

Chromosomal disorders associated with epilepsy

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ABSTRACT – Epilepsy is among the most common findings associated with chromosome aberrations, particularly those involving autosomal chromosome imbalances. Most chromosome aberrations can be associated with different seizure types, but there are a few aberrations featuring specific seizure and electroencephalographic (EEG) patterns. The analysis of electro-clinical patterns associated with chromosomal aberrations is a major tool in the identification of epilepsy susceptibility genes. Advances in molecular cytogenetic techniques will certainly increase the diagnostic yield, and an increasing number of individuals previously diagnosed as having “cryptogenic” epilepsy will turn out to have an underlying chromosomal aberration. We review the types of seizures, EEG findings, and their natural history in the chromosomal disorders that are consistently associated with epilepsy.

Key words: chromosomal disorders, malformation syndromes, epilepsy, seizures

Epilepsy is among the most common findings associated with chromosome aberrations, particularly those involving autosomal chromosome imbalance. Virtually all known chromosomal abnormalities lead to anatomofunctional impairment of the central nervous system and most are accompanied by developmental delay and mental retardation. Although the risk of epilepsy is greater in individuals with chromosomal disorders than in the general population (Holmes 1987) such genetic disorders do not represent *per se*, a frequent cause of epilepsy (Jennings and Bird 1981). Most chromosome aberrations can be associated with a variety of seizure types, but there are certain aberrations featuring specific seizure and electroencephalographic (EEG) patterns. Despite the increasing interest in the genetics of epilepsy, little attention has been paid to cytogenetics as a resource with which to identify putative epilepsy ge-

nes. The analysis of electro-clinical patterns associated with chromosomal aberrations is a major tool in the identification of epilepsy susceptibility genes. Advances in molecular cytogenetic techniques, such as fluorescent *in situ* hybridization (FISH), subtelomeric analysis, and comparative genomic hybridization (CGH) microarray, have great diagnostic potential, allowing for the detection of submicroscopic or “cryptic” chromosome rearrangements. Such recent laboratory methods will certainly increase the diagnostic yield, and a number of individuals previously diagnosed as having “cryptogenic” epilepsy will turn out to have a causative chromosomal aberration. Chromosome aberrations may be caused by abnormalities in number or structure. Abnormalities of chromosome number include polyploidy, and autosomal and sex chromosome aneuploidy. Aneuploides of the auto-

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somes are among the most clinically important of the chromosome abnormalities. Aneuploidies consist primarily of "monosomy" (the presence of only one copy of a chromosome in an otherwise diploid cell) and "trisomy" (three copies of a chromosome). Abnormalities of chromosome structure consist primarily of translocations (interchange of genetic material between nonhomologous chromosomes); deletions (caused by a chromosome break and subsequent loss of genetic material); and duplications (partial trisomy of genetic material) (Jorde *et al.* 2003).

Accurate information on the epilepsy phenotype, specific electroclinical findings and their natural history is of paramount importance to pediatricians and child neurologists who provide health care to patients with epilepsy associated with chromosome aberration. Here, we present a review of the most common chromosomal disorders that are consistently associated with epilepsy.

Del 1p36 syndrome

The del 1p36 syndrome is a recently characterised clinical entity, associated with distinct congenital anomalies and mental retardation. The incidence is estimated to be 1 in 5,000 to 1 in 10,000, making it the most common terminal deletion (Shaffer and Heilstedt 2001). There seems to be a female predilection of 1.5:1 (Heilstedt *et al.* 2003, Battaglia *et al.* 2004). About 100 cases have been reported (Heilstedt *et al.* 2003, Magenis *et al.* 1987). Monosomy 1p36 may be the result of pure terminal deletions, interstitial deletions of varying sizes and different breakpoints (Wu *et al.* 1999) derivative chromosome 1, or more complex rearrangements (Heilstedt *et al.* 2003, Battaglia *et al.* 2004). Conventional cytogenetics may not detect these different rearrangements, particularly those that are derivative chromosomes. FISH analysis with subtelomeric, region-specific probes is necessary in most cases. Determination of the parental origin has shown discordant results. In one series, 24/40 (60%) of *de novo* 1p36, terminal deletions arose from the maternally inherited chromosome (Heilstedt *et al.* 2003), whereas in another study, 4/5 (80%) terminal deletions arose from the paternally inherited chromosome (Battaglia *et al.* 2004). Overall, deletions of paternal origin seem to be larger than deletions derived from the maternally inherited chromosome (Heilstedt *et al.* 2003, Battaglia *et al.* 2004). Pre- and/or postnatal growth retardation (Magenis *et al.* 1987, Yunis *et al.* 1981, Blennow *et al.* 1996, Reish *et al.* 1995, Keppler-Noreuil *et al.* 1995, Giraudeau *et al.* 1997, Shapira *et al.* 1997, Riegel *et al.* 1999, Hain *et al.* 1980, Biegel *et al.* 1993, Slavotinek *et al.* 1999), as well as obesity and hyperphagia (Keppler-Noreuil *et al.* 1995, Sandlin *et al.* 1995, Shapira *et al.* 1997, Eugster *et al.* 1997) have been reported.

