American Journal of Medical Genetics Part A

WILEY

AMERICAN JOURNAL OF medical genetics PART A

CASE REPORT

The Attenuated Phenotype of *CNTNAP1*-Related Neuropathy Mimics Spastic–Dystonic Cerebral Palsy

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Received: 20 November 2024 | **Revised:** 19 May 2025 | **Accepted:** 9 June 2025

Funding: This work was supported by German Federal Ministry of Education and Research, 01GM2302; Else Kröner-Fresenius-Stiftung, 2022_EKSE.185; Technical University of Munich-Institute for Advanced Study; M.Z. receives research support from the German Research Foundation (DFG 458949627, ZE 1213/2–1).

Keywords: cerebral palsy | *CNTNAP1* | dystonia | hypomyelination | neuropathy | spasticity

ABSTRACT

CNTNAP1 encodes a contactin-associated protein 1, which is essential for formation and organization of myelinated nerve fibers. Biallelic pathogenic variants in *CNTNAP1* cause a severe congenital hypomyelinating neuropathy, characterized by hypotonia, arthrogryposis, respiratory failure, and early lethality. We describe two brothers, seven and 13 years old, with spastic tetraparesis and limb dystonia, in whom we identified compound heterozygous variants in *CNTNAP1*. Comprehensive neurophysiological evaluation revealed an unusual, asymmetric pattern of hypomyelination that spared lower limb nerves. Moreover, brain neuroimaging showed only mild terminal zone hypomyelination. This report extends the phenotypic spectrum of *CNTNAP1* encephalopathy to primarily upper motor neuron disease with the predominant spastic features. In addition, it provides further evidence for the association of *CNTNAP1* with dystonia. Importantly, *CNTNAP1* mutations should be suspected in individuals with unexplained hypotonia and pyramidal syndrome even in the absence of apparent hypomyelination on brain imaging and normal conduction velocities in routinely examined nerves.

1 | Introduction

Cerebral palsy (CP) is a group of disorders of movement and posture, caused by permanent, nonprogressive abnormality of the developing brain. The etiology of CP is complex with possible contribution of numerous antenatal, perinatal, and postnatal factors to abnormal central nervous system (CNS) development at an early stage (Sadowska et al. 2020). In addition, CP is an umbrella term for a variety of monogenic neurodevelopmental and metabolic conditions that present with early-onset movement symptoms, named as CP mimics (Pearson et al. 2019). Recognizing the primary etiology of CP is of greatest importance for the proper management, prognosis, identifying clinical and developmental comorbidities, as well as genetic counseling.

CNTNAP1 (MIM*602346) encodes a contactin-associated protein 1 (CASPR1), a member of a high molecular mass complex in the paranodal junction, essential for the formation and organization of myelinated axons and nerve signaling in myelinated fibers (Bhat et al. 2001; Laquérriere et al. 2014). Biallelic pathogenic variants in *CNTNAP1* result in a severe congenital hypomyelinating neuropathy (CHN), associated with arthrogryposis, respiratory distress, profound neurological impairment, and early death (Laquérriere et al. 2014). Here we describe

two brothers, seven and 13 years old, with a phenotype of spastic–dystonic CP, in whom we identified compound heterozygous frameshift and missense variants in *CNTNAP1*.

2 | Material and Methods

2.1 | Patient Case Description

Patient 1 (P1) is a 13-year-old boy, born after uncomplicated pregnancy and delivery with normal birth parameters. From birth, he presented hypotonia with poor suck and poor body mass gain, but he never required respiratory support or nasogastric feeding. With time, he gradually developed bilateral pyramidal syndrome and upper limb dystonia. Psychomotor development was delayed in all areas—he started to roll over at around 2–3 years of age, speak simple words at 3 years, and chew at 5 years. Currently, he can crawl and sit with support, and he communicates using simple words. His recent neurological examination was notable for microcephaly, horizontal nystagmus, axial hypotonia, spastic tetraparesis, exaggerated tendon reflexes in the upper and lower limbs, bilateral Babinski sign, knee and Achilles contractures, and upper limb dystonia.

Patient 2 (P2), a 7-year-old brother of P1, is presenting a similar phenotype of spastic–dystonic CP. In the neonatal period, he required nasogastric feeding for 1 month due to poor suck and swallowing problems. He started to roll over at around 2–3 years of age, and currently he can sit with support and move efficiently using a wheelchair, with upper limb muscle strength well preserved. The boy is communicating using simple words and two-three-word sentences. His neurological examination was notable for microcephaly, horizontal nystagmus, dysarthria, spastic tetraparesis with axial hypotonia, and upper limb dystonia (Video S1). Both brothers presented dysmorphic features, including bitemporal narrowing, synophrys, bushy eyebrows, downslanting palpebral fissures, flattened philtrum, high-arched palate, and micrognathia. In addition, in P2, mild gingival hypertrophy was noted. Neuropsychological evaluation in P1 and P2 showed moderate intellectual disability.

