Copy Number Variants and Epilepsy: New Emerging Syndromes

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Abstract In the last 10 years, advances in the genetic techniques including oligonucleotide array and the following large scale studies have yielded to the identification of recurrent copy number variants (CNVs) associated with epilepsy. Among these a small number has been increasingly reported in association with a distinct epileptic phenotype, delineating emerging epileptic syndromes. To date, none of these CNVs underlying a specific epileptic condition has been included in the ILAE Classification of the Epileptic Syndromes as a distinct form. However once the features and prognosis of these conditions have been completely delineated a proposal for new epileptic syndromes should be considered.

Introduction

The classification of epilepsies of the International League against epilepsy includes the categories of genetic, structural-metabolic and unknown causes (Berg et al. 2010). Many studies have proven that genetic plays a major role in epilepsy, mainly by identifying the involvement of ion channels subunits and neurotransmitters mutations. More recently, thanks to the whole genome higher definition technique, some CNVs have been increasingly reported in association with a peculiar epilepsy phenotype or syndrome. Again genes codifying for ion channels subunits or neurotransmitter protein are often the candidate genes within these segments (Mulley and Mefford 2011; Poduri and Lowenstein 2011). Even if rare, the clinical features and prognosis of these conditions are now better known defining new emerging syndromes. Here we describe an overview of the most reported CNVs associated syndromes presenting with a distinctive epilepsy phenotype.

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Genetic Method for Detecting Copy Number Variation

Routine cytogenetic analysis, namely G-banding karyotype and fluorescence in situ hybridization, have been implemented by "molecular karyotype" techniques. These refer to the evaluation of chromosome content using DNA hybridization, such as array-comparative genomic hybridization (CGH), multiplex ligation-dependent probe amplification (MLPA), single nucleotide polymorphisms (SNP) array, rather than direct observation of chromosome under the microscope, allowing clinicians and researchers to investigate the entire genome for CNVs in one experiment. The defects are then referred as genomic coordinates from the human DNA reference sequence. These have allowed the identification of micro-rearrangements including apparent "balanced" reciprocal translocation as diagnosed by light microscopy. However classical cytogenetic analysis cannot be completely replaced by "molecular karyotype", because the latter cannot detect truly balanced translocations or inversion.

Emerging Epilepsy Syndrome Associated to CNVs

Among the genome, some regions are more prone to micro-rearrangements because of the presence of breakpoint (BP) hotspots (blocks of segmental duplications that flank the deleted or duplicated sequence). Micro-rearrangements usually recur within these regions through a mechanism called nonallelic homologous recombination (NAHR). These CNVs have thus the same size and are known as "recurrent". In the last ten years many recurrent micro-rearrangements have been reported in association with epileptic phenotype (Striano et al. 2011a; Scheffer and Berkovic 2010; Heinzen et al. 2010; Dibbens et al. 2009). Among these, some present with distinct epileptic features or a specific epilepsy syndrome as the hallmark of the clinical condition. We will discuss here the emerging phenotype of epileptic conditions underlined by a micro-rearrangement including 2q24.4 deletion, 5q14.3 deletion, 6q terminal deletion, 14q12 deletion and duplication, 15q13.3 deletion and Xp11.2 duplication. Table 1 summarizes the clinical features of these emerging phenotypes. Other CNVs associated with epilepsy of minor interest are also reported (2q23.1 deletion and 7q11.23 deletion) (Mizugishi et al. 1998; Marshall et al. 2008; van Bon et al. 2010).

2q24.4 Deletion

Patients with a clinical and EEG picture of Dravet syndrome (DS) who result negative for SCN1A mutations may present SCN1A exonic or larger deletions involving SCN1A and contiguous genes (Madia et al. 2006; Mulley et al. 2006;

Table 1 Summary of the clinical features of the emerging CNVs syndromes associated to epilepsy