The craniofacial features of these individuals are distinct and remarkably similar, representing a hallmark of the

condition. They include: micro-brachycephaly; large and late-closing anterior fontanelle; prominent forehead; straight eyebrows; deep-set eyes; short palpebral fissures; broad/flat nasal bridge; midface hypoplasia; pointed chin; abnormal ears.

All subjects have developmental delay/mental retardation varying from moderate to profound (Shaffer and Heilstedt 2001, Heilstedt *et al.* 2003, Battaglia *et al.* 2004, Shapira *et al.* 1997). Expressive language is significantly impaired, being absent or very poor in most. However, three patients with the smallest documented deletions had mild mental retardation and complex speech abilities (Wu *et al.* 1999, Slavotinek *et al.* 1999). The craniofacial features, together with the neurodevelopmental manifestations, should prompt clinical recognition of the syndrome.

Seizures occur in about 50% of patients (Heilstedt *et al.* 2003, Battaglia *et al.* 2004). There does not appear to be one seizure type that is predominant, and infantile spasms, simple and complex partial seizures, generalized tonic-clonic seizures, myoclonic seizures, and absence spells have been reported (Blennow *et al.* 1996, Reish *et al.* 1995, Slavotinek *et al.* 1999, Keppler-Noreuil *et al.* 1995, Giraudeau *et al.* 1997, Shapira *et al.* 1997, Riegel *et al.* 1999, Knight-Jones *et al.* 2000). Age at seizure-onset is difficult to retrieve from the literature. However, from the available data it appears that seizures start in infancy or childhood, and are well controlled by antiepileptic drugs (Battaglia *et al.* 2004, Eugster *et al.* 1997, Slavotinek *et al.* 1999). EEG abnormalities are also variable, including hypersarrhythmia, focal and multifocal spikes, and asymmetry of slow wave activity (Battaglia *et al.* 2004, Knight-Jones *et al.* 2000, Wenger *et al.* 1988).

Of note, a severe seizure phenotype (including infantile spasms and medically intractable seizures) or epileptiform activity on the EEG has been associated with hemizygosity for the voltage-gated K⁺ channel β -subunit gene, *KCNAB2* (Heilstedt *et al.* 2001).

Cerebral atrophy, ventricular dilatation/asymmetry, hydrocephalus, delay in myelination, focal cortical dysplasia, and a leukodystrophic picture have been documented on brain neuroimaging (Battaglia *et al.* 2004, Yunis *et al.* 1981, Keppler-Noreuil *et al.* 1995, Shapira *et al.* 1997, Riedel *et al.* 1999, Hain *et al.* 1980, Slavotinek *et al.* 1999, Heilstedt *et al.* 2001, Faivre *et al.* 1999, Battaglia 2005a).

Del 4p (Wolf-Hirschhorn) syndrome

Wolf-Hirschhorn syndrome (WHS) is a well-known, multiple congenital anomalies/mental retardation syndrome (Cooper and Hirschhorn 1961). Its frequency is estimated as one per 50,000 births, with a female predilection of 2:1 (Lurie *et al.* 1980, Gorlin *et al.* 1990). However, it is possible that this rate is an underestimation in view of the frequency of missed diagnosis due to lack of recognition or inadequate cytogenetic analysis (Battaglia *et al.* 2001).

The disorder is caused by partial loss of material from the distal portion of the short arm of chromosome 4. The minimal deleted segment causing the phenotype is 4p16.3 (Lurie *et al.* 1980). While most individuals (75%) have a *de novo* deletion (Lurie *et al.* 1980) of preferential paternal origin (Tupler *et al.* 1992, Dallapiccola *et al.* 1993), about 12% have an unusual chromosome abnormality (such as ring 4), and about 13% have deletion of 4p16 as the result of having inherited an unbalanced chromosome rearrangement from a parent with a balanced rearrangement. Standard cytogenetics detects about 60-70% of deletions, while FISH (using the WHSCR probe) detects > 95%. Sub-telomeric FISH analysis can be useful to determine if a deletion is the result of an unbalanced translocation (Battaglia *et al.* 2002-2004).

