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# MRI in CLN2 disease patients: Subtle features that support an early diagnosis

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ABSTRACT

Neuronal ceroid lipofuscinosis type 2 (CLN2) disease is a rare, paediatric-onset, neurodegenerative disorder characterised in its early stages by language delay, seizures and loss of motor function. It is rapidly progressive and ultimately results in the premature death of patients. We aim to highlight common magnetic resonance imaging (MRI) features seen in early CLN2 disease and increase disease awareness among clinicians in order to facilitate early diagnosis and treatment of patients with disease-modifying enzyme replacement therapy.

We obtained MRI scans from 12 Turkish children with CLN2 disease, at symptom onset or time of diagnosis, and at various times during disease progression. Patient details including age at onset of symptoms, age at diagnosis and clinical presentation were collected. MRIs were analysed to identify common features present in patients with CLN2 disease.

The median diagnostic delay in this cohort was 2 years, highlighting the need for increased disease awareness among clinicians. Key MRI features suggestive of CLN2 disease that were identified included cerebellar atrophy in 11 patients, linear hyperintensity of central white matter in 10 patients, cerebral atrophy in 8 patients and thinning of the corpus callosum in 6 patients. Thalamic hypointensity was seen in 1 patient and may also indicate CLN2 disease.

It is important to consider the presenting symptoms alongside clinical test results in order to support early diagnosis of CLN2 disease. Clinical suspicion of CLN2 disease accompanied by the detection of any of the above-mentioned features on MRI should encourage healthcare professionals to test for CLN2 disease.



## 1. Introduction

Neuronal ceroid lipofuscinosis type 2 (CLN2) disease is one of the most common of the neuronal ceroid lipofuscinoses (NCLs), a group of rare lysosomal storage disorders, with an incidence ranging from 0.15 to 9 in 100,000 live births globally [1]. This autosomal recessive neurodegenerative disorder is caused by mutations in the *TPP1* gene, resulting in deficient activity of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), intra-lysosomal accumulation of ceroid lipofuscin, and neuronal and retinal cell death [1,2]. Affected individuals suffer language delay, seizures, loss of motor function, loss of vision, and dementia, with death commonly occurring by early adolescence [1,3]).

Cerliponase alfa, a disease-modifying enzyme replacement therapy granted regulatory approval in the United States and Europe in 2017, slows the rate of decline in patients with CLN2 disease [2,3]. Early diagnosis is critical to ensure prompt disease-specific treatment, along with involvement of the multidisciplinary team, and appropriate support and family planning [1]. However, a lack of disease awareness among healthcare professionals, non-specific presenting symptoms and limited access to

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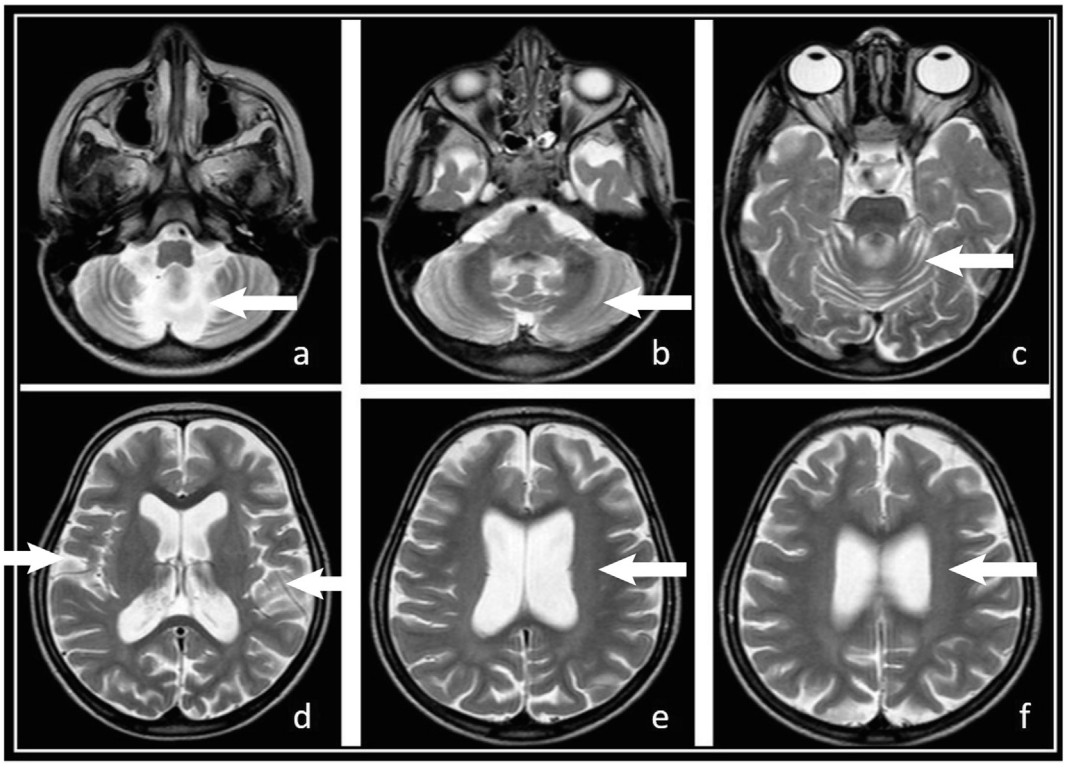


**Fig. 1A** Patient 1 – T2-weighted axial sections from an MRI scan taken 1 year after the onset of symptoms. This scan demonstrates mild to moderate cerebellar (a, b, c) and cerebral (d) atrophy, and linear hyperintensity of central white matter (e, f).

