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Late-onset childhood neuronal ceroid lipofuscinosis: Early clinical and electroencephalographic markers

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ABSTRACT

Purpose: The objective of the study was to describe the initial clinical and electroencephalographic findings in children with late-infantile neuronal ceroid lipofuscinosis (LINCL).

Method: The clinical charts of 35 patients seen between 1990 and 2016 were reviewed. The patients were divided into two groups: Group 1 (G1) consisting of 12 patients with NCL type 2 (CLN2) disease confirmed by enzymatic activity in dried blood spots on filter paper and/or genetic studies, and Group 2 (G2) consisting of 23 patients with a diagnosis of LINCL based on pathology studies by muscle biopsy.

Results: Mean age at symptom onset was 3 years in G1 and 3.4 years in G2. Symptoms at onset were epilepsy in 58%, language delay in 34%, and gait disturbances in 8% of patients in G1 and epilepsy in 52.1%, language delay in 26%, gait disturbances in 17.4%, and loss of visual acuity in 4.5% in G2. The most common seizure types in G1 patients were myoclonic in 3/7, generalized tonic-clonic in 2/7, focal motor in 1/7, and febrile seizures in 1/7; in G2 patients they were myoclonic in 5/12, generalized tonic-clonic in 3/12, myoclonic-atonic in 2/12, and febrile seizures in 2/12. A photoparoxysmal response to intermittent photic stimulation (IPS) was found in the initial EEG in 9/12 patients in G1 (mean age 3.8 years) and in 10/13 patients in G2 (mean age 3.9 years).

Conclusions: There were no significant differences between both groups. Seizures, especially myoclonic, are the most common symptom at onset followed by language delay and gait disturbances. Low-frequency IPS is a useful study that may help facilitate the diagnosis of the disease.

1. Introduction

The neuronal ceroid lipofuscinoses (NCL) are the most common neurodegenerative disorders of children. In the pre-genetic era, NCL were diagnosed using electron microscopy studies. Currently, different genes have been identified, of which the NCL type 2 (*CLN2*) gene is the most common and is associated with concrete therapeutic possibilities (Kohan et al., 2011; Mole et al., 2005; Wiseman et al., 2017). In the majority of patients with LINCL, mutations in the *CLN2* gene are found.

CLN2 disease is an autosomal recessive, neurodegenerative lysosomal storage disorder with onset in late infancy caused by deficient activity of the tripeptidilpeptidase 1 (TPP1) enzyme. CLN2 disease is characterized by language delay, epilepsy, ataxia, movement disorders, regression of motor skills, dementia, blindness, and death at an early age. TPP1 deficiency leads to abnormal intralysosomal storage of autofluorescent material and is associated with neuronal necrosis, although the pathophysiology is still poorly understood.

The disorder is extremely rare, with an estimated incidence ranging from 0.15 per 100,000 live births in Portugal (Teixeira et al., 2003), 0.46 per 100,000 live births in West Germany (Claussen et al., 1992), and 0.78 per 100,000 live births in the United Kingdom (Williams et al., 2006) to up to 9.0 per 100,000 live births in Newfoundland.

The classic phenotype of CLN2 disease has a predictable clinical course marked by epilepsy and rapid psychomotor regression (Nickel et al., 2016; Steinfeld et al., 2002; Worgall et al., 2007). The most common initial symptoms are language delay and seizures that start between two and four years of age, with language delay often preceding the seizure onset (Nickel et al., 2016; Steinfeld et al., 2002). Patients typically present with unprovoked seizures, although onset with febrile seizures has also been reported (Pérez-Poyato et al., 2013). Other initial symptoms include peripheral and truncal ataxia, behavioral disturbances, and signs of developmental delay. The seizures may be

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polymorphic (e.g., generalized tonic-clonic, myoclonic, and/or atonic seizures) and are most often drug resistant. After seizure onset, rapid decline of cognitive and motor functions over a period of two to three years is seen to result in a complete loss of speech and voluntary movements by the age of six years (Steinfeld et al., 2002; Worgall et al., 2007). Patients develop movement disorders, such as myoclonus, dystonia, and spasticity. Myoclonus (epileptic and non-epileptic) is an important feature that can be particularly difficult to treat and may disturb sleep (Caraballo et al., 2005; Williams et al., 2006). Visual disturbances start as early as four years of age but usually do not become apparent until the disease is advanced and the children present with amaurosis by the age of 7–10 years (Steinfeld et al., 2002).

Early diagnosis of CLN2 disease is essential, as irreversible damage may occur between disease onset and diagnosis (Worgall et al., 2007). Unfortunately, early diagnosis is hindered by the lack of reliable clinical markers and poor awareness of the disease, as well as limited access to diagnostic tests in some areas. The detection of a photoparoxysmal response (PPR) to intermittent photic stimulation (IPS) at a low frequency on electroencephalography (EEG) has been suggested as a sensitive complementary study to improve the diagnosis (Nickel et al., 2016). Currently, however, the gold standard for the definitive diagnosis is deficient TPP1 enzyme activity associated with the detection of pathogenic mutations in each allele of the gene encoding TPP1 (the *CLN2* gene). Nevertheless, ultrastructural findings of curvilinear bodies in tissue samples (e.g. skin) on electron microscopy may have diagnostic value (although not definitive) in regions where molecular testing is not available.

The aim of this study was to describe the clinical and electroencephalographic findings of children with LINCL in the pre- and post-molecular testing era, respectively.

2. Method

Clinical charts were reviewed of 35 patients who met the diagnostic criteria of LINCL seen at the Department of Neurology of Hospital JP Garrahan between February 1990 and February 2017; 15 of the 35 patients described were previously reported (Caraballo et al., 2005).