The most striking features of del 4p are the typical "Greek warrior helmet appearance of the nose" (*i.e.* the broad bridge of the nose continuing to the forehead), pre and post-natal growth delay, congenital hypotonia, mental retardation and seizures (Battaglia *et al.* 2001).

According to different reports, epileptic seizures constitute a major medical concern during the first years of life, and occur in 50% to 100% of WHS patients (Battaglia *et al.* 2001, Guthrie *et al.* 1971, Centerwall *et al.* 1975, De Grouchy and Turleau 1984, Stengel-Rutkowski *et al.* 1984). These seizures usually begin within the first two years of life, with a peak incidence at around 9-10 months of age. They may be clonic or tonic, unilateral with or without secondary generalisation, or generalised as tonic-clonic from the onset (Battaglia *et al.* 2001, Reid *et al.* 1996, Estabrooks *et al.* 1994, Ogle *et al.* 1996, Battaglia 1997, Battaglia *et al.* 1999a, Battaglia *et al.* 1999b, Battaglia and Carey 1999, Battaglia and Carey 2000). They are frequently triggered by fever; may last 15 minutes or longer, and often occur in clusters (Battaglia 1997, Battaglia *et al.* 1999a and b, Sgrò *et al.* 1995, Zankl *et al.* 2001). In over 50% of the patients, unilateral or generalised clonic or tonic-clonic status epilepticus occurs during the early years, despite adequate antiepileptic treatment (Battaglia *et al.* 2001). Between 1 and 5 years of age, almost two thirds of the patients develop atypical absences, often accompanied by a mild myoclonic component, mainly involving the eyelids and axorizomelic muscles (Battaglia *et al.* 2001, Battaglia *et al.* 2004, Battaglia 1997, Battaglia *et al.* 1999, Battaglia *et al.* 1999, Sgrò *et al.* 1995). These episodes are accompanied by generalised slow spike/wave complexes. Interictal EEG shows high amplitude, fast spikes-polyspikes/wave complexes over the posterior temporal and parieto-occipital regions, triggered by eye closure. Other seizure types associated with del 4p have been described in a minority of patients, and include myoclonic seizures (Zankl *et al.* 2001), tonic spasms, and complex partial seizures (Kanazawa *et al.* 1991).

In our experience, the seizures observed in WHS can be effectively controlled by valproate (VPA) alone or

associated with ethosuximide (ESM). In a minority of patients there may be a need to add a benzodiazepine (Battaglia and Carey, in preparation). However, the use of carbamazepine (CBZ) may worsen the electroclinical picture. Despite early severity, the long term outcome of epilepsy seems to be good, as seizures tend to disappear with age (Battaglia 2005b, Battaglia and Carey 2005). The $GABA_A$ receptor gene was a candidate gene for epilepsy in WHS. However, this gene maps proximal to the critical deletion region (WHSCR), specifically, 4p12-p13 (Buckle *et al.* 1989). Whereas, *LETM1*, a gene possibly involved in Ca^{2+} signalling or homeostasis, seems to be a good candidate for the seizures and neuromuscular problems in WHS (Endele *et al.* 1999, Van Buggenhout *et al.* 2004). Initially, *LETM1* was suggested to flank the WHSCR (Battaglia *et al.* 2001, Endele *et al.* 1999), but a recent report implies that it falls within the newly proposed critical region of WHS, nearer the telomere (Zollino *et al.* 2003).

The most frequent brain abnormality is corpus callosum hypoplasia, occasionally associated with decreased white matter volume, and hypoplasia or agenesis of the posterior lobe of the cerebellum. Hypoplastic brain with narrow gyri, heterotopias, and dysplasias of nuclear structures have been described in a minority of cases (Lazjuk *et al.* 1980, Gottfried *et al.* 1981).

Trisomy 12p syndrome

Just over twenty cases of duplication of the short arm of chromosome 12 have been reported (Schinzel 2001). Trisomy 12p is estimated to occur at a rate of 1 to 50,000 births (Stengel-Rutkowski *et al.* 1981). The patient's face shows some similarity to Down syndrome, and, in addition, turri-brachycephaly, bushy eyebrows, hypoplastic philtrum, everted lower lip, full cheeks, short hands and club feet can be present. Mental retardation is usually severe.

Most cases of trisomy 12p are due to familial translocations; a minority occur as a *de novo* isochromosome with translocation (Allen *et al.* 1996) or as a *de novo* translocation (Ray *et al.* 1985).