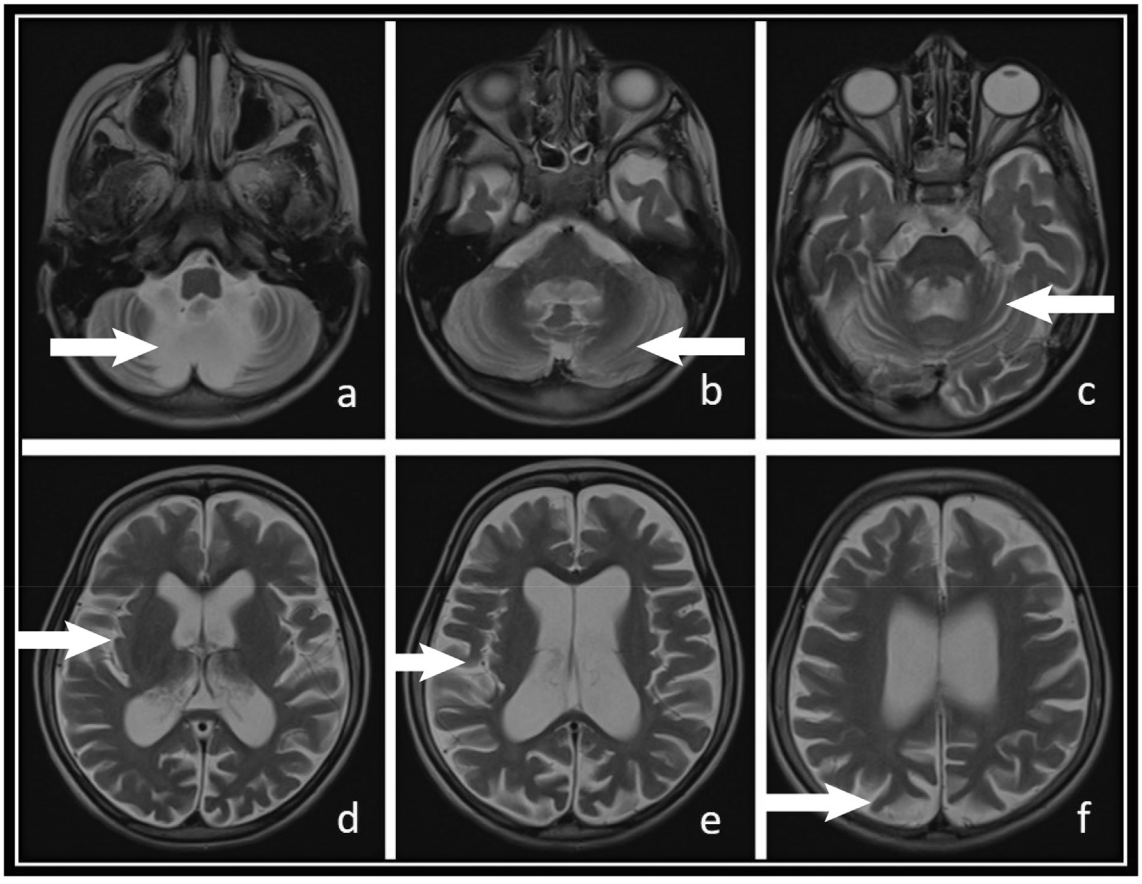


**Fig. 1B** Patient 1 – T2-weighted axial sections from an MRI scan taken 2 years after the onset of symptoms. This scan reveals significant progression of cerebellar (a, b, c) and cerebral (d, e, f) atrophy compared with the scan taken 1 year earlier.

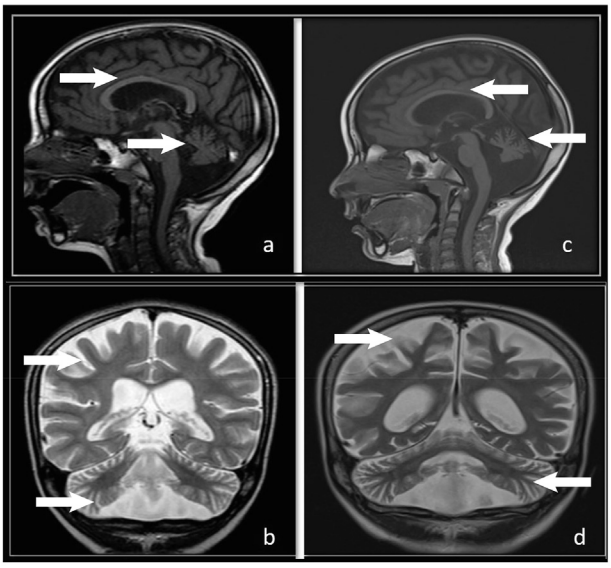


**Fig. 1C** Patient 1 – T1-weighted sagittal sections (a, c) and T2-weighted coronal sections (b, d) from two different MRI scans. Sections a and b were taken 1 year after the onset of symptoms. Sections c and d were taken 2 years after the onset of symptoms. This figure clearly demonstrates progression of cerebral (b, d) and cerebellar (a, b, c, d) atrophy and thinning of the corpus callosum (a, c).

diagnostic testing in some regions mean that many patients are only diagnosed when they enter a period of rapid disease progression, an average of 2–3 years after the onset of symptoms [1,2,4].

Genetic tests and enzyme assays that detect mutations in *TPP1* and measure the activity of the TPP1 enzyme are the gold standards for the laboratory diagnosis of CLN2 disease [1]. Clinical suspicion of the disease may initially be raised by a number of tests, including magnetic resonance imaging (MRI) of the brain.