The following study variables were analyzed: sex, age at disease onset and seizure semiology. Neuroimaging studies (MRI or CT scan), neurometabolic studies, electroretinography, and visual evoked potentials (VEP) were performed in all cases. Pathology studies were performed in 25 cases, and enzymatic and molecular analysis in 12 and seven cases, respectively. Repeated EEGs were performed during sleep and wakefulness, with and without IPS, at different frequencies in all patients. Background organization and topography and morphology of the paroxysms were evaluated. The electrodes were placed according to the international 10–20 system. As this study was retrospective, the repeated EEGs were not performed at the same time and with the same procedures; however, IPS was performed using the same methodology in most of the patients. Age at each EEG, whether IPS was performed, presence of PPR, frequency (in hertz) of PPR, and presence or absence of a flash-per-flash response on IPS were recorded. Patients were sat at a distance of 30 cm from the photic stimulator and were asked to look at the center of the lamp. Ambient lighting was sufficient to facilitate observation of the patient while controlling ocular fixation on the center of the lamp and being attentive to any subtle clinical ictal phenomena. Separate trains of flashes of 5-s duration were used at the following frequencies: 1, 2, 3, 4, 5, 6, 7, 8, 10, 14, 16, 18, 20, 25, 30, 40, 50, and 60 Hz. Flash trains were separated by a pause of at least 10 s. These ranges were assessed in two distinct eye conditions in the same sequence for all patients: eyes closed and eyes opened. To discriminate between spontaneous and IPS-evoked discharges, the EEG was initially recorded without IPS for at least 5 min.

Of a total of 35 patients with LINCL included in this study, we recognized two groups. In Group 1 (G1), consisting of 12 patients, the diagnosis of CNL2 was confirmed using enzymatic studies testing for deficient TPP1 enzyme activity in dried blood spots on filter paper. In the remaining 23 patients, Group 2 (G2), the diagnosis was made using electron microscopy studies confirming the presence of curvilinear bodies. Patients in this latter group were evaluated in the pre-molecular analysis period.

3. Results

Of a total of 35 patients with LINCL and CLN2 disease included in this study. In 12 (G1) the diagnosis was confirmed by enzymatic studies, while in the remaining 23 patients (G2), evaluated in the pre-molecular analysis period, the diagnosis was made using electron microscopy studies confirming the presence of curvilinear bodies.

In G1, of 12 patients, six were female; and in G2, of 23 patients, 14 were female. Mean age at symptom onset was 3 years (range 2.1–3.5 years) in G1, and 3.4 years (range, 2–4.1 years) in G2. Symptoms at onset were epilepsy in 58%, language delay in 34%, and gait disturbances in 8% in G1, and epilepsy in 52.1%, language delay in 26%, gait disturbances in 17.4%, and loss of visual acuity in 4.5% in G2. The most common seizures in G1 were myoclonic in 3/7, generalized tonic-clonic in 2/7, focal motor in 1/7, and febrile seizures in 1/7, and in G2, myoclonic in 5/12, generalized tonic-clonic in 3/12, myoclonic-atonic in 2/12, and febrile seizures in 2/12.

In 75% (9/12) of the patients in G1, the initial EEG, performed at mean age of 3.8 years, revealed PPR to low-frequency IPS. The response was positive in 77% (10/13) of the patients in G2 in whom IPS was performed in the first EEG at a mean age of 3.9 years (Figs. 1 and 2). The mean time between symptom onset and IPS study was 8 and 12 months in group 1 and 2 respectively.

The PPR seen in the initial EEG was characterized by an occipital spike-wave response to the photic stimuli. The response occurred at low-frequency IPS (1–7) Hz in 19 patients; in two of them the response also occurred at middle and high frequencies. None of the patients had seizures during the IPS. In these 19 patients PPR disappeared over time; in 10 patients we were able to document it between 1 and 3 years after first recognizing it on the EEG.

On the first EEG, background activity was normal in 6/12 (50%) and the EEG was slow and/or poorly organized in 6/12 patients in G1. The background activity was normal in 12/23 (52%) and the EEG was slow and/or poorly organized in 11/23 (47.8%) patients in G2. In two patients in G2 the background activity was asymmetric. Focal abnormalities were present in 5/12 of G1 and in 13/23 of G2. The focal abnormalities were located predominantly in the temporal and occipital

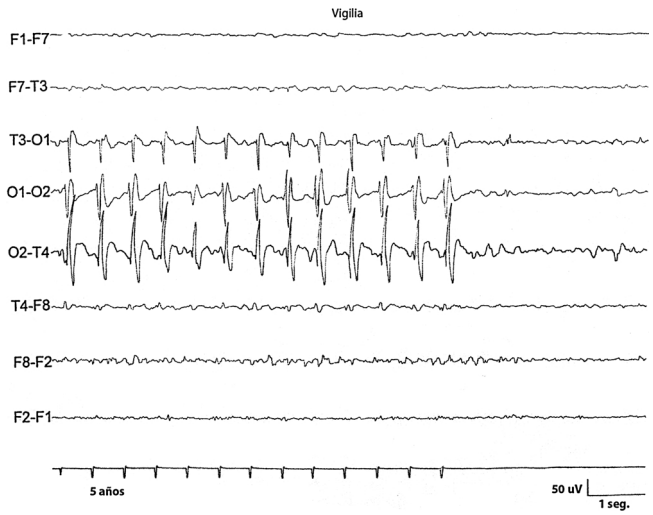

Fig. 1. In a 3-year-old boy with CLN2 disease (group 1), the EEG recording shows bilateral occipital spikes triggered by slow-frequency intermittent photic stimulation.