Lateralized microgyria, internal hydrocephalus, cortical dysplasia and ectopic glial tissue in the leptomeninges have been observed at neuropathology examination, in three neonates with severe malformations (Nielsen *et al.* 1977).

Description of seizures has been very scant. Generalised convulsive seizures, on occasions triggered by fever, or myoclonic seizures are the most frequently reported. Of note, is the occurrence of generalised 3 Hz spike/wave complexes in 4 patients, 3 of whom had childhood-onset myoclonic absences or myoclonic seizures, which were well controlled by AEDs (Guerrini *et al.* 1990, Elia *et al.* 1998).

Ring chromosome 14 syndrome

Ring chromosome 14 (r14), is a rare chromosomal disorder, reported so far in more than 30 patients, and consistently associated with seizures. In all cases, dysmorphic features are mild, and almost invariably seizures occur in infancy and are intractable (Schinzel 2001, Singh *et al.* 2002). A variety of types has been described, including generalized tonic-clonic, myoclonic, complex partial seizures, and "minor motor" seizures (Lippe and Sparkes 1981, Schmidt *et al.* 1981, Fryns *et al.* 1983, Matalon *et al.* 1990, Zelante *et al.* 1991). Brain atrophy with ventricle dilatation has been observed in several subjects. The degree of mental impairment varies from mild to severe. In most individuals the breakpoints in 14q were detected in the terminal band 14q32. Familial occurrence has been noted in two instances (Matalon *et al.* 1990, Riley *et al.* 1981).

Angelman syndrome

Angelman syndrome (AS) has emerged as an important neurogenetic disorder due to its incidence of about 1/12,000-20,000 (Steffenburg *et al.* 1996), and easier confirmation of the diagnosis by improved genetic testing. Owing to its nonspecific clinical features, AS poses diagnostic challenges to the clinician during the first years of life. In later childhood however, developmental delay/mental retardation, absent or very poor speech (<10 words), ataxia, jerky movements, and the happy countenance with frequent laughter usually present as a recognisable clinical entity.

AS results from the absence or nonfunctioning of the normally active maternal allele at 15q11-q13.

From 70 to 75% of subjects show a deletion of region 15q11-q13 of the maternally-derived chromosome; 2-5% show paternal uniparental disomy (UPD) of chromosome 15; 2-5% have an imprinting centre (IC) defect; 20-25% show *UBE3A* and other presumed, single gene mutations. A few individuals with the apparent clinical phenotype of AS have no, as yet detectable genetic abnormality.

The suggested first line testing is either FISH (plus a standard karyotype) or DNA methylation analysis. Methylation analysis will diagnose 80% of patients with classic AS, but when this is the first investigation, further evaluation with FISH and/or DNA polymorphism analysis is recommended to identify the molecular class of AS (deletion; UPD; IC defect), for genetic counseling purposes (Williams 2005). *UBE3A* gene mutation analysis should be pursued when there is a strong clinical suspicion of AS and a negative methylation test. The rare cases of familial recurrence of AS show either IC or *UBE3A* mutations (Guerrini *et al.* 2003).

All patients have severe developmental delay/mental retardation, becoming apparent by age 6-12 months; absent

or very poor speech; ataxic gait; tremulousness of limbs; and a distinct behavior profile with unprovoked and frequent laughter, excitable personality, hand flapping, and short attention span. Microcephaly becomes evident by age 2 years. Additional, less frequent findings have also been reported (Battaglia and Gurrieri 1999). Neuroimaging usually shows a structurally normal brain. However, small temporal and frontal lobes with disorganized and irregular gyri, irregular distribution of neurons in layer 3, and minor heterotopias in both the cerebrum and cerebellum have been reported in two patients (Jay *et al.* 1991, Kyriakides *et al.* 1992).