MRI is increasingly used as a tool in the early diagnosis of various neurodegenerative disorders, including NCLs. There is limited literature on the subtle MRI features associated with early CLN2 disease; however, progressive cerebral and cerebellar atrophy and periventricular white matter changes have been described as suggestive of this disease [4]. A study of 14 patients with CLN2 disease by Specchio et al. identified cerebellar atrophy in 100% of patients (14/14), alteration of periventricular white matter signal in 79% of patients (11/14) and some degree of cerebral atrophy in 43% of patients (6/14) at the first neuroimaging evaluation. Cerebral atrophy was present in all patients with advanced stages of CLN2 disease [4]. Similarly, a case series of 13 patients with CLN2 disease by Johnson et al. reported cerebellar or cerebral atrophy in all patients with available MRI scans (10/10). Additional notable features included mild or moderate ventriculomegaly (10/10), thinning of the brainstem (9/10), decreased clarity of internal hippocampal architecture (7/10), thinning of the corpus callosum (5/10) and thalamic hypointensity (5/10) [5].

This case series aims to examine further early MRI features seen in patients with CLN2 disease that should raise suspicion of the disease and support an early diagnosis.

## 2. Methods

This is a case series of 12 children who were referred as part of their routine care from various Turkish centres to Kürşad Aydın, a

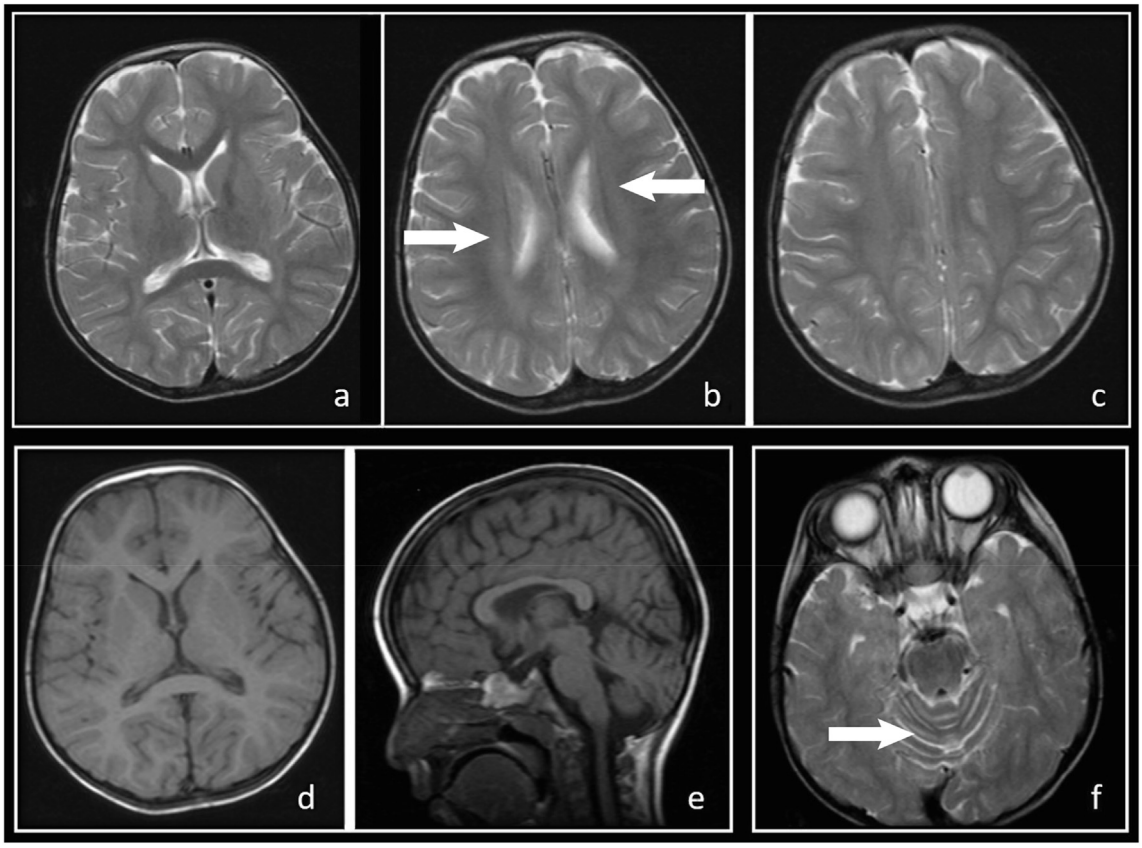


**Fig. 1D** Patient 2 – T2-weighted axial sections (a, b, c, f), T1-weighted axial section (d) and T1-weighted sagittal section (e) from an MRI scan taken after the first seizure. Linear hyperintensity of central white matter can be seen (b), and prominent cerebellar folia, indicating mild cerebellar atrophy, is clearly demonstrated (f).

