Brain & Development 36 (2014) 837–843

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Review article

Epileptic features in Cornelia de Lange syndrome: Case report and literature review

Elena Pavlidis [a,*], Gaetano Cantalupo [b], Sara Bianchi [a], Benedetta Piccolo [a], Francesco Pisani [a]

[a] Child Neuropsychiatry Unit, Department of Neuroscience, University of Parma, Parma, Italy
[b] Department of Life and Reproduction Sciences, University of Verona, Verona, Italy

Received 14 September 2013; received in revised form 20 December 2013; accepted 22 December 2013

Abstract

Introduction: Cornelia de Lange syndrome is a rare genetic disease, caused by mutations in three known different genes: NIBPL (crom 5p), SMC1A (crom X) and SMC3 (crom 10q), that account for about 65% of cases. This syndrome is characterized by distinctive facial features, psychomotor delay, growth retardation since the prenatal period (second trimester of pregnancy), hands and feet abnormalities, and involvement of other organs/systems. SMC1A and SMC3 mutations are responsible for a mild phenotype of the syndrome. *Methods:* We report the electroclinical features of epilepsy in a child with a mild Cornelia de Lange syndrome and furthermore we reviewed the descriptions of the epileptic findings available in the literature in patients with such syndrome. *Results:* A large heterogeneity of the epileptic findings in the literature is reported. *Conclusion:* The presence of epilepsy could be related to pathophysiological factors independent of those implicated in the characterization of main classical phenotypic features. A more detailed description of the epileptic findings could help clinicians in the diagnosis of this syndrome in those cases lacking of the typical features.

Keywords: Cornelia de Lange syndrome; Mild variant of Cornelia de Lange syndrome; SMC1A; Epilepsy; Seizures; Febrile seizures

1. Introduction

Cornelia de Lange syndrome (CdLS), also known as Brachmann-de Lange syndrome, is a rare genetic disease with a prevalence range from 1:10,000 [1] to 1:40,000 [2]. A recent epidemiologic study estimated that the overall prevalence for mild and classical CdLS would be 1.6–2.2 per 100,000 or 1:62,000–1:45,000 [3]. Although Vrolik in 1849 [4] and Brachmann in 1916 [5] already reported subjects with the characteristics of CdLS, the first to describe this syndrome as a separate entity and to identify its salient features was Cornelia de Lange [6]. Since then, mutations in three known different genes were found, NIBPL (crom 5p), SMC1A (crom X), and SMC3 (crom 10q), accounting for about 65% of individuals with CdLS [7]. Etiological factors responsible for the remaining 35% of cases are still unknown. This syndrome, notwithstanding its variable phenotypic expression, is characterized by multiple malformations, particularly involving the cardiac, gastrointestinal and musculoskeletal systems, abnormalities of hands and feet, distinctive facial features, pre- and postnatal growth retardation, psychomotor delay and behavioral abnormalities [8]. Even if the detection of the previously mentioned mutations suffices to formulate a definite diagnosis, the diagnosis is primarily based on clinical

* Corresponding author. Address: U.O. di Neuropsichiatria Infantile, Dipartimento Materno-Infantile, Azienda Ospedaliero-Universitaria di Parma, Via Gramsci 14, 43126 Parma (PR), Italy. Tel.: +39 0521 702205; fax: +39 0521 704708.
E-mail address: elena.pavlidis@studenti.unipr.it (E. Pavlidis).

0387-7604/$ - see front matter © 2013 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.braindev.2013.12.008

criteria, recently revised by Kline and colleagues, who also proposed a severity scoring system based on clinical data [8]. As part of CdLS we can find the classical type and mild phenotype variants; some studies suggested that mutations of SMC1A and SMC3 are responsible for the "mild" phenotype [9,10]. The facial features of an individual with classical CdLS are easily recognizable; a milder CdLS phenotype has been reported characterized by less significant psychomotor and growth retardation, a lower incidence of major malformations, and milder limb anomalies, accounting for 20–30% of the CdLS population [8]. To our knowledge little attention has been previously placed on the electroclinical features of epilepsy and/or seizures of these patients [11]. Here, we describe the epileptic electroclinical findings in a child with a mild phenotype of CdLS.