CNV (candidate gene)	Epileptic phenotype/syndrome	Seizure's onset/type	EEG features	Dysmorphisms	Other neurological abnormalities	Brain abnormalities	Other associated condition	Ref
2q23.1 del (EPC2 and MBD5)	Rett-like	0–10 yo/ absences	Not reported	Broad forehead, microcephaly, brachycephaly, synophrys, arched eyebrows, long palpebral fissures, full everted lower lip, broad chin, downturned corners of the mouth, teeth anomalies	Severe MR, absent speech, ataxia, disturbed sleep, behavioral problems	Slight atrophy or normal	Hirsutism, hyperphagia	(van Bon et al 2010)
2q24.4 del (SCN1A and contiguous genes)	Dravet-like	2–10 mo/ absences, GTCS, myoclonic, febrile seizures, febrile SE, CPS	Those typically reported in DS	Microcephaly, bitemporal narrowing or frontal bossing, down-slanting or short palpebral fissures, bulbous nose or broad nasal bridge, low-implanted ears, thick helix, bow-shaped mouth, anterior open bite, single palmar creases bilaterally, and partial syndactyly of 2nd–3rd toes	Mild to severe MR, ataxia, muscle hypotonia, autistic behavior	One patient with diffuse lesions in the periventricular white matter and basal ganglia (postmortem abnormalities as seen in Leigh syndrome: spongiosis and increased gliosis of the internal and external pallidum, and less pronounced lesions in the brainstem	Not reported	(Madia et al. 2006; Suls et al. 2006; Davidsson et al. 2008; Marini et al. 2009)
5q14.3 (MEF2C)	Rett-like	1–10 mo/ febrile, CPS, spasms, myoclonic	Not reported	Broad, high forehead, relatively large, backward rotated ear lobes, mildly upward-slanting palpebral fissures and cupid bowed or tented upper lip	Severe MR, hypotonia, strabism	Periventricular heterotopia, mild undermyelinisation	Not reported	(Le Meur et al. 2010; Engels et al. 2009; Zweier et al. 2010)

Table 1 (continued)

CNV (candidate gene)	Epileptic phenotype/ syndrome	Seizure's onset/type	EEG features	Dysmorphisms	Other neurological abnormalities	Brain abnormalities	Other associated condition	Ref
6qter del	Occipital epilepsy	4 mo–4 yo/CPS	Posterior SW complexes, more pronounced during sleep	Low frontal hairline, abnormal hair pattern, asymmetric face, bilateral epicanthus, horizontal or upslanting or short palpebral fissures, broad nasal bridge, micrognathia, high palate, a large gap between upper central incisors, posteriorly rotated or low-set ears, short neck, camptodactyly, phimosis, hypospadia, flat feet with valgus position of the calcaneus	Mild-moderate MR, hypotonia, diffuse joint laxity, strabism	Colpocephaly, dysgenesis of the corpus callosum and brainstem, hypertrophic massa intermedia	Not reported	(Elia et al. 2006; Striano et al. 2006; Bertini et al. 2006; Lee et al. 2011)
7q11.23-q21.11 del (MAGI2)	IS	Infancy/ spasms focal seizures	Hypsarrhytmia	Same as in Williams-Beuren syndrome; microcephaly	Hypotonia, severe MR	Not reported		(Mizugishi et al. 1998; Marshall et al. 2008)
14q12 del (FOXg1)	Rett-like	Infancy/ mainly generalized	Multifocal pattern with spikes and sharp waves	Microcephaly, downslanting palpebral fissures, bilateral epicanthic folds, depressed nasal bridge, bulbous nasal tip, tented upper lip, everted lower lip and large ears	Stereotypies; severe MR	Thin CC	Feeding problems	(Mencarelli et al. 2009)
14q12 dup (FOXg1)	IS	3–8 m/IS	Hypsarrhytmia, modified hypsarrhytmia	Frontal hairline, deep set eyes, hypotelorism	Delay/absent speech, MR	Thin CC	Non reported	(Brunetti-Pierri et al. 2011; Striano et al. 2011b)

Table 1 (continued)

CNV (candidate gene)	Epileptic phenotype/ syndrome	Seizure's onset/type	EEG features	Dysmorphisms	Other neurological abnormalities	Brain abnormalities	Other associated condition	Ref
15q13.3 (CHRNA7)	"Idiopathic generalized epilepsy"	Infancy/ absences, myoclonic absences, GTCS	Generalized S, PS, SW	Hypertelorism, upslanting palpebral fissures, prominent philtrum with full everted lips, clinodactyly	Mild MR, psychiatric problems	Absent	Not reported	(Dibbens et al. 2009; Sharp et al. 2008; Masurel-Paulet et al. 2010; Helbig et al. 2009; Muhle et al. 2011)
Xp11.22-11.23 dup	ESES	6 mo–12 yo/ absences, myoclonic, GTCS	Focal SW, generalized SW, PSW	Non specific facial dysmorphic features, lower-extremity anomalies, (flat or arched feet, fifth-toe hypoplasia, and syndactyly)	Borderline functioning to severe MR, speech delay, poor speech articulation, hoarse and/or nasal voice	Lateral ventricles and subarachnoid spaces dilation, slight peritrigonal hyperintensity	early puberty, overweight	(Giorda et al. 2009; Broli et al. 2011)