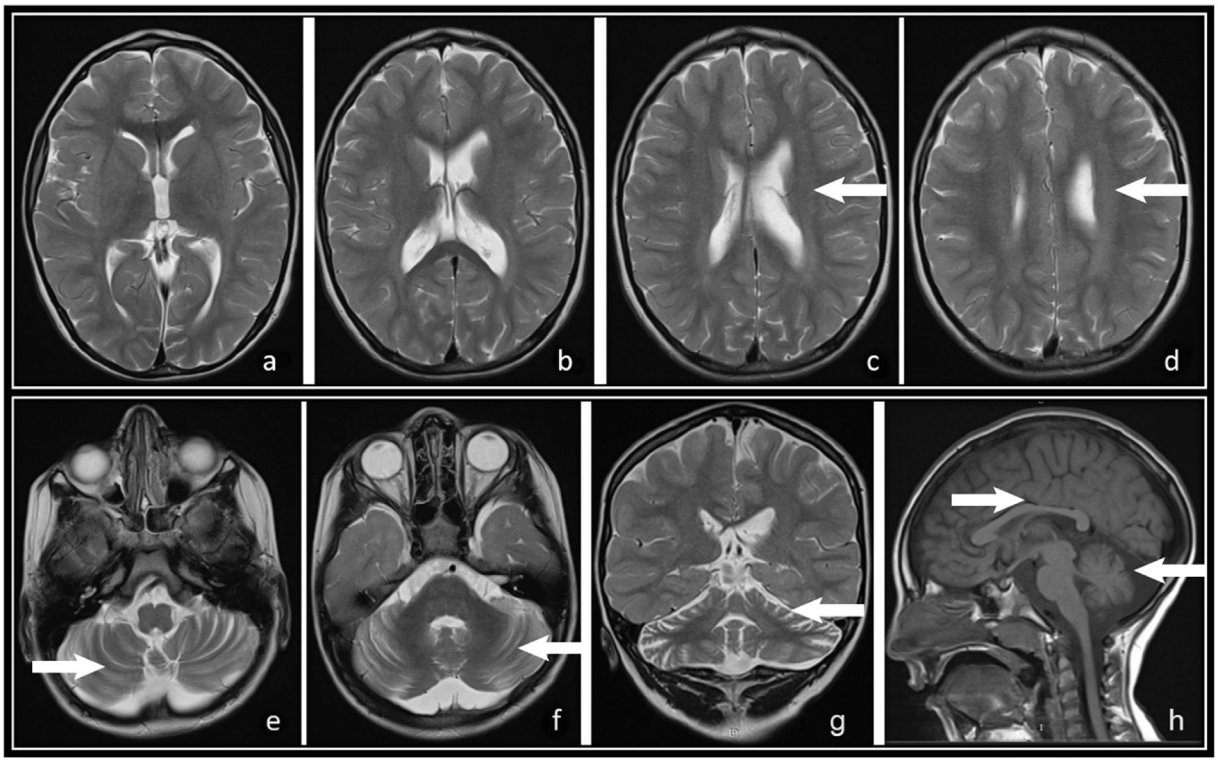


**Fig. 1E** Patient 3 – T2-weighted axial sections (a, b, c, d, e, f), T2-weighted coronal section (g) and T1-weighted sagittal section (h) from an MRI scan taken after the first seizure. Linear hyperintensity of central white matter is highlighted (c, d), alongside mild cerebellar atrophy (e, f, g, h) and thinning of the corpus callosum (h).

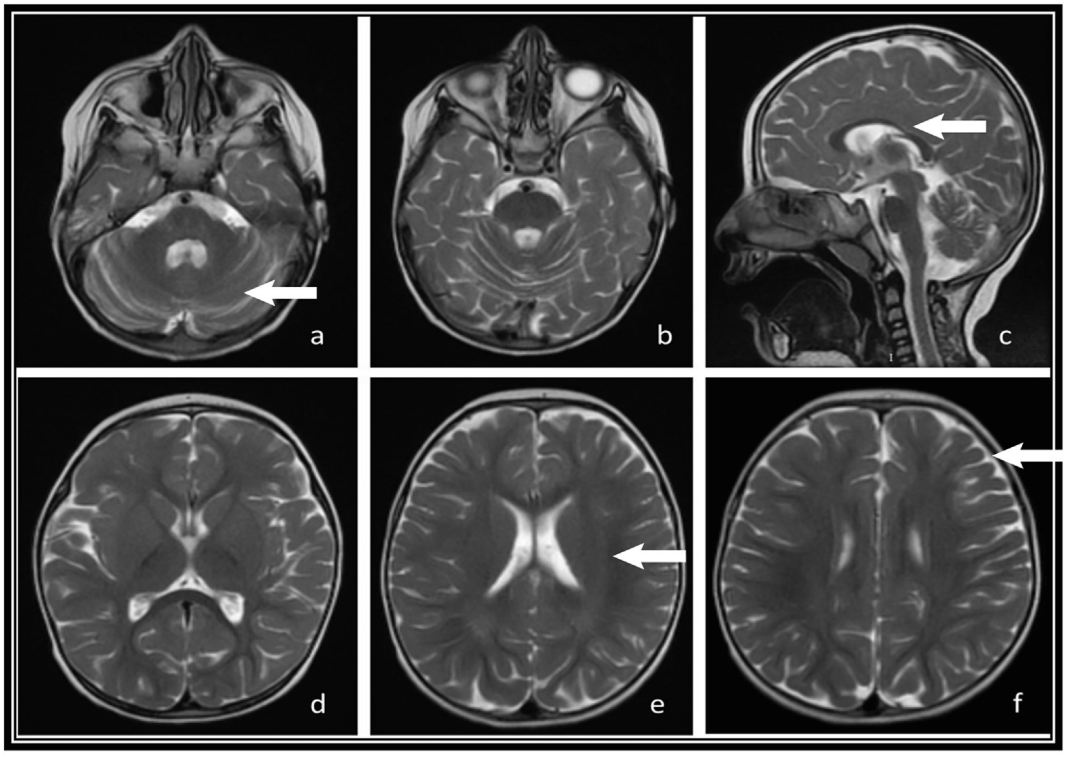


**Fig. 1F** Patient 4 – T2-weighted axial sections (a, b, d, e, f) and T2-weighted sagittal section (c) from an MRI scan taken during the asymptomatic stage from this patient with an affected sibling. These sections show mild cerebellar atrophy (a), thinning of the corpus callosum (c), linear hyperintensity of central white matter (e) and mild cerebral atrophy (f).