Epilepsy is very frequent, affecting as much as 90% of children (Angelman 1965, Matsumoto *et al.* 1992, Viani *et al.* 1995, Zori *et al.* 1992). Apparently, fewer than 25% of patients develop seizures before age 1 year; most starting before age 3. Initial occurrence later in life is not infrequent (Matsumoto *et al.* 1992, Viani *et al.* 1995, Zori *et al.* 1992, Sugimoto *et al.* 1994). The first seizures are often precipitated by fever (Matsumoto *et al.* 1992, Sugimoto *et al.* 1994). Atypical absences, myoclonic seizures, generalised tonic-clonic and unilateral seizures are among the main ictal patterns (Battaglia and Gurrieri 1999, Matsumoto *et al.* 1992, Viani *et al.* 1995, Sugimoto *et al.* 1994). Complex partial seizures with eye deviation and vomiting, possibly indicating occipital lobe origin, seem to occur frequently (Viani *et al.* 1995), whereas infantile spasms with hypsarrhythmia are exceptional. Over half the subjects suffer from episodes of decreased alertness and hypotonia, lasting for days or weeks, described as nonconvulsive status epilepticus (Matsumoto *et al.* 1992, Sugimoto *et al.* 1994). Often a concomitant mild jerking (Dalla Bernardina *et al.* 1992, Guerrini *et al.* 1996) may be observed. Video-EEG-polygraphic recordings during myoclonic status or short myoclonic seizures show diffuse, irregular, 2 Hz spike/wave complexes, accompanied in some patients by EEG-spikes that are time-locked to myoclonic potentials. Myoclonic jerks typically cease during sleep (Viani *et al.* 1995, Guerrini *et al.* 1996) and, in some patients, may remain erratic, with no apparent relation to the EEG discharges. In addition, AS patients exhibit quasi-continuous, 11 Hz, multifocal, rhythmic cortical myoclonia, mainly involving the hands and face, which are responsible for mild jerking or twitching, easily mistaken for a tremor (Guerrini *et al.* 1996).

Although initially rather difficult to treat, seizures often remit after puberty (Matsumoto *et al.* 1992, Bower and Jeavons 1967, Boyd *et al.* 1988), and myoclonic status is rare after age 6, providing additional support for age-dependence of seizure expression (Zori *et al.* 1992). Complete seizure remission is however, rare (Laan *et al.* 1997, Minassian *et al.* 1998), the number of subjects still having seizures as adults being unknown.

Subjects with AS have distinctive EEG patterns varying with age (Matsumoto *et al.* 1992, Viani *et al.* 1995, Sugimoto *et al.* 1994, Boyd *et al.* 1988, Laan *et al.* 1997,

Minassian *et al.* 1998). The most characteristic consists of interictal bursts of high amplitude 1-3 c/s bilateral anterior slow waves, which tends to diminish with age (Matsumoto *et al.* 1992).

Myoclonic status epilepticus, although frequently relapsing (Matsumoto *et al.* 1992), is well controlled by intravenous benzodiazepines (BDZs) (Viani *et al.* 1995, Guerrini *et al.* 1996) or by VPA in association with ethosuccimide (ESM) (Dalla Bernadina *et al.* 1992). Nonconvulsive status epilepticus is also well controlled by *i.v.* benzodiazepines (Viani *et al.* 1995, Guerrini *et al.* 1996). The association of clobazam-valproic acid (VPA) is particularly effective for long-term treatment (Viani *et al.* 1995, Guerrini *et al.* 1996), whereas carbamazepine (CBZ) or vigabatrin (GVG) may increase both myoclonia and absence seizures (Viani *et al.* 1995, Kuenzle *et al.* 1998). Cortical myoclonia, when particularly disabling, may respond best to piracetam in high doses (Guerrini *et al.* 1996).

Among the genes residing in the deleted region are the *UBE3A* and three GABA_A receptor subunits ($\beta 3$, $\alpha 5$, $\gamma 3$). *UBE3A* is imprinted in brain but not in other tissues, a finding that is compatible with the brain being the most affected organ in AS (Rougelle *et al.* 1997). Patients with the large 15q11-q13 deletion show a more severe electro-clinical picture than those with UPD (Minassian *et al.* 1998). This observation suggests that one or more genes in the deleted region, including the GABA receptor subunit genes, may modify the AS phenotype caused by the lack of maternal *UBE3A* function. A possible mechanism for the seizures is dysfunction of inhibition due to deletion or other genetic disruption of GABA_A receptor subunits.

Inv-dup (15) or Idic (15) syndrome

The chromosome region 15q11-q13 is known for its instability (Donlon *et al.* 1986), and many rearrangements may occur in this imprinted segment, including deletions, translocations, inversions, and supernumerary marker chromosomes formed by the inverted duplication of proximal chromosome 15. Interstitial duplications and triplications are much less frequent. The inv dup(15) is the most common of the heterogeneous group of extra-structurally abnormal chromosomes (ESACs), and accounts for about 50% of supernumerary marker chromosomes (Hook and Cross 1987). Of the two identified cytogenetic types of inv dup(15) marker chromosomes, one is a metacentric, smaller or similar to a G group chromosome, not containing the PWS/AS critical region (PWS/ASCR), and is found in children with a normal phenotype (Cheng *et al.* 1994). The second type of inv dup(15) is as large as or larger than a G group chromosome, contains the PWS/AS critical region (Robinson *et al.* 1993, Blennow *et al.* 1995), and is associated with an abnormal phenotype (Battaglia *et al.* 1997). Its cytogenetic description is dic(15)(q12 or q13). Most dic(15)(q12 or q13) derive from the two homologous

