Neuronal ceroid lipofuscinosis 11 (CLN11) presenting with early-onset cone-rod dystrophy and learning difficulties

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BRIEF COMMUNICATION

Neuronal ceroid lipofuscinosis 11 (CLN11) presenting with early-onset cone-rod dystrophy and learning difficulties

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Abstract

Neuronal Ceroid Lipofuscinosis 11 (CLN11) is an ultra-rare subtype of adult-onset Neuronal Ceroid Lipofuscinosis. Its phenotype is variable and not fully known. A 21-year-old man was evaluated in our neurogenetic outpatient clinic for early onset complex phenotype, including learning difficulties, cerebellar ataxia, cone-rod dystrophy, epilepsy, and dystonia. The patient was submitted to neurological and neuropsychological assessment, neuro-ophthalmological tests, brain MRI, EEG and whole exome sequencing. A homozygous frameshift variant (NM_002087.4: c.768_769dup; p.Gln257Profs*27) was found. Distinct type descriptions, as in this case, increase the clinical spectrum of the disease.

Keywords Lipofuscinosis · CLN11 · Deep phenotyping

Abbreviations

ACMG	American College of Medical Genetics and Genomics
bvFTD	behavioral variant of Frontotemporal Dementia
CLN11	Neuronal Ceroid Lipofuscinosis 11
CRD	Cone-Rod Dystrophy
DPR	Dominance of the Posterior Rhythm
EEG	Electroencephalogram
FAZ	Foveal Avascular Zone
FTD	Frontotemporal Dementia
GRN	Granulin
MRI	Magnet Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NCL	Neuronal Ceroid Lipofuscinosis
RP	Retinitis Pigmentosa

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Background

Neuronal Ceroid Lipofuscinosis (NCL) is the most common neurodegenerative disorder in childhood [1]. They are characterized by the intracellular accumulation of ceroid lipopigment, mainly within lysosomes. The typical clinical progression encompasses advancing dementia, gradual visual deterioration, seizures, and premature death [1]. To date, 14 distinct types have been identified [2], varying in the age of onset and the primary symptoms, which heterogeneity is likely attributable to the different types of proteins involved in the pathology of each NCL (CLN1-CLN14) [2, 3].

We sought to describe the case of a young boy diagnosed with CLN11. This description contributes to global literature, where fewer than fifty cases have been described [1, 3, 4].

Case presentation

A 21-year-old male presented in his first decade of life with a complex phenotype encompassing abnormal visual defects,

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atypical behavior, and learning disabilities. His family history was unknown because the patient was adopted. At age of 3, he was noted to interact poorly with other children and became aggressive. Upon enrollment in mainstream school, he was diagnosed with both attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). During this period, he exhibited significant learning disabilities, struggled with writing, and underwent a progressive decline in visual acuity along with difficulties in distinguishing colors. By the age of 10, he presented with gait difficulties, and experienced exacerbated behavioral issues, leading to the initiation of neuroleptic medication (haloperidol, followed by risperidone). At the age of 14, he started recurrent seizures, which were controlled using 1250 mg of valproic acid.

At 16 years of age, his neurological examination revealed normal cranial nerves and deep tendon reflexes, with preserved strength and sensory function. He exhibited slurred speech, visual acuity limited to counting fingers at 1 m bilaterally. He had a wide-based cerebellar ataxic gait. Abnormal movements included facial choreic movements, cervical dystonia, choreoathetotic hand movements, and stereotyped jerks in the arms during walking (Supplementary material, Video e1).

Patient´s EEG recordings at ages 18, 19, and 20 years-old (Fig. 1 and Supplementary material 2) revealed background abnormalities including increased theta slow rhythms, reduced fast activity, and diminished dominance of the posterior rhythm (DPR) during wakefulness. At 18 years, the EEG was moderately abnormal, with a DPR frequency of 8 Hz. Subsequent recordings at 19 and 20 years showed abnormal low-voltage backgrounds (5–10 μV), minimal fast activity, and reduced posterior alpha rhythm (8–9 Hz) with voltages below 15 μV. Alpha reactivity to eye opening was inconsistent. No epileptiform paroxysms were registered in any of those tracings. Intermittent photic stimulation and hyperventilation failed to show abnormal patterns.

Neuro-ophthalmologic evaluation at the age of 19 years revealed a cone-rod dystrophy (CRD) (Fig. 2). Brain MRI performed at the ages of 15 and 18 revealed marked cerebellar atrophy and mild pontine atrophy (Fig. 3). For volumetric analysis, the FreeSurfer pipeline was used [5, 6], revealing a volume reduction from 72.357 cm^3 to 57.224 cm^3 (20.9%).