2. Methods

We report a child with a mild phenotype of CdLS describing her epilepsy and the related electroencephalographic abnormalities. Moreover, we carried out a review of the available English or Italian literature on the subject, using the following search terms in PubMed: ((Brachmann AND "de Lange") OR "Cornelia de Lange") AND (seizures OR convulsions OR spells OR fits OR epilepsy OR crisis); we also included secondary sources of data, such as reference lists of articles reviewed. We also performed a further search, using the following terms in Pubmed: ((Brachmann AND "de Lange") OR Cornelia de Lange) AND (EEG OR electroencephalography), including relative secondary sources of data.

3. Case report

The patient was born preterm in the 33rd week of gestional age by cesarean section for breech presentation and cardiotocographic abnormalities. Apgar score at first minute was 8. At birth, microcephaly was present, weight and height parameters were around 25th percentile. At the age of two years a CdLS was suspected, because of the presence of some typical facial dysmorphic features, such as arched eyebrows, synophrys, thick and long eyelashes, broad nasal bridge, and thin upper lip, associated with psychomotor delay, poor growth and hearing loss. However, due to the absence of some important features of the syndrome, such as hirsutism, feeding difficulty, gastro-esophageal reflux, significant heart or kidney disease, upper limb malformations, and clear behavioral disorders or sleep disturbances, a "mild" phenotype of CdLS was investigated. Gene SMC1 sequencing was performed, and a de novo mutation in position c.1487G → A was found, causing an aminoacid substitution (p.Arg496His) at codon 496. At the age of 2 years and 10 months the child experienced two brief (about 1 min of duration), self-limiting unprovoked seizures, occurring upon awakening. The first one was a partial seizure with secondary generalization (PSG). The child showed a left tonic deviation of the mouth, ipsilateral eye closure, left upper limb and wrist flexion lasting a few seconds, subsequent stiffening, and generalized tonic-clonic seizure with eye rolling, trismus, apnea and severe paleness. At the end, a post-ictal state was evident. The second episode was a partial complex seizure (PCS), characterized by left upper limb tonic-clonic seizure, subsequent staring and drooling. The neurological examination showed alternating divergent squint, gait ataxia and language disorder. Neuroimaging (neonatal cerebral ultrasound and brain magnetic resonance imaging -MRI- performed at the age of 1 year and 9 months) detected a mild cerebellar vermis hypoplasia. An electroencephalogram (EEG), performed at the age of 21 months, before the first seizure, showed an inadequately organized background activity and focal epileptiform abnormalities over the frontal areas, with bi-hemispheric spreading. Post-ictal EEG showed a focal slowing over the right posterior quadrant associated with apparently generalized epileptiform abnormalities, with no further activation during photic stimulation and hyperventilation (Fig. 1a). A subsequent sleep EEG recording, performed after partial sleep deprivation, disclosed interictal epileptiform abnormalities characterized by atypical complexes of bilateral spikes and polispikes and waves, particularly prominent over the right fronto-temporal areas (Fig. 1b). The patient was treated with valproic acid obtaining a complete seizure freedom. Currently, she is 5 years and 11 months and is still in follow up. On the follow-up EEG recordings the epileptiform abnormalities decreased progressively up to complete absence, while the background activity did not improve considerably.

4. Literature review

We found out 24 published papers with reports of subjects with CdLS and epilepsy/seizures, specifically: 2 single case reports [12,13], 19 case series [9,10,14–30] and 3 review studies [8,31,32], accounting for about 324 subjects with seizures and/or epilepsy (Table 1). Of those, in only 18 articles is described at least one characteristics (familiarity for epilepsy/seizures, type of seizure/epilepsy, EEG findings, response to antiepileptic drugs -AEDs- or neuroradiologic findings) for about 97 subjects (an additional table shows these features in detail [see Supplementary Table 1]) and only for 18 patients all of these characteristics are available. In Table 2 we summarized the main electroclinical features of the 97 subjects. The EEG features of CdLS patients without history of convulsive disorders are reported in Table 3. In our literature review, we found different