2.2 | Editorial Policies and Ethical Considerations

This study was approved by the Medical University of Gdansk Bioethics Committee (NKBBN/13/2023). Written informed consent for publishing genetic and clinical data, including MRI and videos, was obtained from the patient's legal guardian.

2.3 | Neurophysiological, Neuroimaging and Exome Sequencing Studies

In both cases, nerve conduction study identified a moderate bilateral hypomyelination of the median nerves. Sensory conduction velocities (CV) ranged from 31 to 49 m/s, whereas motor CV ranged from 22 to 46 m/s (Table S1). Amplitudes of motor and sensory potentials in median nerves were normal. Interestingly, we found normal conduction parameters in motor fibers of peroneal nerves and sensory fibers of sural nerves in P1 and P2. Visual evoked potentials (VEPs) in both cases showed P100 potentials with prolonged latency and abnormal morphology (Figure S1A). Electromyography (EMG) of deltoid muscles in P1 and P2 demonstrated chronic myopathic degeneration, with small amplitude and short duration MUAPs (Figure S1B).

On brain magnetic resonance imaging (MRI) in P1 and P2, most of the white matter showed a normal myelination pattern. Delayed myelination was not observed, except for the "terminal zone" at the level of the peritrigonal area, mainly in the precentral region. The signal at the peritrigonal area was increased in T2WI and intermediate in T1WI in all tests performed, also after the third year of life. In P1, we observed no normally myelinated low-signal T2 white matter between the high-signal patches and the lateral ventricle, whereas in P2 a very thin layer of normally myelinated white matter was present in this area. In both patients, morphological analysis showed hypoplasia of the posterior part of corpus callosum and enlarged cisterna magna. However, there was no brain atrophy or ventricular dilatation (Figure 1B).

Exome sequencing (ES) was performed on DNA from the index patient (P1) as previously described (Frasuńska et al. 2024). In silico pathogenicity prediction of variants was performed using an in-house developed platform GeneBe together with Varsome data (Kopanos et al. 2019; Stawiński and Płoski 2024). The variants considered as disease-causing have been validated by amplicon deep sequencing (ADS). Two heterozygous *in trans* variants within *CNTNAP1* were identified in P1 and P2: (Hg38)chr17:42685232-AT>A, NM_003632.3:c.530delT and (Hg38)chr17:42688926-T>C, NM_003632.3:c.1507T>C (Figure 1A). The c.530del(p.Phe177SerfsTer47) variant causes a frameshift change. The variant was absent in the GnomAD project and in the ClinVar database v. 05-Aug-2024. The variant most likely results in nonsense-mediated mRNA decay. According to ACMG criteria, the variant is classified as pathogenic (PVS1, PM2, PP1) (Stawiński and Płoski 2024; Richards et al. 2015). The c.1507T>C(p.Phe503Leu) variant causes a missense change involving the alteration of a conserved nucleotide. The variant allele has a frequency of 0.0000112 in 1,613,998 control chromosomes in the GnomAD database, with no homozygous occurrence. In silico tools predict a pathogenic outcome for this variant. The variant has been reported in ClinVar v. 05-Aug-2024 as uncertain significance (one submission, Accession: VCV001929512.3). According to ACMG criteria, the variant is classified as likely pathogenic (PM2, PM3, PP1, PP2 and PP3) (Stawiński and Płoski 2024; Richards et al. 2015). Furthermore, recently ES for the family quartet (P1, P2, and both parents) was independently performed at another institute as previously described, yielding a similar conclusion (Zech et al. 2025). Detailed methods are described in Supporting Information.

3 | Discussion

The association of *CNTNAP1* with human disease was first described in 2014 by Laquérriere *et* al., who identified homozygous frameshift *CNTNAP1* variants in families with non-syndromic arthrogryposis multiplex congenita (Laquérriere et al. 2014). Affected individuals exhibited severe prenatal motor impairment, leading to polyhydramnios, arthrogryposis, hypotonia, respiratory failure, and early death. Deep tendon reflexes