Cognitive evaluation at age 21, using adapted neuropsychological tests to overcome visual and motor impairments, revealed a mildly impaired global cognitive profile, characterized by predominant executive dysfunction and deficient verbal reasoning (Fig. 4). Verbal episodic and semantic memory remained intact. Impulsiveness and mental inflexibility were also noted (Supplementary material 1).

The proband's exome analysis through next-generation sequencing identified a homozygous class 5 frameshift variant, c.768_769dup; p.Gln257Profs*27 in granulin gene (GRN, NM_002087.4) [7, 8].

Discussion and conclusions

CLN11 is a rare subtype of NCL first described in 2012, is caused by biallelic pathogenic variants in the GRN gene. Initially identified in siblings with retinal dystrophy,

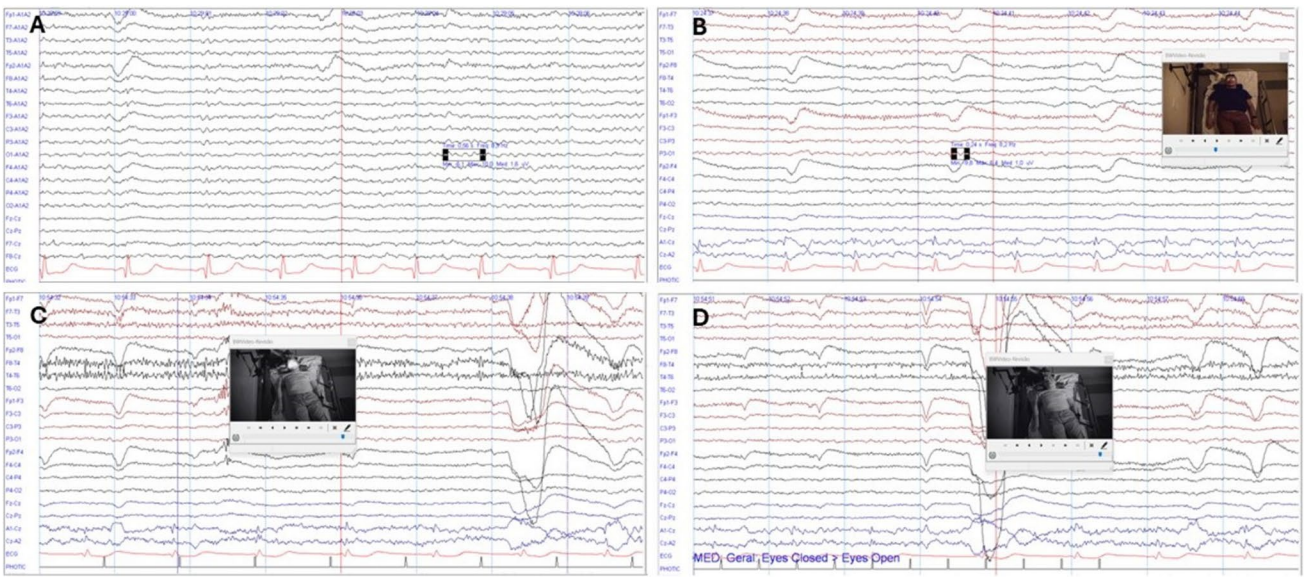


Fig. 1 Electroencephalogram (EEG) with scalp electrode placement including bipolar and linked ears referential montages revealed abnormal low-voltage backgrounds (5–10 μV), minimal fast activity, and a reduced posterior alpha rhythm (8–9 Hz) with voltages below 15 μV (**A** and **B**). Photic stimulation at 1 (**C**) and 2 flashes per second (**D**) fail to show occipital spikes or photic driving

