.
ter control, absence of language and inability to walk unaided. At that time the patient still suffered from daily events including absence, tonic and atonic seizures while GTC seizures occurred at a frequency of 3–4/year. Interictal EEG showed generalized and focal paroxysmal activity mainly over the left temporal and posterior regions (see Fig. 1e); in some occasions the presence of a spike/ polyspike-slow wave complex was clinically related to head drop (see Fig. 1f). At that time he was on treatment with VPA at the dose of 800 mg/day. Rufinamide was added up to a dosage of 1,200 mg/day obtaining a slight reduction in frequency of tonic and atonic seizures.

**CYTOGENETICS**

Array-CGH analysis using a Human Genome CGH Microarray Kit 8 × 60 (Agilent) showed a 25.9 MB duplication at 18q12.3-q22.1 (chr18:39,792,312-65,676,291; HG 19) involving 100 protein-coding genes (see NCBI Ensembl for information on each gene in the region and Fig. 1). A schematic illustration of the duplication is shown in Figure 1g. The rearrangement was de novo.

**DISCUSSION**

Structural abnormalities of the central nervous system have been reported in about 5% of infants with trisomy 18; the most common are cerebellar hypoplasia, agenesis of corpus callosum, microgyria, hydrocephalus, and myelomeningocele [Carey, 2010; Kinoshita et al., 1989].

Epilepsy is commonly described in patients with trisomy 18 [Jones, 2006; Carey, 2010] and only few cases can be ascribed to structural malformations. There is still a lack of detailed descriptions of epilepsy associated with Edwards syndrome and this is probably due to the high mortality of these patients in the first year of life. Literature reports an overall prevalence ranging from 25 to 50% [Carey, 2010] to 64% [Kumada et al., 2012]. The prevalence of epilepsy seems lower in partial trisomy, ranging from 10% [Wilson et al., 1979] to 31% [Strathdee et al., 1995]. There are not reported data about the prevalence of epilepsy in mosaic trisomy 18. (Table I reports all data from literature about association of epilepsy with trisomy 18 including the present case).

A recent report by Kumada et al. [2012] described epilepsy in seven out of 11 (64%) patients with full trisomy 18 and concluded that over half of children develop epilepsy during infancy or early childhood, which can be focal as well as generalized; infantile spasms might also occur. Seizures are usually drug-resistant in half of the children, especially those presenting with generalized epilepsy. The same author [Kumada et al., 2010] described a case of a full trisomy 18 with onset of epilepsy at 10 months characterized by autonomic seizures presenting as epileptic apnea. Yamanouchi et al. [2005] found epilepsy in only one out of 29 patients with trisomy 18. The patient had full trisomy 18 with onset of epilepsy at four years of age; his generalized seizures were poorly controlled with phenobarbital.

Grosso et al. [2005] analyzed epilepsy linked to chromosome 18 aberrations in 14 patients: five with 18p deletion syndrome (18pDS), six with 18q deletion syndrome (18qDS), one with 17–18 translocation and two with 18p trisomy. They described epilepsy in seven out of 14 patients; two of them had 18p trisomy and epilepsy, presenting with complex partial seizures and EEG abnormalities over the posterior regions. They both had a good outcome.

Finally, to the best of our knowledge, there are only two detailed descriptions of epilepsy in 18q trisomy. The first report is by Ceccarini et al. [2007] who described three siblings carrying an interstitial duplication of the long arm of chromosome 18 (18q21.31-q22.2) inherited from a healthy mosaic carrier mother. They were presenting with borderline or mild intellectual disability and minor dysmorphic features. Out of the three siblings only one had a history of epilepsy with generalized and focal seizures. He suffered from generalized seizures from age 19, while focal seizures appeared at the age of 21 years. These were characterized by myoclonus of the perioral muscles associated with a sensation of numbness of the tongue lasting for few seconds. These episodes mostly occurred during a loud reading activity, suggesting a “reading epilepsy.” EEG showed isolated, interictal short (1 sec) saw-tooth theta waves sequences over the fronto-centro-temporal area bilaterally, triggered by hyperpnoea and photic stimulation. The other two siblings never suffered from seizures; however they both had EEG abnormalities as their epileptic brother.

The second report is by d’Orsi et al. [2013] who described a 30-year-old man with a trisomy of the 18q12.2q22.3 region. Epilepsy history is characterized by seizure onset at 25 years with GTC seizures, atonic drop attacks and eating-induced repetitive epileptic spasms. The EEG showed symmetric or asymmetric paroxysmal activity over the posterior regions associated with generalized spikes and spike and wave discharges.