CC corpus callosum, *CPS* complex partial seizures, *DS* Dravet syndrome, *ESES* electrical status epilepticus during slow sleeps, *GTCS* generalized tonic clonic seizures, *IS* infantile spasms, *MR* mental retardation, *PS* polispike, *PSW* polyspike-and-wave, *S* spikes, *PSW* polyspike-and-wave, *SE* status epilepticus, *SW* spike-and-wave, *yo* years old
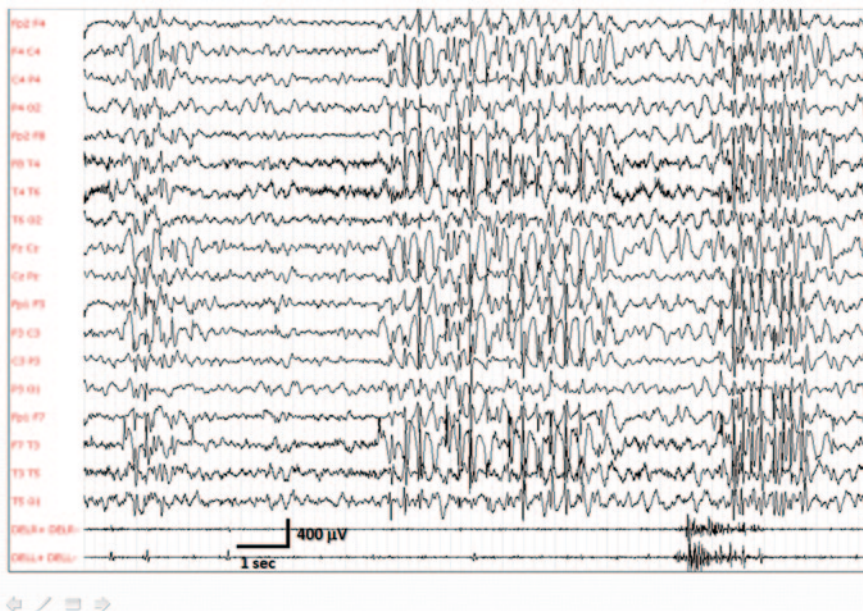
Fig. 1 Wakefulness EEG of a 4-year-old male with 2q24.4 deletion showing some generalized spike-and wave discharges

Suls et al. 2006; Davidsson et al. 2008) . These deletions account for 2–3 % of all DS cases and for about 12.5 % of patients with DS who are negative for mutations on sequencing (Marini et al. 2009).

Deletions extending beyond SCN1A and including variable numbers of contiguous genes can be associated with additional dysmorphic features, depending on the genes involved (Madia et al. 2006), or with a more severe epilepsy phenotype when other voltage-gated sodium channels (VGSC) α subunit genes clustered on chromosome 2q such as SCN2A, SCN3A, SCN7A, and SCN9A are involved (Davidsson et al. 2008; Pereira et al. 2004).

In particular, facial features were reported, such as microcephaly, bitemporal narrowing or frontal bossing, down-slanting or short palpebral fissures, bulbous nose or broad nasal bridge, low-implanted ears, thick helix, bow-shaped mouth, anterior open bite, single palmar creases bilaterally, and partial syndactyly between the second and third toes (Madia et al. 2006; Pereira et al. 2004). Davidsson et al. 2008 reviewed 43 previously published cases with a del(2)(q24.3q31.1). For the 22 seizure-positive cases, 2q24.3 region constituted the smallest commonly deleted region among the majority of the cases, where 2q22.1 and 2q33.3 regions represented the most proximal and distal breakpoint, respectively. The most common dysmorphic features were ear abnormalities, microcephaly, micrognatia and brachysyndactyly.

Seizures start always in the first year of life. The clinical and EEG picture (Fig. 1) is that typical of the classical DS with severe drug resistance, mild to severe mental retardation (MR), autistic behavior, ataxia, muscle hypotonia.