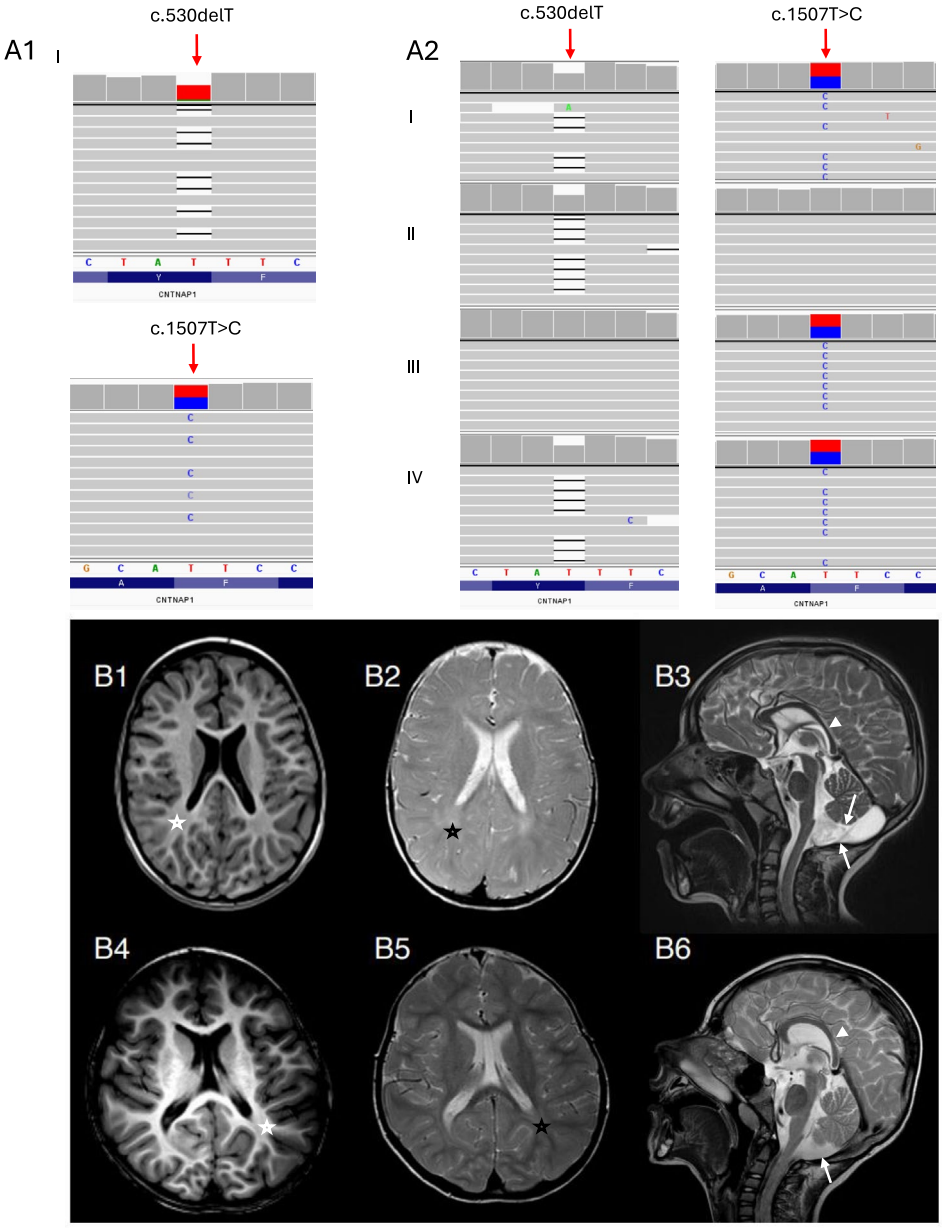

FIGURE 1 | (Part A) Results of molecular genetic testing. (A1) results of exome sequencing; (A2) results of amplicon deep sequencing in the index case (P1), his parents and brother (P2) (I –P1, II-mother, III- father, IV –P2). Arrows indicate the c.530delT and c.1507T>C positions in *CNTNAP1*. (Part B) Patient P1 presenting decreased signal on T1-weighted images in "terminal zone" at the level of the peritrigonal area (B1) and increased signal on T2-weighted images (B2). In the sagittal plane, enlarged cisterna magna and hypoplastic posterior part of the body of the corpus callosum are present (B3). Patient P2 presenting mildly decreased signal on T1-weighted images in "terminal zone" at the level of the peritrigonal area (B4) and increased signal on T2-weighted images (B5). In the sagittal plane, moderately enlarged cisterna magna and hypoplastic posterior part of the corpus callosum are present (B6).

were absent and motor nerve conduction velocity markedly reduced (< 10 m/s). Subsequent reports confirmed that biallelic *CNTNAP1* variants cause severe CHN, but not universally leading to lethality (Low et al. 2018; Sabbagh et al. 2020; Lesmana et al. 2019; Garel et al. 2022). Lesmana *et* al. reviewed 17 affected individuals, and all had severe hypotonia and respiratory distress, but 32% survived beyond infancy with aggressive medical intervention (Lesmana et al. 2019). Moreover, Garel *et* al. described six patients who survived over the neonatal period and suggested that missense variants may be associated with milder phenotypes (Garel et al. 2022). Low *et* al. speculated that hypomorphic missense variants may modify the deleterious effect on development of paranodal junctions and partially ameliorate the phenotype (Low et al. 2018).

