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Review article

Electroclinical features of epilepsy associated with 1p36 deletion syndrome: A review

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ABSTRACT

1p36 terminal deletion is a recently recognized syndrome with multiple congenital anomalies and intellectual disability. It occurs approximately in 1 out of 5000 to 10,000 live births and is the most common subtelomeric microdeletion observed in human. Medical problems commonly caused by terminal deletions of 1p36 include developmental delay, intellectual disability, seizures, vision problems, hearing loss, short stature, brain anomalies, congenital heart defects, cardiomyopathy, renal anomalies and distinctive facial features. Although the syndrome is considered clinically recognizable, there is significant phenotypic variation among affected individuals. Genotype-phenotype correlation in this syndrome is complicated, because of the similar clinical evidence seen in patients with different deletion sizes. We review 34 scientific articles from 1996 to 2016 that described 315 patients with 1p36 delection syndrome. The aim of this review is to find a correlation between size of the 1p36-deleted segments and the neurological clinical phenotypes with the analysis of electro-clinical patterns associated with chromosomal aberrations, that is a major tool in the identification of epilepsy susceptibility genes. Our finding suggest that developmental delay and early epilepsy are frequent findings in 1p36 deletion syndrome that can contribute to a poor clinical outcome for this reason this syndrome should be searched for in patients presenting with infantile spasms associated with a hypsarrhythmic EEG, particulary if they are combined with dismorphic features, severe hypotonia and developmental delay.

1. Introduction

1p36 terminal deletionis a recently recognized syndrome with multiple congenital anomalies and intellectual disability (Shapira et al., 1997; Heilstedt et al., 2001).It occurs approximately in 1 out of 5000 to 10,000 live births and is the most common subtelomeric microdeletion observed in humans (Heilstedtet al., 2003; Shaffer and Lupski, 2000; Battaglia et al., 2008). A majority of the cases (52–67%) results from heterozygous deletion of the most distal chromosomal band on the short arm of chromosome 1 whereas other rearrangements, namely interstitial deletions (9.7–29%)or more complex rearrangements are much less common (Wu et al., 1999a, 1999b; Battaglia, 2005; Shiba et al., 2013; Õiglane-Shlik et al., 2014).The age at diagnosisranges from the newbornto adult age. Medical problems commonly caused by terminal deletions of 1p36 include developmental delay, intellectual disability, seizures, vision problems, hearing loss, short stature, brain anomalies, congenital heart defects, cardiomyopathy, and renal anomalies. Distinctive facial features include micro-brachycephaly, large and late-closing anterior fontanelle, prominent forhead, straight eyebrows, deep-set eyes, short palpebral fissures, broad/flat nasal bridge, midface hypoplasia, pointed chin, and abnormal ears. These craniofacial dysmorphism (see Fig. 1 from Shinoda et al., 2014), togetherwith the neurodevelopmental manifestation, should prompt clinical recognition of the syndrome (Shapira et al., 1997; Heilstedt et al., 2001; Battaglia, 2005; Shaffer and Heilstedt, 2001). Furthermore, terminal deletions of 1p36 could cause macrocephaly at birth, intrauterin growth retardation, hypotiroidism, cardiac malformations, skeletal and urogenital anomalies, sensoneural hearing loss, behavioral

Abbreviations: AED, anti, epilepsy drugs; PB, phenobarbital; VPA, valproate; GTC, generalized tonic clonic seizure,CZP,clonazepam; GT, generalized tonic seizure; PHA, phenytoin; ESM, ethosuximide; BZD, benzodiazepine; IS, infantile spasms, FS, focal spasms; CC, cerebral cortex

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Fig. 1. Facial features of the patients with variably sized 1p36 deletions: a) shows edematous eyelids rather than deep-set eyes; b) c) and d) share characteristic features, including deep-set eyes, hypotelorism, and pointed chins; e) and f) do not exhibit such characteristic features, with round faces rather than hypotelorism and pointed chins; g) exhibits distinctive features with arched eyebrows and hypertelorism (from Shimada et al., 2015).

disorders and epileptic apnea (Shapira et al., 1997; Heilstedt et al., 2001; Battaglia, 2005; Kanabar et al., 2012; Slavotinek et al. 1999; Gajecka et al., 2007). Although the syndrome is considered clinically recognizable, there is significant phenotypic variation among affected individuals. Genotype-phenotype correlation in this syndrome is complicated, because ofthe similar clinical evidence seen in patients with different deletion sizes (Wu et al., 1999a, 1999b).For this reason, there are very limited published data in literature on epileptic phenotype, on EEG findings, and on natural history of epilepsy n 1p36 deletion syndrome. The aim of this paper isto review the cases of 1p36 delection syndrome described in the literature from 1996 to 2017 and carry out a detailed analysis of epileptic phenotypes, EEG abnormalities and long-term prognosy of these patients.

2. Methods

We reviewed the papers published on 1p36 deletion syndrome and epilepsy starting from 1996. A PubMed search indexed for MEDLINE and EMBASE was undertaken to identify studies in children using terms “1p36 deletion syndrome” “Monosomy 1p36 syndrome” “Epilepsy and 1p36 deletion syndrome” “1p36 subtelomeric rearrangement” “Epilepsy” and “seizures”. Only English language articles were reviewed. References of the selected article wereconsulted for possible additional relevant articles. The date of our last search is March 2017. In this work, we listened tothe major groups of 1p36 deletion syndrome aberrations and tothe main types of epileptic manifestations. The recordeddata included patients’ age, gender, chromosomal abnormality, epileptic features, brain MRI findings, and response to therapy. The classification of seizures is based on the clinical and EEG findings according to criteria of International League Against Epilepsy (Berg et al., 2010).

3. Results

From literature we checked and analyzed 34 scientific articlesthat described315 patients with 1p36 deletion or more complex rearrangement that involved chromosome 1p (Table 1). All patients showed specific craniofacial features that included straight eyebrows, deep-set eyes, flat nasal bridge, midface hypoplasia and pointed chin. All patientshaddevelopmental delay or different degrees of cognitive impairment, ranging from profound or severe (the majority of the cases, about 90%) to moderate (about 10%), and global hypotonia. All patientshad feeding difficulties, mostly on infant period, and had poor social interaction and poor language skills.Behavioural disorders, e.g. temper tantrum, self-biting, or manual apraxia are also common.The variable phenotypic expression of 1p36 deletions was initially thought to be caused by a parent-of-origin effect in which deletions of paternally-derived copy of 1p36 are not equivalent to deletions of maternally-derived copy, due to imprinting differences. However, thanks to the use of DNA polymorphism analysis it is now clear that there was no obvious parent-of-origin effect, and the phenotypic variability was more likely caused by differences in the location and extension of the 1p36 deletions (Shapira et al., 1997). The breakpoints of the deletions ranged from 1 p36.13 to 1p36.33, with most of them occuring at the 1p36.2 (Slavotinek et al., 1999). In a large study, the critical region for moderate to severe mental retardation is defined distally by D1S243 and proximally by D1S468. This region was subsequently referred to as the distal or classical critical region (Wu et al., 1999a, 1999b). The widespread use of array comparative genome hybridation (aCGH) allowed investigating genotype-phenotype association in an increasing number of small interstitial deletions identified in individuals with mental retardation and developmental disabilities (Battaglia, 2005; Zaveri et al., 2014;). Kang et al. (Kang et al., 2007) identified interstitial deletion affecting 1p36.23–1p36.11 in five individuals, concluding that the features seen in these children might constitute a distinct proximal 1p36 deletion syndrome. Alternatively, they suggested that the region