maternal chromosomes at meiosis, and are associated with increased maternal age at conception. The presence of large inv dup(15) results in tetrasomy 15p and partial tetrasomy 15q. Incidence at birth is estimated as 1 to 30,000 with a sex ratio of 1 (Schinzel and Niedrist 2001). In order to detect the rearrangement, standard cytogenetics must be associated with FISH analysis, with probes both from proximal chromosome 15 and from the PWS/ASCR (Luke *et al.* 1994, Webb *et al.* 1998). For detection of parent-of-origin, microsatellite analysis of parental DNA, or methylation analysis of the proband DNA are also needed (Luke *et al.* 1994, Webb *et al.* 1998). The most consistent clinical findings are represented by moderate-profound developmental delay/mental retardation, severe epilepsy, diffuse hypotonia, and autistic behavior (Battaglia *et al.* 1997, Cabrera *et al.* 1998, Borgatti *et al.* 2001, Takeda *et al.* 2000, Battaglia 2005c). Overall, there are either no dysmorphic findings or only "minor anomalies", such as epicanthus, downslanting of the palpebral fissures, low-set ears, and skin pigmentary changes.

In most individuals, epilepsy shows the characteristics of the Lennox-Gastaut syndrome or of a similar syndrome, with very poor outcome. West syndrome has been reported in a minority of subjects (Battaglia *et al.* 1997, Cabrera *et al.* 1998, Takeda *et al.* 2000, Battaglia 2005c, Torrisi *et al.* 2001). Myoclonic and complex partial seizures have also been observed (Gillberg *et al.* 1991, Aguglia *et al.* 1999). A milder clinical presentation with adult-onset generalized epilepsy has been reported in two patients with large inv dup(15) (Chifari *et al.* 2002). Various genetic mechanisms have been hypothesized to explain clinical heterogeneity, beyond the size of chromosomal duplication, including dosage effect of genes located within the duplicated region (Battaglia 2005c, Torrisi *et al.* 2001). Considering that a mild epileptic phenotype does not rule out a diagnosis of inv dup(15), it has been suggested that such a chromosome rearrangement be ruled out as a possible, though rare, cause of atypical "cryptogenic" or idiopathic generalized epilepsy (Chifari *et al.* 2002).

Ring chromosome 20 syndrome

Ring chromosome 20 (r20) is a rare chromosomal disorder, of which epilepsy is a striking feature. Conversely, the absence of a consistent pattern of dysmorphic signs, and very rare malformations, makes the diagnosis difficult. Psychomotor development tends to be initially normal. Seizures occur in almost all subjects, with onset between infancy and age 17, and tend to be refractory to treatment (Singh *et al.* 2002, Zuberi and Biraben 2004). The distinct electro-clinical pattern is represented by a "non-convulsive status" with repetitive, prolonged episodes of confusion, speech difficulties and complex automatisms,

usually lasting from several minutes to one hour, accompanied by continuous, 2-3 Hz, bilateral, high amplitude slow waves with occasional spikes, with frontal predominance. Such episodes often occur daily, and can be interspersed with perioral jerking and eyelid myoclonia (Singh *et al.* 2002, Lancman *et al.* 1993, Inoue *et al.* 1997, Petit *et al.* 1999, Canevini *et al.* 1998). Typical spike and wave discharges are rarely seen. Frontal lobe ictal-onset was shown by means of subdural electrodes during typical confusional episodes (Inoue *et al.* 1997). On the basis of ictal SPECT studies, a possible role for subcortical structures in the genesis of such a characteristic ictal pattern has been hypothesized (Biraben *et al.* 2001). Hyperventilation, specific mental activities or adverse psychological situations play a triggering role in some children (Roubertie *et al.* 2000). Prolonged seizures are still at risk of being misinterpreted as behavioral, non-epileptic manifestations, particularly in young children, unless video-EEG recording is available (Inoue *et al.* 1997). Partial motor, complex partial and generalized tonic-clonic seizures have also been reported. Interictal EEG, normal in some individuals, can show spikes over both fronto-temporal regions in others.