However, other studies did not find significant clinical differences between DS patients with deletions involving only SCN1A and those with deletions of contiguous genes (Mulley et al. 2006; Suls et al. 2006; Marini et al. 2009). It has been suggested that the usually severe DS phenotype might mask subtle clinical differences which may be determined by contiguous genes (Marini et al. 2009).

MRI is usually normal, although Suls et al. (2006) reported one patient who at 14 months of age showed diffuse lesions in the periventricular white matter and basal ganglia. Postmortem brain examination showed abnormalities as seen in Leigh syndrome, with spongiosis and increased gliosis of the internal and external pallidum, and less pronounced lesions in the pons and mesencephalon (central tegmental tract).

Such deletions can be easily identified by means of multiplex ligation-dependent probe amplification (MPLA) and array-comparative genomic hybridization (CGH) is able to determine the size of the abnormality and the additional genes involved. Haplotype analysis with microsatellite markers and single nucleotide polymorphisms (SNPs) can also be used to identify small chromosomal abnormalities affecting SCN1A (Madia et al. 2006; Suls et al. 2006; Marini et al. 2009).

5q14.3 Deletion

Microdeletions within chromosomal bands 5q14.3q15 were recently identified as a current cause of a Rett-like phenotype. Most of these patients do not show classical Rett syndrome with acquired microcephaly and developmental regression after an initial normal interval, but show primary hypotonia, severe mental and motor retardation, early onset seizures, and occasionally autistic behavior, stereotypic hand movements and episodic hyperventilation (Le Meur et al. 2010; Cardoso et al. 2009; Engels et al. 2009). Seizures onset between 1 and 10 months of age, usually with infantile spasms. Febrile seizures, myoclonic and complex partial seizures may also occur. These patients can also present with distinctive dysmorphic features including broad, high forehead, relatively large, backward rotated ear lobes, mildly upward-slanting palpebral fissures and cupid bowed or tented upper lip (Zweier et al. 2010) . The finding of periventricular heterotopia on a brain MRI scan is also possible (Cardoso 2009). MEF2C is the candidate gene for this phenotype. It encodes for a transcriptor factor and its activity relies on the recruitment of, and cooperation with, many other transcription factors, as well as on translational and posttranscriptional modifications (Potthoff and Olson 2007). Its deleterious activity resulting in a Rett-like phenotype may be explained by a common pathway among MEF2C, MECP2 and CDKL5 which are the main mutations responsible for classical Rett syndrome and atypical Rett syndrome respectively. Indeed patients with MEF2C defects showed diminished MECP2 and CDKL5 expression, and MEF2C mutations in vitro resulted in diminished transactivation of both the MECP2 and CDKL5 promoters (Zweier et al. 2010). A mutational screening for MEF2C microdeletion can be considered in patients with early onset Rett-like phenotype and negative for MECP2, CDKL5 and FOXG1 deletion.

6q Terminal Deletion

In 2006 a peculiar clinical, EEG, and neuroradiologic pattern was reported in five unrelated patients with a 6q terminal deletion ranging between 9 and 16 Mb (Elia et al. 2006).

The phenotype was characterized by low frontal hairline, abnormal hair pattern, asymmetric face, bilateral epicanthus, horizontal or upslanting or short palpebral fissures, broad nasal bridge, micrognathia, high palate, a large gap between upper central incisors, posteriorly rotated or low-set ears, short neck, camptodactyly, phimosis, hypospadia, flat feet with valgus position of the calcaneus.

Neurological picture was characterized by mild-moderate mental retardation, hypotonia, diffuse joint laxity, strabismus.

Interestingly, epilepsy was a feature of 6q terminal deletions in all patients. In particular, they shared a distinct clinical and EEG pattern not previously reported in this condition. Epilepsy started in the first or second decade of life. In all cases, seizures had a focal onset, characterized by the ictal signs of vomiting, cyanosis, and head and eye version with or without loss of consciousness. No status epilepticus or prolonged seizures occurred. Prognosis of epilepsy was generally good in our patients, in terms of both seizure control and evolution. In all subjects but one, interictal EEG was characterized by posterior spike-and-wave complexes which became more pronounced during sleep. The ictal signs and the EEG patterns in our patients suggested that the seizures originated in the occipital lobes. Given the early onset of seizures (between ages 4 months and 4 years), it was conceivable that an age-related low threshold of emetic centers caused the ictal vomiting, as occurs in Panayiotopoulos-type occipital epilepsy.

