SHORT COMMUNICATION

Neurophysiological findings in lipofuscinoses of the neuronal ceroid

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ABSTRACT

New NCLs (neuronal ceroid lipofuscinoses) are a diverse group of neurodegenerative illnesses marked by progressive cerebral atrophy caused by a lysosomal storage abnormality. Epileptic seizures, gradual cognitive and motor impairment, and vision loss are common clinical symptoms that occur over varying time periods depending on the subtype. Many improvements have been made in the field of targeted treatments in recent years, and gene therapies and enzyme replacement treatments for numerous NCL variations may be available in the near future. Because NCLs grow quickly, early detection is critical, and neurophysiological aspects may play a vital role in this. Electroencephalogram (EEG) is characterised by a progressive worsening of brain activity with slowing of background activity and removal of spindles during sleep throughout the different subtypes of NCLs. Many NCL variants describe a variety of heterogeneous abnormalities, both diffuse and localised, that affect the temporal and occipital areas. A characteristic EEG result is photoparoxysmal response to low-frequency Intermittent Photic Stimulation (IPS), which is usually seen in CLN2, CLN5, and CLN6 disorders. Visual Evoked Potentials (VEPs) are used to track visual functioning, and an Electroretinogram (ERG) with no response indicates retinal neurodegeneration. EEG, VEPs, and ERG may be useful techniques in the early detection of NCLs when used collectively.

Key Words: *lipofuscinoses; Electroencephalogram; Photoparoxysmal*

INTRODUCTION

NCLs are a diverse category of autosomal recessive neurodegenerative illnesses characterised by progressive brain atrophy caused by a broad accumulation of autofluorescent storage material within lysosomes. Defective lysosomal processing enzymes or receptors produce NCLs. So far, 14 different varieties of NCLs have been identified; they all share some similar clinical markers, such as epileptic seizures, progressive cognitive and motor loss, and visual impairment, which manifest in different ways depending on the subtype [1].

The most common cause of dementia in children is neuronal ceroid lipofuscinoses, which have a global occurrence. Because of the presence of non-specific presenting symptoms, neuronal ceroid lipofuscinoses are frequently misdiagnosed at the outset, causing the diagnosis to be delayed. Although considerable efforts have been made in recent years to identify specific treatments, such as Enzyme Replacement Therapy (ERT) and genetic therapy for each of the NCL variations, clinical care is primarily palliative. Nonetheless, only for CLN2 disease is a targeted treatment with human recombinant enzyme currently accessible [2]. Early diagnosis is critical given the rapid course of the disease and the development of novel targeted treatments. Early diagnosis is also beneficial for genetic counselling, as it avoids a family voyage to several hospitals in search of a diagnosis, as well as the repeat of ineffective studies. Next-generation sequencing approaches have been successful in detecting hereditary childhood epilepsies and CLN2 illness early. A recent study found target re-sequencing to be beneficial in patients with hereditary childhood epilepsies, implying that this technology could be useful in the early diagnosis of CLN2 patients. Neurophysiological data may play a major role in the diagnosis of NCLs in this scenario. EEG and evoked potentials may be particularly useful for this purpose since they can provide essential information at a reasonably early stage of the disease and are simple to perform in a short amount of time and at a low cost [3].