Our patient shares genetic, clinical and EEG features with the patient described by d’Orsi et al. They both have a partial duplication of the long arm of chromosome 18 (18q) and present with intellectual disability and a severe epilepsy including spams, GTC and atonic seizures. The EEG showed predominantly paroxysmal activity over the posterior regions in both cases. Interestingly they both presented with late onset infantile spasms, although in our patient this was much earlier (6 years old compared to 25 years old.). The patient reported by Ceccarini et al. shows a milder phenotype with borderline intellectual functioning and late onset drug-responsive epilepsy. Interestingly reflex seizures were present both in the case described by Ceccarini (reading epilepsy) and our case (eating epilepsy).

Even if the descriptions are rare, epilepsy in partial trisomy 18 (18p and 18q) seems to have a common clinical and electroencephalographic pattern being characterized by late onset epilepsy with generalized and focal seizures (18q) or only focal (18p) and an EEG pattern with generalized and focal discharges mainly over the posterior regions. Outcome in terms of seizures’ frequency and duration can vary with better prognosis in 18p than 18q trisomy [Grosso et al., 2005; d’Orsi et al., 2013].

More data are available for full trisomy 18: epilepsy appears to be characterized by the occurrence of both focal and generalized seizures and an EEG showing focal and generalized discharges; onset is usually during infancy, commonly in the first year of life, and West syndrome is not unusual. Outcomes can be different:
TABLE I. Clinical Data of the Reported 18 Trisomy Cases Including the Present Case

<table>
<thead>
<tr>
<th>Pt</th>
<th>Genetic</th>
<th>Onset of epi.</th>
<th>Gender</th>
<th>Main type of seizures</th>
<th>Brain MRI</th>
<th>Interictal EEG</th>
<th>Outcome</th>
<th>Article</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Full trisomy 18</td>
<td>4 years</td>
<td>Male</td>
<td>Brief tonic convulsion</td>
<td>Cerebellar hypogenesis, dysplastic hippocampus</td>
<td>Multifocal spikes in the right parietal and left temporal areas</td>
<td>Poorly controlled</td>
<td>Yamanouchi et al. [2005]</td>
</tr>
<tr>
<td>2</td>
<td>Full trisomy 18</td>
<td>10 months</td>
<td>Female</td>
<td>Epileptic apnea, GTC, tonic</td>
<td>Mild atrophy</td>
<td>Focal [right parietal, left temporal] and generalized paroxysmal activity</td>
<td>Good</td>
<td>Kumada et al. [2010]</td>
</tr>
<tr>
<td>3</td>
<td>Full trisomy 18</td>
<td>2 years 9 months</td>
<td>Female</td>
<td>Complex Partial</td>
<td>n.d.</td>
<td>Normal</td>
<td>Good</td>
<td>Kumada et al. [2012]</td>
</tr>
<tr>
<td>4</td>
<td>Full trisomy 18</td>
<td>1 months</td>
<td>Female</td>
<td>GTC</td>
<td>Severe atrophy</td>
<td>Good</td>
<td>Good</td>
<td>Kumada et al. [2012]</td>
</tr>
<tr>
<td>5</td>
<td>Full trisomy 18</td>
<td>4 months</td>
<td>Female</td>
<td>Spasms, tonic, absence</td>
<td>Mild atrophy</td>
<td>Poorly controlled</td>
<td>Poorly controlled</td>
<td>Kumada et al. [2012]</td>
</tr>
<tr>
<td>6</td>
<td>Full trisomy 18</td>
<td>3 years 6 months</td>
<td>Female</td>
<td>Tonic</td>
<td>Severe atrophy</td>
<td>Good</td>
<td>Good</td>
<td>Kumada et al. [2012]</td>
</tr>
<tr>
<td>7</td>
<td>Full trisomy 18</td>
<td>2 years 5 months</td>
<td>Female</td>
<td>Spasms</td>
<td>Mild atrophy</td>
<td>Poorly controlled</td>
<td>Poorly controlled</td>
<td>Grosso et al. [2005]</td>
</tr>
<tr>
<td>8</td>
<td>Full trisomy 18</td>
<td>11 months</td>
<td>Male</td>
<td>Spasms, tonic, myoclonic</td>
<td>Severe atrophy</td>
<td>Good</td>
<td>Good</td>
<td>Elia, Sueri unpublished data</td>
</tr>
<tr>
<td>9</td>
<td>Full trisomy 18</td>
<td>10 months</td>
<td>Female</td>
<td>Epileptic encephalophaty</td>
<td>Cerebellar hypoplasia, enlargement of ventricular system</td>
<td>Paroxysmal activity prevalent over the posterior regions generalized and bioccipital Spike and Spike-Waves</td>
<td>Good</td>
<td>Grosso et al. [2005]</td>
</tr>
<tr>
<td>10</td>
<td>18p trisomy</td>
<td>4 years</td>
<td>Male</td>
<td>Complex Partial</td>
<td>Agenesis of the splenium of the corpus callosum</td>
<td>Generalized and bioccipital Spike and Spike-Waves</td>
<td>Good</td>
<td>Grosso et al. [2005]</td>
</tr>
<tr>
<td>11</td>
<td>18p trisomy</td>
<td>5 years</td>
<td>Male</td>
<td>Complex Partial Seizures</td>
<td>Enlarged cisterna magna and cerebellar hypoplasia</td>
<td>Generalized and bioccipital Spike and Spike-Waves</td>
<td>Good</td>
<td>Grosso et al. [2005]</td>
</tr>
<tr>
<td>12</td>
<td>18q trisomy</td>
<td>19 years</td>
<td>Male</td>
<td>GTC, Reflex</td>
<td>Bilateral opercula dysplasia and corpus callosum hypoplasia</td>
<td>Generalized and bioccipital Spike and Spike-Waves</td>
<td>Good</td>
<td>Ceccarini et al. [2007]</td>
</tr>
<tr>
<td>13</td>
<td>18q trisomy</td>
<td>25 years</td>
<td>Male</td>
<td>Atonic, GTCS, Reflex, epileptic spasms</td>
<td>Bilateral opercula dysplasia and corpus callosum hypoplasia</td>
<td>Focal and generalized paroxysmal activity with prevalence over the posterior regions generalized, Focal discharge over posterior regions</td>
<td>Poorly controlled</td>
<td>d’Orsi et al. [2013]</td>
</tr>
<tr>
<td>14</td>
<td>18q trisomy</td>
<td>6 years</td>
<td>Male</td>
<td>Spams, GTC</td>
<td>Mild Atrophy</td>
<td>Poorly controlled</td>
<td>Poorly controlled</td>
<td>Present Case</td>
</tr>
</tbody>
</table>