However, the occipital epilepsy in these patients should be considered symptomatic because of the mild/moderate mental retardation and brain anomalies.

In four of five cases, MRI revealed colpocephaly and dysgenesis of the corpus callosum and of the brainstem; three patients also had a hypertrophic massa intermedia (or interthalamic adhesion).

Subsequently, other seven patients with 6q subtelomere deletions and a similar clinical and EEG pattern were ascertained with a size of the deletion ranging from 3 to 13 Mb (Striano et al. 2006; Bertini et al. 2006).

In a recent review, 28 cases with pure 6q terminal deletion were counted (Lee et al. 2011). The most common breakpoint found in 14 cases was in the 8.0–9.0 Mb interval from the 6q terminus. There are approximately 34 known genes and six OMIM morbid genes in this ~9.0 Mb region.

A comparison of the case with the smallest deletion (~ 0.4 Mb; 3 known genes) reported to date and the case that has the largest deletion (<11 Mb;>34 known genes) showed no specific phenotype differences, with respect to developmental delay, intellectual disability, dysmorphic features, hypotonia, microcephaly, seizure and brain anomalies. The region of greatest interest resulted the smallest overlapped portion of the most distal part of chromosome 6q. The genes located in the region within 0.4 Mb of the 6q terminus were PSMB1, TBP and PDCD2. The TBP gene

has been implicated as a candidate gene for phenotypes in patients with 6q terminal deletion; mutations of TBP gene are associated with spinocerebellar ataxia 17. However, the possibility of other genes playing a role in the phenotypes resulting from this deleted region cannot be ruled out.

The mechanism of chromosome 6q terminal deletion, in some cases, may be related to the fragile site, FRA6E.

It has been estimated that 6q terminal deletion is present in ~ 0.05 % of patients with intellectual disability and/or development delay (Lee et al. 2011). 6q terminal deletion should be suspected in children with occipital epilepsy, MR, colpocephaly and malformative features, and in these cases multiprobe FISH, MLPA or array-CGH should be included in the diagnostic work-up.

14q12 Deletion and Duplication

14q12 microdeletion has been claimed as responsible for the congenital variant of Rett syndrome (Ariani et al. 2008). This CNV encompasses FOXG1 gene, a brain specific forkhead-box transcriptional repressor which is now considered the third gene responsible for Rett syndrome (Mencarelli et al. 2009) . The phenotype is characterized by early deterioration, postnatal microcephaly, hypotonia, seizures, stereotypies (Ariani et al. 2008; Mencarelli et al. 2009). Patients with 14q12 deletion differ from MECP2 mutated patients because they tend to exhibit abnormal development in early infancy, while also lacking the characteristic autonomic disturbances of Rett syndrome (Brunetti-Pierri et al. 2011). Seizures onset is in infancy with mainly generalized tonic-clonic convulsions. EEG can show multifocal pattern with spikes and sharp waves (Ariani et al. 2008). The clinical picture also includes mild dysmorphic features such as downslanting palpebral fissures, bilateral epicanthic folds, depressed nasal bridge, bulbous nasal tip, tented upper lip, everted lower lip and large ears (Mencarelli et al. 2009). Corpus callosum thinning can be reported (Mencarelli et al. 2009). FOXG1 deletion should be considered in children with atypical presentation of Rett syndrome including early onset infantile spasms, severe developmental delay, postnatal microcephaly, stereotypies and absence of autonomic features.

14q12 duplications have been reported in patients with various degree of developmental delay, delayed/absent speech and epilepsy, especially infantile spasms (Brunetti-Pierri et al. 2011; Striano et al. 2011b). The phenotype is different from that showed by patients with 14q12 deletions and inactivating mutations of FOXG1. Patient with duplication show a major involvement of speech and an early onset (3–8 months) developmental epilepsy mainly characterized by infantile spasms (Brunetti-Pierri et al. 2011; Striano et al. 2011b). This can be accompanied or not by hypsarrhytmic pattern at the EEG (Brunetti-Pierri et al. 2011). Dysmorphic features, when present, are mild and include high frontal hairline, deep set eyes, hypotelorism (Brunetti-Pierri et al. 2011).