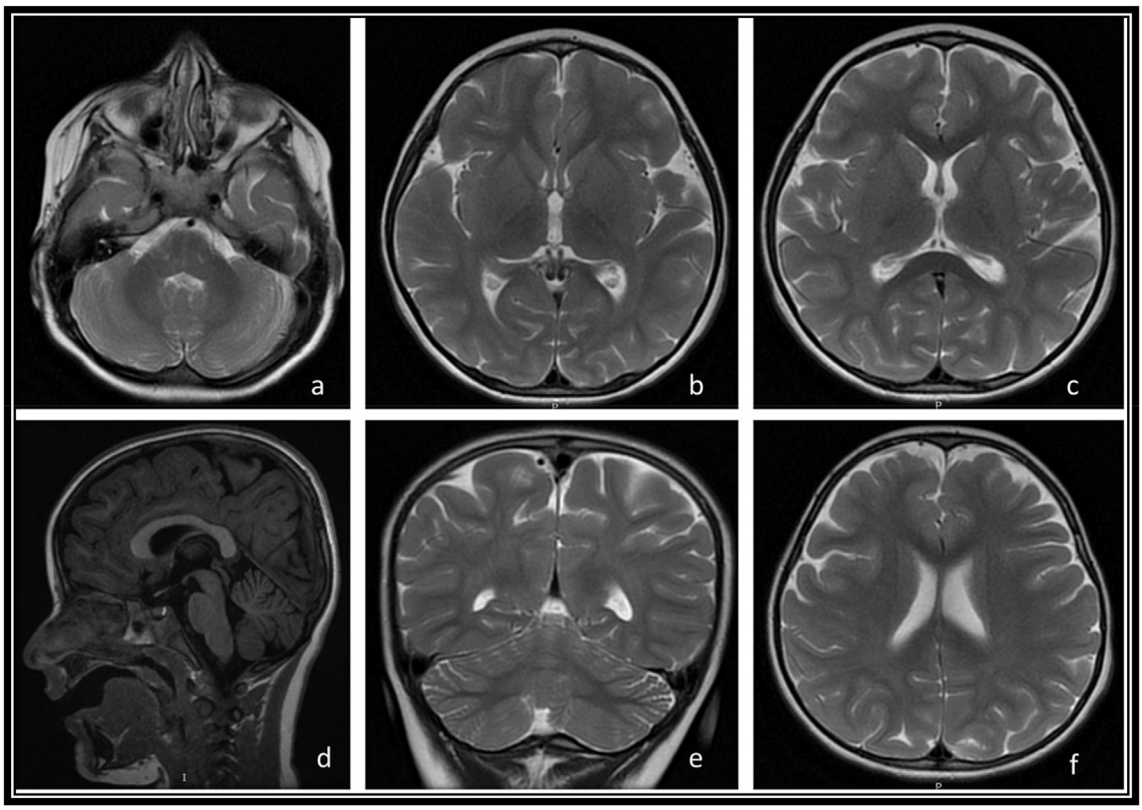


**Fig. 1G** Patient 5 – T2-weighted axial sections (a, b, c, f), T2-weighted coronal section (e) and T1-weighted sagittal section (d) from an MRI scan taken at the onset of symptoms. This MRI scan is normal (a, b, c, d, e, f).