The description of more than 30 cases has highlighted the uniqueness of the electro-clinical presentation of the r20 syndrome (Singh *et al.* 2002), which should always prompt a request for karyotyping. In view of the fact that the percentage of lymphocytes carrying the chromosome rearrangement may be low, this analysis should be performed looking at, at least, 100 mitoses (Roubertie *et al.* 2000). In most cases the locus of fusion between the deleted short and long arms in the ring chromosome was p13q13 or p13q13.3 or p13q13.33 (Singh *et al.* 2002, Inoue *et al.* 1997). The loss of telomeric material on both arms of chromosome 20 is usually identified by FISH (Brandt *et al.* 1993). Cases with a mosaicism for r20 have also been observed. Most cases are sporadic, but a few are familial (Canevini *et al.* 1998). The severity of cognitive impairment seems to correlate with the percentage of mosaicism, whereas that of epilepsy does not (Inoue *et al.* 1997).

Trisomy 21 (Down's) syndrome

Down's syndrome (DS) has an incidence of about 1/650 to 1/1,000 live births (Smith and Berg 1976). It is associated with triplication of chromosomes 21 in 95% of individuals; with chromosomal translocation in 4%; and with mosaicism of a trisomic cell line in 1%. The full phenotype appears to manifest when band 21q22 is triplicated, sub-band 21q22.12 being the most critical (Epstein 1997). The incidence of seizures in DS individuals is estimated as 5-10% (Tatsuno *et al.* 1984, Pueschel *et al.* 1991). However, there seems to be an age-related incidence of epilepsy, with peaks respectively within the first 12 months,

and in the fourth and fifth decades of life (Veall 1974). The first peak may be related to early medical complications (Silva *et al.* 1996), while the second peak coincides with the development of the neuropathological, Alzheimer-like, changes (Friede 1989). All seizure types may occur in DS, with GTC being the most common (Tatsuno *et al.* 1984, Pueschel *et al.* 1991, Stafstrom *et al.* 1991). Infantile spasms (IS) in DS are 8-10 times more common than in the general population (Stafstrom and Konkol 1994). Prognosis of IS is usually good with regard to both seizure control and cognition. Remission is obtained with ACTH or steroids, without relapse of seizures (Guerrini *et al.* 1989) and, if later seizure types occur, they are usually of the idiopathic age-related variety (Silva *et al.* 1996). An exception to such a favourable trend is represented by infantile spasms following a perinatal hypoxic injury (Stafstrom and Konkol 1994, Guerrini *et al.* 1993).

Reflex seizures, in the context of a startle epilepsy, seem to be particularly frequent in DS (Gimenez-Roldan and Martin 1980, Sàenz-Lope *et al.* 1984, Guerrini *et al.* 1990, Pueschel and Louis 1993). Age at seizure onset is variable, with no evidence of etiological factors other than DS. Most individuals present "pure" forms of reflex epilepsy, with almost all seizures being precipitated by acoustic or tactile stimuli.

Lennox-Gastaut syndrome, although rare, has been well documented in DS. Its *de novo* occurrence at a mean age of 10 seems quite distinctive (Guerrini *et al.* 1993). Lennox-Gastaut syndrome rarely follows infantile spasms. Febrile seizures are uncommon (Tatsuno *et al.* 1984, Stafstrom *et al.* 1991, Guerrini *et al.* 1986, Guerrini *et al.* 1993).

DS brains look smaller, with fronto-temporal lobe hypoplasia, a reduced hindbrain/cerebrum ratio, and a narrowed superior temporal gyrus (Jerrigan *et al.* 1993). Cortical dysgenesis with fewer GABAergic interneurons has been observed (Wisniewski *et al.* 1984). These structural brain abnormalities may play a role in the occurrence of epilepsy in DS, in association with other factors, such as intrinsic physiological alterations or neurochemical processes affecting synaptic transmission.

Fragile X syndrome

Fragile X syndrome is the most common inherited cause of mental retardation, and represents 30% of all cases of X-linked mental retardation (Sherman 2002). It is caused by a trinucleotide repeat expansion of the three bases cytosine-guanine-guanine (CGG) occurring in the *FMR1* gene at Xq27.3. An expansion > 230 CGG repeats (full mutation) is associated with the syndrome. Smaller expansion of 55-200 CGG repeats (premutation) is usually not associated with cognitive impairment, and has been detected in 1 in 259 females, and in 1 in 813 males in the general population (Rousseau *et al.* 1995, Dombrowski *et*