15q13.3 Deletion

Among the CNV associated epileptic phenotype the 15q13.2-13.3 microdeletion has raised the highest interest in the field. It has been first described by Sharp as a recurrent CNV associated with mental retardation and epilepsy (Sharp et al. 2008) . Soon after many reports described this abnormality together with a broad variety of phenotype including schizophrenia, severe neurodevelopmental disorders, autism and epilepsy (Dibbens et al. 2009; Ben-Shachar et al. 2009; Masurel-Paulet et al. 2010; van Bon et al. 2009; Shinawi et al. 2009). The different clinical manifestations have been correlated to the different breakpoints where the interruption occurs, and the breakpoints 4 and 5 (BP4 and BP5) have been associated to the epilepsy phenotype (Sharp et al. 2008). Furthermore a major severe phenotype has been mainly reported in the homozygous loss situation (Lepichon et al. 2010; Endris et al. 2010).

In the last few years the 15q13.3 CNV has been widely reported as a common risk factor for epilepsy, being detected in about 1% of patients with idiopathic generalized epilepsy with or without other neurological manifestations (Dibbens et al. 2009; Helbig et al. 2009). Interestingly, the 15q13.3 deletion resulted to be negative in a wide group of 3000 patients with partial epilepsies, suggesting that the deletion may confer a specific risk for generalized epilepsy (Heinzen et al. 2010; Kasperaviciute et al. 2010). Dibbens et al indicated a complex inheritance and incomplete penetrance for the IGE component of the phenotype in multiplex families (Dibbens et al. 2009). Among the idiopathic generalized epileptic syndromes, absences have been recently described in three out of 570 children with epilepsy and a various degree of intellectual disability (Muhle et al. 2011).

No brain abnormalities have been reported in association to this CNV. Dysmorphisms are not always present and the most common are hypertelorism, upslanting palpebral fissures, prominent philtrum with full everted lips, clinodactyly (Sharp et al. 2008).

Haploinsufficiency of CHRNA7, which encodes for the α7 subunit of the acetylcholine receptor is postulated as the most likely responsible factor for this phenotype (Dibbens et al. 2009; Mulley and Dibbens 2009). We recently observed two families with multiple affected individuals presenting with absences or myoclonic absences associated to mild intellectual disability, confirming the data reported by Muhle et al (Coppola et al. 2013). The ictal EEG showed generalized polispike and wave or spike and waves discharges (Fig. 2). Apparently these patients presented with a common idiopathic generalized epilepsy; however their seizures tended to persist in the elderly and were difficult to control requiring an association of at least two AEDs (Coppola et al. 2013). These features together with the occurrence of intellectual disability make the diagnosis of idiopathic generalized epilepsy unlikely. Thus in the presence of apparently generalized idiopathic epilepsy with absences and mild intellectual disability clinicians should consider a genetic test for 15q13.3 deletion.
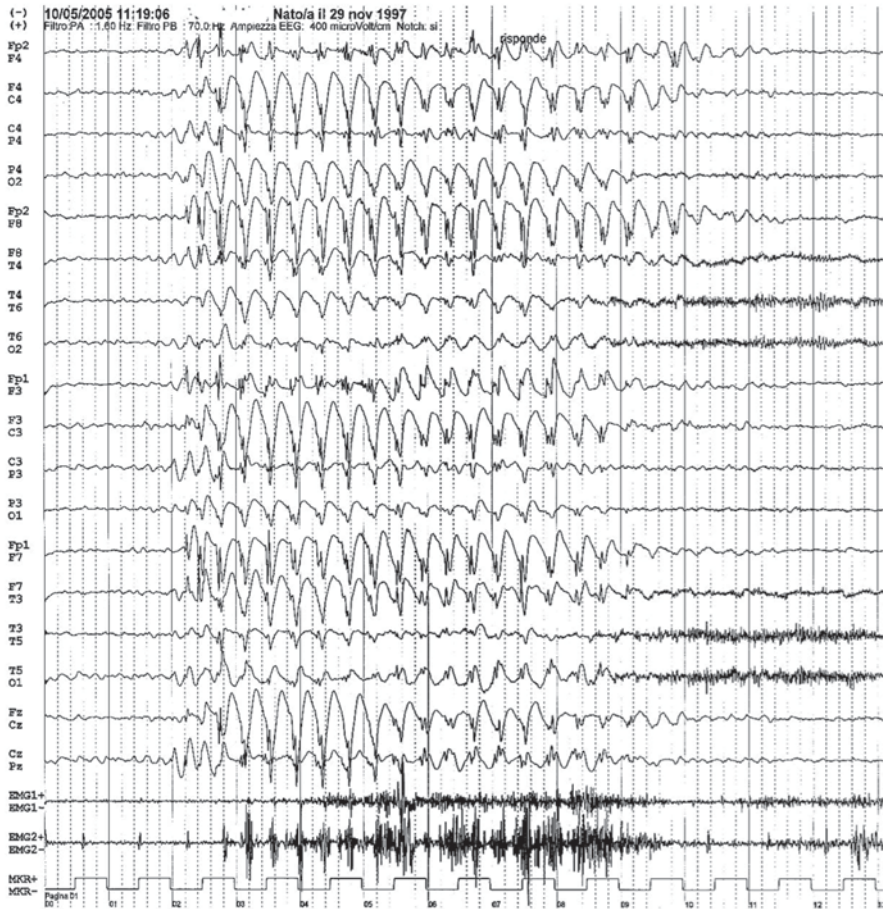
Fig. 2 Critical EEG of a 15q13.3 deletion patient showing generalized spike and wave activity