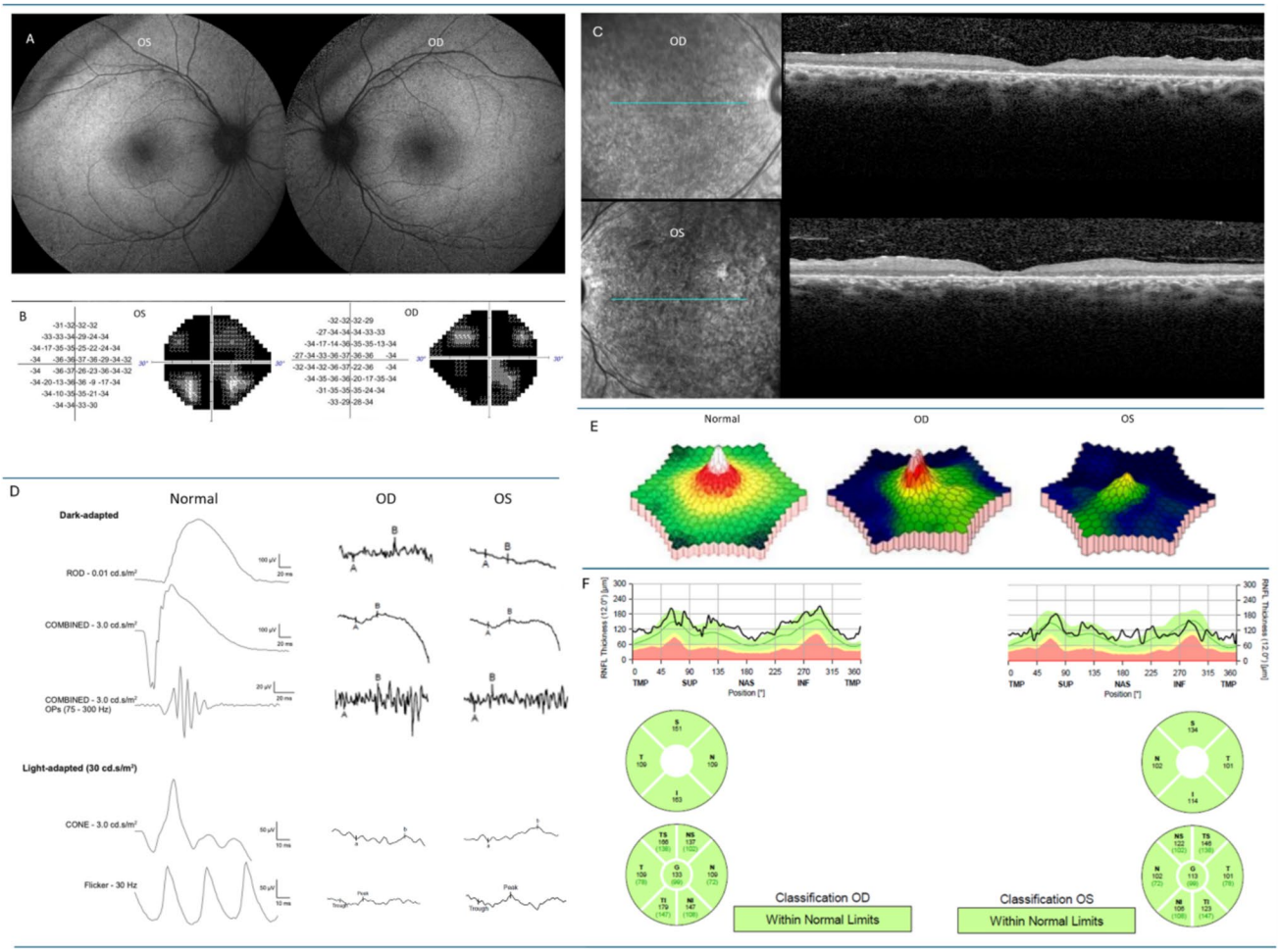
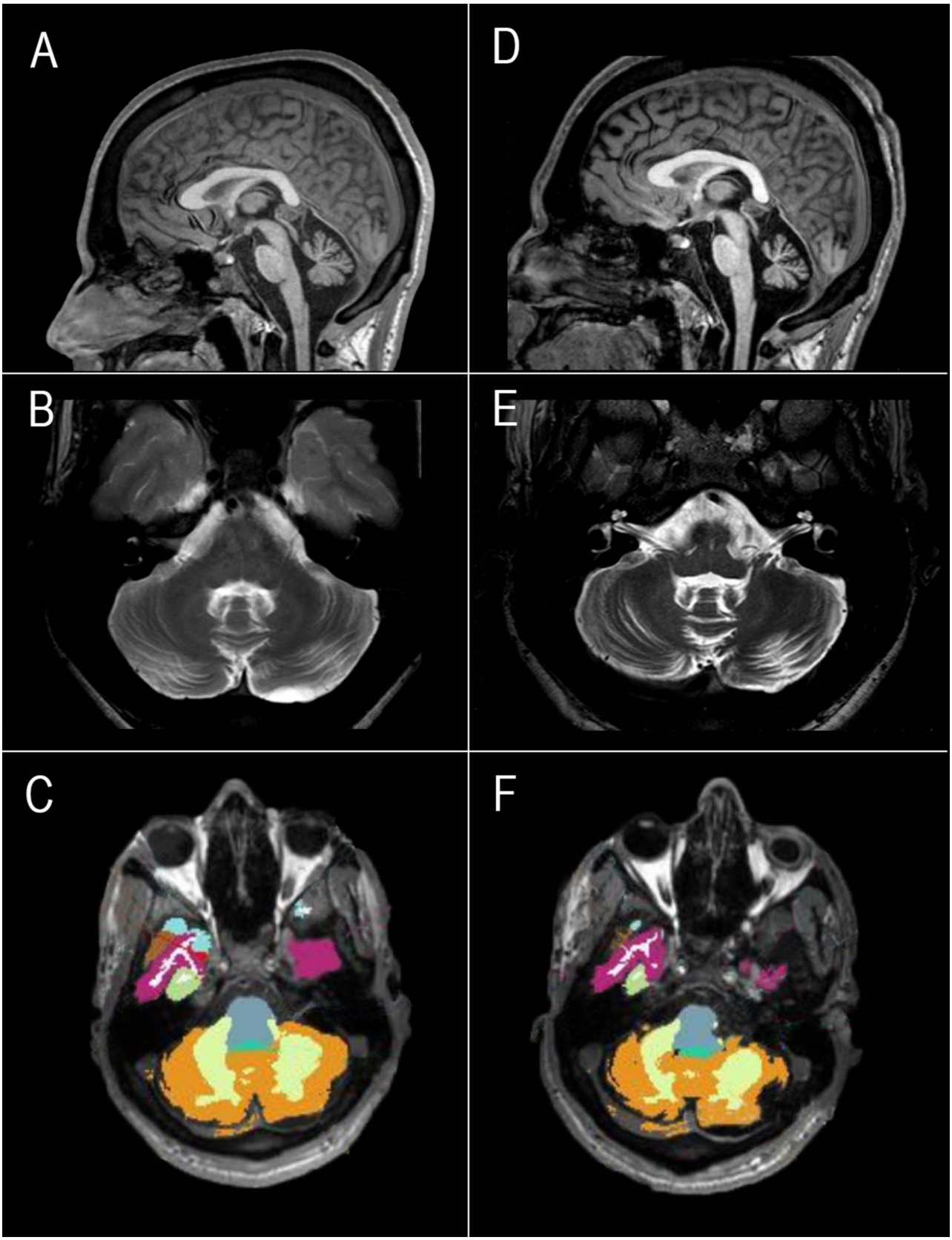