In our cases, we identified hypomyelination of peripheral nerve motor and sensory fibers. However, the asymmetric pattern of hypomyelination that spares lower extremity nerves is atypical for *CNTNAP1*-related CHN. Furthermore, the severity of hypomyelination, resulting in CV reduction, is significantly milder in comparison to previously reported cases, ranging from 22 to 49 m/s versus 10 to 18 m/s (Mehta et al. 2017). Interestingly, CV wasn't homogeneously slowed, as in most hereditary neuropathies, demonstrating unequal involvement of nerve fibers.

EMG studies in P1 and P2 showed myopathic reconstitution of proximal muscles. Neuropathy and myopathic degeneration lead to generalized hypotonia with diminished tendon reflexes and muscle weakness, resulting in severe disability and respiratory distress as core features of CHN (Low et al. 2018; Sabbagh et al. 2020; Lesmana et al. 2019; Garel et al. 2022). In our patients, the features of limb spasticity and hyperreflexia suggest the predominant upper motor neuron involvement. This finding aligns with Garel et al.'s description of four individuals with missense variants who exhibited axial hypotonia and four-limb spasticity (Garel et al. 2022). Importantly, similarly to our cases, the two oldest patients (14- and 11-years old) had no abnormalities of white matter on MRI and no signs of axonal or demyelinating neuropathy. This suggests that hypomorphic missense *CNTNAP1* alleles are associated with an attenuated phenotype, characterized by lack of visible central white matter alterations on MRI and even normal CVs, especially in the lower limbs. The absence of deterioration of neurological symptoms and the slow, gradual progress of psychomotor development over the years indicate that, unlike hypomyelinating leukodystrophies, *CNTNAP1* encephalopathy results from congenital, nonprogressive damage to the nervous system, which may mimic cerebral palsy.

Lastly, our report confirms the presence of dystonia as a rare feature of *CNTNAP1*-related disease. Dystonia has been so far reported in only four patients, aged from 4 to 15 years, all carrying missense *CNTNAP1* variant in at least one allele (Low et al. 2018; Garel et al. 2022). Although the pathophysiology of this feature remains unknown, we hypothesize that similarly to *POLR3*-related hypomyelinating leukodystrophies, dystonia may result from diffuse hypomyelination of the basal ganglia and the cerebellothalamic pathways. Interestingly, the distribution and severity of dystonia in our patients is also consistent with symptoms observed in hypomyelinating leukodystrophies, in which most individuals showed mild to moderate bilateral and symmetric limb involvement (Al Yazidi et al. 2019). Further studies are needed to assess the prevalence and further characterize the dystonic phenotype of *CNTNAP1* encephalopathy.

In conclusion, our report expands the spectrum of phenotypes associated with biallelic *CNTNAP1* variants to primarily upper motor neuron disease with stable spastic tetraparesis and limb dystonia. Importantly, *CNTNAP1*-associated neuropathy should be suspected in individuals with unexplained hypotonia and pyramidal syndrome even in the absence of visible hypomyelination on brain MRI and normal CV on NCS studies. A comprehensive neurophysiological examination may be crucial for diagnosis.

Author Contributions

Magdalena Krygier, **Magdalena Chylińska:** conceptualization, formal analysis, investigation, and writing – original draft. **Michael Zech**, **Rafał Płoski:** writing – review and editing, supervision, investigation, funding acquisition, formal analysis. **Maria Mazurkiewicz-Bełdzińska:** writing – review and editing, supervision, formal analysis. **Dominik Świętoń**, **Marta Zawadzka**, **Agnieszka Pollak**, **Grażyna Kostrzewa:** data curation, methodology, investigation. All authors gave final approval and agreed to be accountable for all aspects of the work.

Acknowledgments

This work was supported by the EJP RD (EJP RD Joint Transnational Call 2022) and the German Federal Ministry of Education and Research (BMBF, Bonn, Germany) awarded to the project PreDYT (PREdictive biomarkers in DYsTonia, 01GM2302). This research was also supported by a "Schlüsselprojekt" grant from the Else Kröner-Fresenius-Stiftung (2022_EKSE.185). In addition, this study has received funding from the BMBF and the Free State of Bavaria under the Excellence Strategy of the Federal Government and the Länder, as well as by the Technical University of Munich–Institute for Advanced Study (to M.Z.). M.Z. receives research support from the German Research Foundation (DFG 458949627; ZE 1213/2–1).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.