Xp11.22–11.23 Duplication

Recently a group of 9 subjects (2 males and 7 females) with a microduplication at Xp11.22-11.23 were identified at a diagnostic genome array screening of 2400 subjects with MR, either isolated or associated with a more complex phenotype. The duplication was either familial or sporadic (Giorda et al. 2009).

The clinical phenotype is characterized by a cognitive disturbance (from borderline functioning to severe MR), speech delay, poor speech articulation, hoarse and/or nasal voice, early puberty, overweight, non specific facial dysmorphic features, lower-extremity anomalies, including flat or arched feet, fifth-toe hypoplasia, and syndactyly.

A subsequent study was aimed to better define the neurological phenotype of this new syndrome (Broli et al. 2011). Electrical status epilepticus during sleep (ESES)

was observed in five of nine patients, particularly in younger ones (from 5 to 13 years), and was associated with speech delay in all cases. ESES was controlled by antiepileptic drugs in three out of five patients; the other two patients remained untreated. Neuroimaging did not disclose specific abnormalities. Therefore, the speech delay may be correlated to the ESES, able to cause local EEG slow-wave activity damage, impairing the plastic changes associated with language development.

Epilepsy was also reported in three of nine patients, with different types of seizures starting in infancy or in childhood, such as clonic jerks of the limbs and stare, generalized tonic-clonic seizures during sleep, absences. Outcome was benign.

Xp11.2 is a gene-rich, rearrangement-prone region within the critical linkage interval for several neurogenetic disorders harboring X-linked mental retardation (MRX) genes which could be responsible for the syndrome phenotype (Giorda et al 2009).

In the presence of MR, speech delay and ESES, array-CGH array should be performed in order to disclose Xp11.22-11.23 duplication.

Conclusions

The availability of whole genome high resolution techniques has shed light on new emerging syndromes underlined by chromosomal micro-rearrangements. Epileptic seizures are often a symptom of these complex conditions and sometimes epilepsy is the distinctive feature of the clinical phenotype. In few such cases the natural history, drug responsiveness and prognosis can resemble well known syndromes. However the association with other neurological symptoms and/or somatic defects and/or dysmorphic features render these conditions unique arising the question whether they can be considered new distinctive syndromes. At least for the conditions here reported it appears that a sufficient knowledge has been reached to consider them unique entities.

A genotype-phenotype correlation of further population studies can help delineating new epileptic phenotypes that recur in such genetic conditions. To this purpose it can be also helpful to report sporadic but well characterized cases. This should allow the clinicians to address the genetic test only in candidate patients avoiding expensive and time consuming analysis where not necessary.

Lastly, the study of the genes involved in these CNVs can be also crucial to better understand the physiopathology underlying some epileptic syndromes (i.e. ESES) or simply epileptic seizures.

In the future, the up coming newer techniques, namely high resolution customized array-CGH and next generation sequencing, will hopefully allow the identification of a greater number of CNV-related syndromes and the role of the clinicians will be in parallel important to validate the genetic data.

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