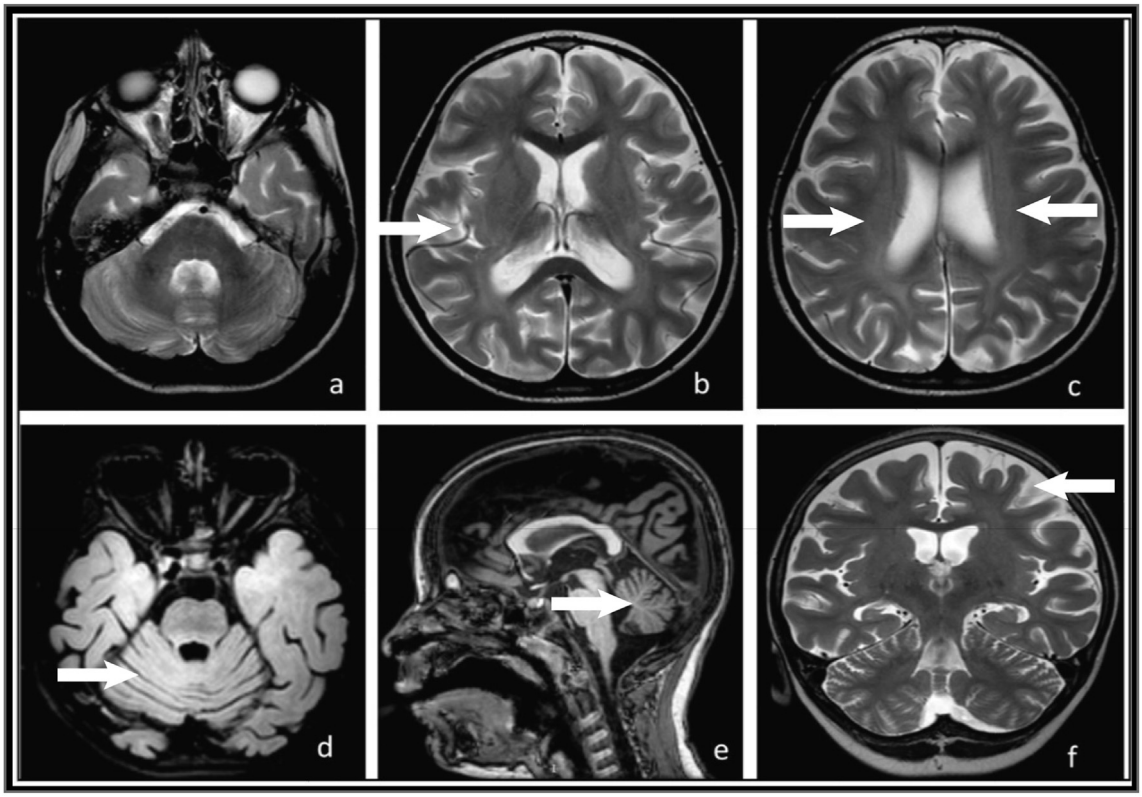


**Fig. 1H** Patient 5 – T2-weighted axial sections (a, b, c), axial FLAIR section (d), T1-weighted sagittal section (e) and T2-weighted coronal section (f) from an MRI scan taken 2 years after the onset of symptoms. This scan clearly shows mild to moderate cerebral (b, f) and cerebellar (d, e) atrophy and linear hyperintensity of central white matter (c), demonstrating rapid disease progression over 2 years.

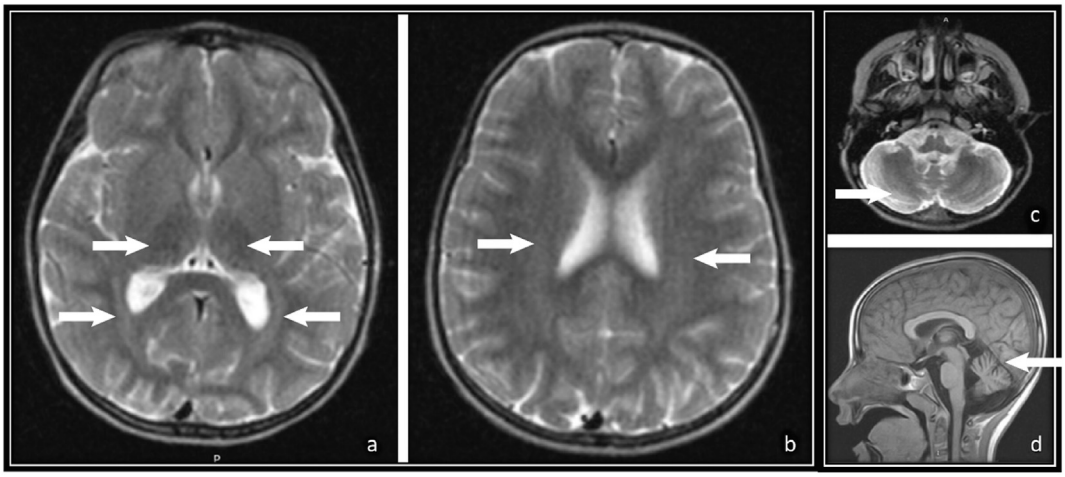


**Fig. 1I** Patient 6 – T2-weighted axial sections (a, b, c) and T1-weighted sagittal section (d) from an MRI scan taken 1 year after the onset of symptoms. Linear hyperintensity of central white matter is highlighted (a, b), and thalamic hypointensity can also be seen (a). Mild cerebellar atrophy is demonstrated (c, d).

senior child neurologist with expertise in neurometabolic disorders and neuroradiology. At time of referral, the children were at different stages in the progression of suspected CLN2 disease, ranging from the asymptomatic stage to 4 years after symptom onset. Patient details including gender, age at onset of symptoms, age at diagnosis, clinical presentation and causative mutation were collected. All patients had MRI scans taken at symptom onset or time of diagnosis, and at various times during disease progression, using 1.5T GE, Siemens or Philips machines. The protocols used included T1- and T2-weighted sequences, fluid-attenuated inversion recovery (FLAIR) imaging, diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping. Dr Aydın analysed the MRI scans and, after clinical, radiological, biochemical and genetic evaluation, diagnosed all patients with CLN2 disease.

## 3. Results

In total, 12 children with CLN2 disease aged between 2 and 7 years old were included from different centres across Turkey. The most common presenting symptoms were seizures, developmental delay and ataxia. The median age at symptom onset was 3 years and the median age at diagnosis was 5 years, resulting in a median diagnostic delay of 2 years. One patient underwent genetic testing because of an affected sibling and was diagnosed while asymptomatic. This patient was not included in our analysis of the median ages at symptom onset and diagnosis.

The median age at first MRI was 3 years and 9 months. A second MRI scan was conducted in 33% of patients (4/12), at a median age of 5 years. The median time between first and second MRI in this