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Electroencephalogram

One of the most common symptoms of NCLs is epilepsy. The age of beginning of epilepsy varies depending on the NCLs variant, ranging from infancy to maturity; both focal and generalised seizures can be present at the time of commencement. In CLN2 and CLN6 disorders, epilepsy may be the first symptom, or it may emerge after vision loss, cognitive and motor impairment, like in CLN3 and CLN5 diseases. In the classic form of CLN1 disease, symptoms appear in infancy, and seizures occur at a young age, usually between the ages of 14 and 36 months. With late infantile, adolescent, and adult onset, additional phenotypes have been documented. Epilepsy usually develops several years after the first symptom of visual impairment, as a result of developmental regression and behavioural abnormalities. There is a scarcity of information on EEG characteristics in CLN1 illness. High-voltage slow waves and spike and waves anomalies have been linked to a slowing of background activity and the loss of sleep spindles. Between the ages of 5 and 12, there is a steady flattening of cerebral activity, which is compatible with severe cortical atrophy caused by enormous neuronal death [4]. In summary, changes in background activity in CLN1 disease can be divided into three stages: decreased posterior rhythm reactivity to eye opening and closing; decreased sleep spindles and subsequent disappearance; and slowing and/or attenuation of EEG to inactivity, the so-called vanishing EEG pattern. In 75% of patients, the first EEG is performed within the fourth year of life and shows normal background activity with isolated or widespread abnormalities. The temporal and occipital areas are dominated by high-voltage focused slow waves. In patients with CLN2, Photoparoxysmal Response (PPR) to Intermittent Photic Stimulation (IPS) applied at a low frequency of stimulation is common in the early stages of the disease. As the condition progresses, the background activity slows down and becomes unresponsive to eye opening. During sleep recordings, there are no spindles. Generalized, focal, and multifocal epileptiform discharges with irregular spikes, poly-spikes, and waves become more prevalent, although a posterior majority continues. The presenting symptom of CLN3 illness, or juvenile neuronal ceroid lipofuscinosis (Spielmeyer–Vogt disease or Batten disease), is gradual vision loss that begins at the age of 6–8 years. Epilepsy usually begins at the age of ten. When seizures first appear, they are frequently bilateral tonic–clonic, although focal seizures become more common during adolescence and are characterised by clonic characteristics. In CLN3 disease, myoclonic seizures are uncommon. EEG demonstrates focal epileptiform abnormalities in the early stages of the disease (before 10 years of age), whereas bilateral and multifocal epileptiform discharges are much more common in the later stages, accompanied with a progressive slowing of background activity. In CLN3 disease, PPR has not been identified as a key characteristic. CLN6 sickness can strike at any age, from childhood to maturity. Epilepsy is one of the presenting symptoms in both situations. Since the beginning, background activity has been disorganised during waking and sleeping hours, with irregular sluggish spikes and waves discharges (at about 2.5 Hz). An early neurophysiological observation is PPR to lower frequency. Low-voltage and spike and waves discharge became rare as the disease progressed, and single spikes with multifocal distribution were frequently replaced by single spikes with multifocal distribution. Background activity is almost retained in adult CLN6 patients in the early stages of the disease. The most common epileptiform abnormalities are found in the posterior areas. Active motions or IPS at a low frequency of stimuli are commonly used to cause myoclonus. PPR abnormalities persist until the disease is progressed [5]. The CLN5 disease, also known as the Finnish variation, manifests itself as clumsiness and mental impairment between the ages of 2 and 6. Seizures begin late in life (median age of 8 years), and myoclonic seizures are the most common form of epilepsy between the ages of 7 and 11. Furthermore, for this LINCL, it has been shown that multifocal epileptiform discharges (spikes, multiple spikes, and spike and wave complexes) and the existence of posterior spikes induced by low-frequency IPS are related with a progressive slowing of background activity.

Photoparoxysmal response

PPR susceptibility differs depending on the diseases that are more prevalent in LINCLs, such as CLN2, CLN5, and CLN6 (Figures 1F–H). PPR has been reported in individuals with CLN2 illness in a range of 27 to 93 percent of cases. The lack of a standardised low frequency IPS method in typical paediatric EEG recordings could explain the large variance. PPR is one of the first signs of a neurodegenerative condition, even before cognitive and motor regression, in NCLs and other progressive myoclonic epilepsies. In Lafora disease and mitochondrial diseases, PPR to low-frequency stimulation has also been documented [6].

Electroretinogram

One of the cardinal indications of NCLs is vision-related issues, which, like CLN3, are often an early sign, showing before motor and mental decline. This occurs as a result of the accumulation of storage material in the retina, which causes it to degenerate. Electroretinogram (ERG) is a method that can be used to assess retinal involvement, and its use decreases as the disease progresses at different ages, depending on the NCL variations. In individuals with NCLs, ERG is currently employed to characterise the physiological changes in the degenerating retina. It enables for the detection of retinopathy, which is characterised by symmetrical cone-rod dystrophy. From the age of 4 years and 10 months, it has been shown that abnormalities in ERG develop even before retinal damage on Optical Coherence Tomography (OCT) in CLN2 patients [7]. At a median age of 4.5 years, abnormal ERG has been found in 66 percent of individuals. However, it's crucial to remember that a flattening of the ERG doesn't always mean total loss of retinal function, especially if some cerebral VEP functions remain. Retinal degeneration has been verified in CLN5 disease between the ages of 6 and 10, when ERG has been reported to be absent in the majority of patients. ERG may be used in the future to assess the efficacy of experimental intravitreal therapy.