al. 2002). The overall prevalence of fragile X syndrome in males and females may be estimated as 1 in 2,000 to 1 in 3,000 (Sherman 2002). The classical phenotype is characterised by long face; large, prominent ears; prognathism; high-arched palate; hyperextensible fingers; mitral valve prolapse; macroorchidism (postpubertally); flat feet; hypotonia. Females are less affected than males, since they have two X chromosomes, and the normal X is producing a normal amount of *FMR1* protein (FMRP), depending on the X inactivation ratio. In both sexes the level of FMRP correlates with the degree of cognitive involvement (Tassone *et al.* 1999). Most individuals with the premutation have normal cognition (Hagerman *et al.* 1996, Tassone *et al.* 2000). In males with the full mutation that is fully methylated (*FMR1* not expressed), little or no FMRP is produced. The average IQ in adulthood of full mutation males with > 50% of the cells unmethylated is about 88, and the average IQ of individuals with a mosaic pattern (some cells with the premutation and some cells with the full mutation) is 60 (Hagerman 2002). Almost 70% of full mutation females will have a borderline cognitive delay (IQ 70-84) or a mild mental retardation (IQ 50/55-70). Hyperactivity, attention problems, anxiety (social anxiety), and obsessive-compulsive behaviour are quite common. The diagnosis of fragile X syndrome is confirmed by DNA testing using Southern blot analysis, which determines the CGG repeat number within the *FMR1* gene. Polymerase chain reaction (PCR) testing will give a more exact CGG repeat number within the premutation range (Brown 2002).

A point mutation within *FMR1*, leading to an abnormally functioning FMRP, has been described in only a few individuals. Deletion of the *FMR1* gene also causes a typical fragile X phenotype (Hagerman *et al.* 2005).

Seizures are observed in almost 20-25% of subjects with fragile X syndrome (Wisniewski *et al.* 1991, Musumeci *et al.* 1991). They usually occur in childhood, resolve by adolescence, and are well controlled by antiepileptic drugs (Guerrini *et al.* 1989, Wisniewski *et al.* 1991, Musumeci *et al.* 1991, Guerrini *et al.* 1992). The seizure types most frequently observed are generalized tonic-clonic, complex partial, or focal motor (Guerrini *et al.* 1989). Background EEG activity may be slow, and, possibly age-related, mid-temporal spikes (similar to those of benign rolandic epilepsy) have been described in a few males, with or without seizures (Guerrini *et al.* 1989, Wisniewski *et al.* 1991, Musumeci *et al.* 1991).

Klinefelter (XXY) syndrome

The incidence of Klinefelter syndrome (KS) is 1.2 per 1,000 live-born males (Hook *et al.* 1992). The additional X chromosome has been shown to be paternally derived in 50-60% of cases, and maternally derived in 40-50% (Lorda-Sanchez *et al.* 1992). When paternally derived, X-Y

nondisjunction must occur in meiosis I; and when maternally derived, nondisjunction occurs in meiosis I in 48% and in meiosis II in 29% of cases; 16% show postzygotic origin, and in 7% the origin is unknown (Lorda-Sanchez *et al.* 1992, Thomas *et al.* 2000). Maternal age is increased, whereas paternal age is not (Thomas *et al.* 2000, Shi *et al.* 2002). Small testes, gynecomastia, and hypergonadotropic hypogonadism are typical, and some degree of learning disability is usually present. Some individuals are tall and thin with a eunucoid appearance.

The prevalence of seizures in KS is estimated as 2-10% (Becker *et al.* 1966, Nielsen and Pedersen 1969, Genton *et al.* 1992, Guerrini *et al.* 1997). Different seizure types have been observed, such as early-onset febrile seizures (Elia *et al.* 1995); absence seizures and/or generalized tonic-clonic seizures, with 3 Hz spike/wave on the EEG (Genton *et al.* 1992, Bolthausen *et al.* 1978, Battaglia [unpublished observation]). Overall, the majority of individuals have partial epilepsy, usually well controlled by the antiepileptic drugs (Guerrini *et al.* 1997).

Conclusion

We discussed ten, disparate, chromosomal disorders, most of which feature seizures as an important part of its phenotype. Until now, the study of individuals with chromosomal rearrangements associated with epilepsy has been insufficiently explored. In these syndromes, there is an obvious diversity of epilepsy, with a wide spectrum of seizure severity and a wide range of seizure mechanisms. Nevertheless, quite a number of syndromes show a fairly distinctive electro-clinical pattern, apparently linked to the underlying gene disruption. A thorough study of larger samples of such cases, with a better characterisation of seizures, together with the constantly increasing sophistication of molecular cytogenetics, may prove to be of paramount importance for the identification of epilepsy genes. □

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