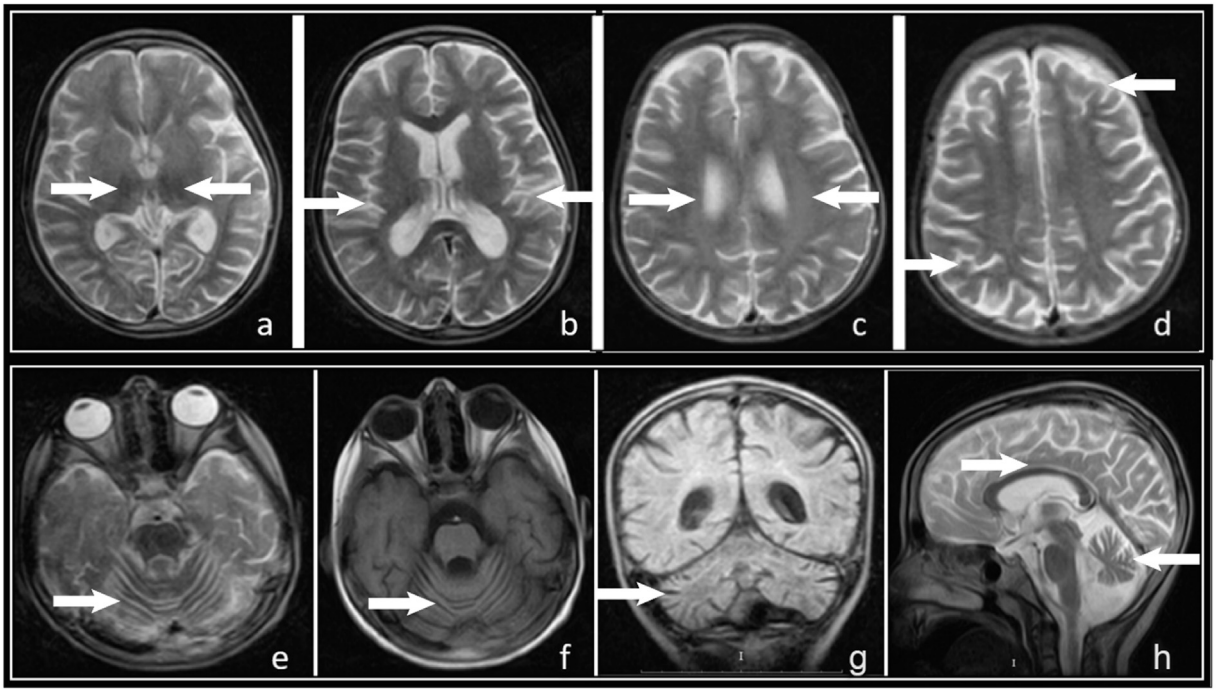


**Fig. 1J** Patient 6 – MRI scan taken 2 years after the onset of symptoms. Significant progression of linear hyperintensity of central white matter is highlighted (c). This figure also reveals significant progression of thalamic hypointensity (a), cerebellar atrophy (e, f, g, h) and cerebral atrophy (b, d) that was not seen on the MRI scan taken 1 year earlier.

**Table 1**
Patient characteristics.

| Patient details | | | | | | | MRI details | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | Fig. number | Sex | Age at onset (years) | Age at diagnosis (years) | Clinical presentation / reason for MRI | Genetic mutation | Age at first MRI (years) | First MRI report | Key retrospective findings | Age at second MRI (years) | Changes on MRI with disease progression |
| **1** | 1A, 1B, 1C | Female | 3.5 | 5.5 | Seizure and ataxia | c.230-2A>G Homozygous | 4.5 | Mild cerebral atrophy | • Mild to moderate cerebral and cerebellar atrophy<br>• Linear hyperintensity of central white matter<br>• Thinning of the corpus callosum | 5.5 | Significant progression of cerebral atrophy, cerebellar atrophy and linear hyperintensity after 1 year |
| **2** | 1D | Female | 3 | 3.5 | Seizure | – | 3 | Normal | • Linear hyperintensity of central white matter<br>• Mild cerebellar atrophy (prominent cerebellar folia) | – | – |
| **3** | 1E | Male | 3.5 | 3.5 | Seizure | – | 3.5 | Mild cerebellar atrophy | • Linear hyperintensity of central white matter<br>• Mild cerebellar atrophy<br>• Thinning of the corpus callosum | – | – |
| **4** | 1F | Female | – | 2 | Asymptomatic, with affected sibling – diagnosed by genetic analysis | c.622C>T Homozygous | 2 | Normal | • Linear hyperintensity of central white matter<br>• Mild cerebral and cerebellar atrophy<br>• Thinning of the corpus callosum | – | – |
| **5** | 1G, 1H | Female | 2.5 | 5.5 | Developmental delay, ataxia and seizure | c.225A>G Homozygous | 2.5 | Normal | • Normal initial MRI | 4.5 | Development of mild to moderate cerebral and cerebellar atrophy, and linear hyperintensity of central white matter after 2 years |
| **6** | 1I, 1J | Male | 3 | 6 | Seizure and ataxia | – | 4 | Normal | • Thalamic hypointensity<br>• Linear hyperintensity of central white matter<br>• Mild cerebellar atrophy | 5 | Significant progression after 1 year and development of cerebral atrophy |
| **7** | – | Male | 3 | 7 | Seizure and ataxia | – | 5 | Mild cerebral atrophy | • Moderate cerebral and cerebellar atrophy | – | – |
| **8** | – | Male | 3 | 5 | Seizure and ataxia | c.622C>T Homozygous | 5 | Mild cerebral atrophy | • Linear hyperintensity of central white matter<br>• Mild to moderate cerebral and cerebellar atrophy | – | – |
| **9** | – | Female | 4 | 4.5 | Ataxia and developmental delay | – | 4.5 | Normal | • Linear hyperintensity of central white matter<br>• Mild cerebellar atrophy<br>• Thinning of the corpus callosum | – | – |
| **10** | – | Female | 3 | 5 | Seizure and ataxia | – | 3 | Moderate cerebral and cerebellar atrophy | • Linear hyperintensity of central white matter<br>• Moderate cerebral and cerebellar atrophy | 5 | Significant progression after 2 years |