Somatosensory evoked potentials

In NCL disorders, Somatosensory Evoked Potentials (SEPs) have received little attention. The existence of high-amplitude evoked potentials, enormous SEPs, which are indications of cortical

hyperexcitability due to neuronal degeneration, has been identified in occasional cases across different types of NCLs.

Cortical myoclonus is one of the key clinical hallmarks of NCLs, and giant SEPs are a typical and particular marker of people with this condition [8-10].

Differentiating NCLs from other DEEs can also be done using neurophysiological tests. DEEs with epilepsy onset between 2 and 6 years of age, primarily characterised by myoclonic seizures, should be distinguished from LINCLs in more detail. Among these, Epilepsy with Myoclonic-Atonic Seizures (EMA) and Lennox–Gastaut Syndrome (LGS) are important to address, as they are characterised by epilepsy with multiple types of seizures, intellectual disability, and medication resistance. Specific EEG abnormalities, such as diffuse spike-and-slow wave complexes at 2.5 Hz during awake and poly-spikes during sleep, characterise LGS [11]. PPR is infrequently recorded in both diseases, and when it occurs, it is not caused by low-frequency IPS. PPR, on the other hand, has been found in various childhood epileptic syndromes, the most common of which being The Dravet Syndrome (DS). Unlike the majority of NCLs, epilepsy in DS begins in the first year of life. Furthermore, in DS, PPR is not frequently produced by low-frequency IPS and does not have the flash-per-flash PPR features [12].

CONCLUSION

The potential importance of neurophysiological properties of NCLs in the early detection of such diseases necessitates a proper characterization of their neurophysiological features. The progressive slowing of background activity, the disappearance of sleep spindles during sleep, and the presence of heterogeneous abnormalities such as bursts of diffuse or focal slow waves prevalent over temporal and occipital regions, as well as diffuse spike and wave paroxysmal discharges, are all common features of different subtypes of NCLs.

REFERENCES

1. Platt FM. Emptying the stores: lysosomal diseases and therapeutic strategies. Nat Rev Drug Discov. 2018;17(2):133-150.

2. Nelvagal HR, Lange J, Cooper JD. et al Pathomechanisms in the neuronal ceroid lipofuscinoses. Biochim Biophys Acta Mol Basis Dis. 2020;1886(9):165570.

3. Mole SE, Cotman SL. Genetics of the neuronal ceroid lipofuscinoses (Batten disease). Biochim Biophys Acta (BBA)-Mol Basis Dis. 2015;1852(10):2237-2241.

4. Donsante A, Boulis NM. Progress in gene and cell therapies for the neuronal ceroid lipofuscinoses. Expert Opin Biol Ther. 2018 Jul 3;18(7):755-764.

5. Solomon M, Muro S. Lysosomal enzyme replacement therapies: Historical development, clinical outcomes, and future perspectives. Adv Drug Deliv Rev. 2017;118(3):109-134.

6. Fietz M, AlSayed M, Burke D, et al. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. Mol Genet Metab. 2016;119(1-2):160-7.

7. Veneselli E, Biancheri R, Buoni S, et al. Clinical and EEG findings in 18 cases of late infantile neuronal ceroid lipofuscinosis. Brain Dev. 2001;23(5):306-11.

8. Specchio N, Bellusci M, Pietrafusa N, et al. Photosensitivity is an early marker of neuronal ceroid lipofuscinosis type 2 disease. Epilepsia. 2017;58(8):1380-8.

9. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001;58(12):1985-1992.

10. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol. 2010;9(11):1118-11127.

11. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in" probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry. 1992;55(10):967-972.

12. Weinberg A, Doyle N. Psychology at work: Improving wellbeing and productivity in the workplace. Br Psychol Soc.