GTCS, generalized tonic clonic seizures; CPS, complex partial seizure.
some patients may respond well to one type of AED, while others can be resistant to all therapies. It is possible that the different phenotype of these conditions (18q, 18p and full trisomy 18) reflect the different gene content of the aberration. The rearrangement occurring in our patient encompasses 100 protein coding genes. Among these, eight genes might be implicated in seizures’ pathophysiology: SYP4 encodes synaptogamin 4, a protein that plays a crucial role in synaptic transmission; expression of synaptotagmin-4 is induced in the rat hippocampus after systemic kainic acid treatment [Tocco et al., 1996]; IER3IP1 encodes the immediate early response 3 interacting protein 1. Homozygous mutations have been found in patients suffering from myoclonic epilepsy occurring with other clinical conditions [Poulton et al., 2011]; MBD1 and MBD2, code for methyl-CpG binding domain proteins 1 and 2. They belong to a family of nuclear PIGN type. [Liu et al., 2007]; perglycemia. The heterozygous mice have an intermediate phenotype. The homozygous knock-out mouse develops maturity onset obesity syndrome called multiple congenital anomalies-hypotonia-seizures syndrome [Allen et al., 2011]; MC4R encodes the melanocortin 4 receptor which is activated by ACTH, the first line drug used to treat infantile spasms. This gene is dosage sensitive: the homozygous knock-out mouse develops maturity onset obesity syndrome associated with hyperphagia, ipermitosuliner, and hyperglycemia. The heterozygous mice have an intermediate phenotype. [Liu et al., 2007]; PIGN encodes the phosphatidylinositol glycan anchor biosynthesis. Mutations have been found in a syndrome called multiple congenital anomalies-hypotonia-seizures syndrome [Ohba et al., 2014]. It is difficult to state, which of these genes play a major role in the pathophysiology of epilepsy for this condition. It is possible that the overall burden of the duplicated products and their interactions lead to the disease. Although the function of the proteins encoded by these genes make them promising as candidate genes for the pathophysiology of epilepsy in this condition, functional studies are needed to clarify their exact role.

Accordingly the clinical phenotype cannot be characterized based on only three detailed reports. The description of single or group cases is essential to understand if a unified phenotype exists and, if it does then its characteristics should be studied in detail for further prognosis.

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REFERENCES