**Table 1** (*continued*)

| Patient details | | | | | | | MRI details | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient number | Fig. number | Sex | Age at onset (years) | Age at diagnosis (years) | Clinical presentation / reason for MRI | Genetic mutation | Age at first MRI (years) | First MRI report | Key retrospective findings | Age at second MRI (years) | Changes on MRI with disease progression |
| **11** | – | Female | 3 | 3.5 | Seizure and ataxia | – | 3 | Normal | • Thinning of the corpus callosum<br>• Linear hyperintensity of central white matter<br>• Mild to moderate cerebral and cerebellar atrophy<br>• Thinning of the corpus callosum | – | – |
| **12** | – | Female | 4 | 4.5 | Seizure and language delay | – | 4.5 | Mild cerebral atrophy | • Linear hyperintensity of central white matter<br>• Mild to moderate cerebral and cerebellar atrophy<br>• Thinning of the corpus callosum | – | – |

Abbreviation: MRI, magnetic resonance imaging.

cohort was 1.5 years.

Six patients had MRIs that were reported as normal by neuroradiologists at the referring centres at initial presentation, and the remaining 6 patients were found to have non-specific, mild cerebral atrophy. However, on analysis by Dr Aydın, 11 of these initial MRIs were found to demonstrate key features suggestive of CLN2 disease. Although the first MRI for the remaining patient was deemed to be normal, key features of CLN2 disease were present on the MRI conducted 2 years later.

Key MRI features included cerebral atrophy, cerebellar atrophy, thinning of the corpus callosum and linear hyperintensity of central white matter. In this cohort, 92% of patients (11/12) had cerebellar atrophy, 83% (10/12) had linear hyperintensity of central white matter, 67% (8/12) had cerebral atrophy, 50% (6/12) had thinning of the corpus callosum and 8% (1/12) had thalamic hypointensity on their first MRI.

Specific MRI sequences were used to identify each of these subtle features. T1-weighted sagittal and T2-weighted coronal sections were used to detect cerebellar atrophy (Fig. 1C). T2-weighted axial sections were used to identify linear hyperintensity of central white matter (Fig. 1A, Fig. 1D, Fig. 1E and Fig. 1F), thalamic hypointensity (Fig. 1I and Fig. 1J) and cerebral atrophy (Fig. 1A and Fig. 1B). The latter was also demonstrated in T2-weighted coronal sections (Fig. 1C). T1- or T2-weighted sagittal sections were used to highlight thinning of the corpus callosum (Fig. 1C and Fig. 1F).

Characteristics of cases that demonstrate each of these MRI signs are presented in Table 1.

## 4. Discussion

The 12 patients included in this case series were referred to Dr Aydın from different centres across Turkey and diagnosed with CLN2 disease. MRI scans were obtained from these children at symptom onset or time of diagnosis, and at various times during disease progression. Reanalysis of MRIs revealed subtle but common features that went unrecognised in the majority of cases at the time of first analysis, including cerebellar atrophy in 92% of patients, linear hyperintensity of central white matter in 83% of patients, cerebral atrophy in 67% of patients and thinning of the corpus callosum in 50% of patients. One case exhibited thalamic hypointensity on MRI; although this sign is suggestive of CLN1 disease, it may also be seen in patients with early CLN2 disease.

Our results support the study conducted by Specchio et al. on 14 patients with CLN2 disease, which found cerebellar atrophy to be the most common MRI feature at the first evaluation (100%), followed by alteration of periventricular white matter signal (79%) and cerebral atrophy (43%) [4]. Furthermore, our findings support a case series of 13 patients with CLN2 disease by Johnson et al. that reported cerebellar or cerebral atrophy in 100% of patients, thinning of the corpus callosum in 50% of patients and thalamic hypointensity in 50% of patients. The prevalence of thalamic hypointensity was substantially higher in this group compared with our cohort [5].

In the majority of patients in our cohort, key features that we believe to be suggestive of CLN2 disease were missed in the initial MRI reports and were detected retrospectively, upon analysis by Dr Aydın. This highlights the need for increased awareness among neuroradiologists of CLN2 disease, its associated MRI features and the most suitable MRI protocols to detect each sign.

The following sequences should be used for the clearest identification of each feature: T1-weighted sagittal and T2-weighted coronal sections for cerebellar atrophy, T2-weighted axial sections for linear hyperintensity of central white matter, T2-weighted axial or coronal sections for cerebral atrophy, T1- or T2-weighted sagittal sections for thinning of the corpus callosum, and T2-weighted axial sections for thalamic hypointensity.

Although these features are suggestive of CLN2 disease, they are not specific and may be associated with other NCL variants. A study by Dozières-Puyravel et al. on 20 patients with various NCLs identified cerebellar and cerebral atrophy at first MRI in patients with CLN1, CLN2 and CLN6 disease [6]. This study also found cerebellar atrophy at first MRI in patients with CLN7 and CLN11 disease [6]. Nevertheless, when considered alongside clinical

findings, the MRI features we have identified may provide an important clue in the early diagnosis of CLN2 disease.

We believe that paediatric neurologists have a vital role to play in communicating any clinical suspicion of CLN2 disease with neuroradiologists, in order to facilitate the detection of subtle suggestive MRI signs during early disease stages. Clinical suspicion of CLN2 disease accompanied by the detection of any of these MRI features should encourage healthcare professionals (including neuroradiologists, paediatric neurologists and paediatric metabolic specialists) to test for CLN2 disease. It is hoped that early diagnosis will allow timely initiation of disease-specific treatment with cerliponase alfa, which may improve patient outcomes.

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