Fig. 2 Neuro-ophthalmologic evaluation showed the phase in which cone damage occurred. 1**A** Autofluorescence retinography showed an increase in the foveal avascular zone and hiperautofluorescence in the appearance of the perimacula. 1**B** Visual field testing performed with perimetry Humphrey field analyzer (Carl Zeiss Meditec AG, Jane, DE) exhibited a diffuse (generalized) sensitivity loss. 1**C** and **F** Optical coherence tomography (OCT) revealed a diffuse loss of the outer retinal layers, including photoreceptors and retinal pigment epithelium (RPE), and no optic nerve alterations. 1**D** and **E** The full-field electroretinogram (ERG) (Diagnosys LLC, Lowell, MA, USA) displayed non-detectable responses during dark adaptation and subnormal responses to adapted light. The electrophysiological assessment was complemented with multifocal ERG (mfERG), which assesses macular function and showed reduced macular amplitude in both eyes. The ERG and mfERG were performed according to ISCEV (International Society for Clinical Electrophysiology of Vision) standards

seizures, and cognitive impairment in their early 20s [9], CLN11 has since been associated with adult-onset presentations, adding myoclonic epilepsy and ataxia as key clinical features.

Progranulin functions as a neurotrophic factor and plays a key role in neuroinflammation [10, 11]. Pathogenic GRN variants, mostly null, lead to nonsense-mediated decay and progranulin deficiency, causing lysosomal dysfunction and neurodegeneration [7]. In CLN11, complete progranulin deficiency is observed in the brain of patients with biallelic null variants, while partial loss of function due to haploinsufficiency occurs in individuals with a single variant and frontotemporal dementia (FTD) [7]. Phenotypic differences include age of onset ranging from the first to the sixth decade, with most cases manifesting in the early 20s [2–4, 9, 12].

Our patient presented, in his first decade of life, abnormal aggressive behavior. It is possible that these symptoms represented early manifestations that were initially misdiagnosed as ADH and ODD. However, despite behavioral changes having been reported in up to 2/3 of patients, it has never manifested as the initial symptom [7]. In GRN-related behavioral variants of FTD and retinitis pigmentosa (RP)-FTD patients commonly present behavioral issues later in their sixth decade of life. At the age of 21, our patient had frontal executive dysfunction with relatively intact verbal episodic and semantic memory, and over the years, there was no clear clinical


A
D
B
E
C
F

◂**Fig. 3** Brain MRI performed at the ages of 15 (**A**, **B**, and **C**) and 18 (**D**, **E**, and **F**). Sagittal FLAIR and axial T2-weighted sequences revealed marked cerebellar atrophy with mild pontine atrophy. Segmentation is projected onto an axial slice of the cerebellum at the ages of 15 (**C**) and 18 (**F**)

progression. Additionally, frontal and anterior temporal lobes seemed normal on brain MRI. As behavioral variant (bvFTD) and RP-FTD have been reported in patients with homozygous variants in GRN, we argue that our patient presented with early-onset behavioral abnormalities as part of his phenotype.

The longitudinal analysis of cerebellar volume highlighted the progressive degenerative nature of the disease. While cerebellar atrophy and ataxia are well-established features [1–3, 9], myoclonus and parkinsonism have been only more recently reported [4]. Interestingly, the patient exhibited stereotyped jerks, dystonia, and choreoathetotic movements. However, these symptoms occurred following neuroleptics use, and tardive dyskinesia cannot be ruled out.

Ophthalmic manifestations can vary between NCL types [12]. Retinal dystrophy, and especially retinitis pigmentosa (RP), have been consistently described in patients with CNL11 [12, 13]. However, our patient's assessment aligns with CRD rather than RP. CRD manifests as a lesion primarily in the cones or macular retinal pigment epithelium with subsequent involvement of the rods, clinically presenting at early stages with a reduction in visual acuity, altered color perception, and adaptation to light. In CRD the rods are affected later during disease progression, when ultimately peripheral vision loss occurs. In RP, rod dysfunction occurs earlier, leading to a restricted visual field and nyctalopia, whilst central vision impairment occurs later. Notably, the progression of CRD tends to be more aggressive, as observed in our patient. This pattern, in which retinal degeneration characterizes CRD rather than typical RP, has been described in some syndromes, including SCA7 [14, 15].

Epilepsy is frequent in NCL [1, 9, 16, 17], and EEG is an important tool. Our patient did not exhibit the occipital spikes triggered by low-frequency (1–2 Hz) light flashes during photic stimulation, as described in NCL2 and NCL6 [18]. Furthermore, as in all NCL subtypes, it showed a progressive slowing of background activity and a decline in EEG amplitudes until it eventually become flat [18, 19]. Our patient had a very low amplitude EEG, differing from the normal low-voltage EEG variant, as it lacked the typical predominance of fast rhythms and instead showed slow theta rhythms with amplitudes lower than 15 microvolts. Notably, even normal low-voltage recordings are more prevalent after 50 years of age and are rare before 20 [20]. The EEG abnormalities in our patient are likely attributable to the progressive attenuation observed in NCL. Regarding background slowing, Larsen et al. (2001) reported total power reduction with increased percentage of theta rhythms in juvenile NCL compared to age-matched controls, along with a reduced fast/slow ratio in these patients [21].

In summary, we report a patient with confirmed CLN11 presenting with early-onset abnormal behavior, progressive cerebellar atrophy, CRD, and epilepsy increasing it the clinical spectrum.

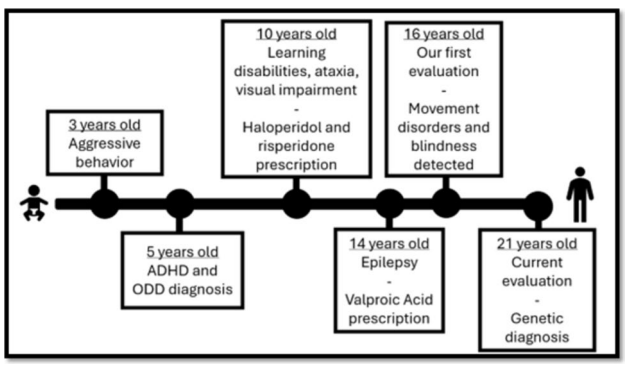


Fig. 4 Timeline of drug treatment and disease progression

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics and consent for publication Written informed consent was obtained from the patient's mother for publication and video recording. The local ethics committee approved this study: CAAE 33838220.9.0000.5440.

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Competing interests The authors declare no competing interests.

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