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ENTPD1-Related Neurodevelopmental Disorder

Synonyms: Autosomal Recessive Spastic Paraplegia 64, HSP-*ENTPD1*, Spastic Paraplegia 64 (SPG64)

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Summary

Clinical characteristics

ENTPD1-related neurodevelopmental disorder (*ENTPD1*-NDD) is characterized by developmental delay / intellectual disability (ranging from borderline/mild to moderate/severe) and onset of progressive spastic paraplegia with progressive gait impairment beginning before age five years. Difficulty with balance and frequent falling are common and can result in loss of independent ambulation and wheelchair dependence in the teenage to young adult years.

Other neuromuscular findings can include abnormal deep tendon reflexes, weakness, neuropathy, epilepsy, dysarthria, and dysphagia. Behavior abnormalities and neurocognitive regression are common. Life span does not appear to be shortened.

Diagnosis/testing

The diagnosis of *ENTPD1*-NDD is established in a proband with suggestive clinical findings and biallelic pathogenic variants in *ENTPD1* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for *ENTPD1*-NDD. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. Multidisciplinary care is recommended by specialists in neurology (including treatment of seizures); developmental pediatrics and education (to address developmental delay / intellectual disability and need for individual education plan); physical medicine and rehabilitation / physical therapy and occupational therapy (including stretching to help avoid contractures and falls, facilitating activities of daily living, and use of positioning and mobility devices); speech-language pathology (to address dysarthria and dysphagia); orthopedics (to address scoliosis); and psychologists,

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behavioral therapists, and/or psychiatrists (to address behavioral issues with behavioral interventions and/or medications and to address issues associated with neurocognitive decline).

Surveillance: Regular clinic visits with the treating specialists are recommended to monitor existing or progressing manifestations and the individual's response to supportive care.

Genetic counseling

ENTPD1-NDD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ENTPD1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *ENTPD1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

ENTPD1-related neurodevelopmental disorder (*ENTPD1*-NDD) **should be considered** in a proband with the following clinical and imaging findings and family history.

Clinical findings

- Developmental delay / intellectual disability
- Abnormal reflexes (hyperreflexia, hyporeflexia, and/or areflexia with gait impairment by age five years)
- Behavioral concerns (attention-deficit/hyperactivity disorder, aggression, autistic features)
- Neurocognitive regression not attributed to progressive spastic paraplegia

Brain MRI. Brain white matter abnormalities were reported in approximately 50% of those individuals for whom brain MRI was obtained [Calame et al 2022]. Nonspecific white matter abnormalities were seen throughout the brain. Abnormal white matter signal intensity ranges from subtle to moderate. A subset of affected individuals had abnormal T_2-signal hyperintensity in the posterior limbs of the internal capsule bilaterally and might be suggestive of a diagnosis of a purine metabolism disorder.

Other findings included thinning of the corpus callosum and cerebellar atrophy; it is unclear if the cerebellar atrophy is static or progressive (see Figure 1).

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *ENTPD1*-NDD **is established** in a proband with suggestive clinical findings and biallelic pathogenic (or likely pathogenic) variants in *ENTPD1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *ENTPD1* variants of uncertain significance (or of one known *ENTPD1* pathogenic variant and one *ENTPD1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the clinical phenotype

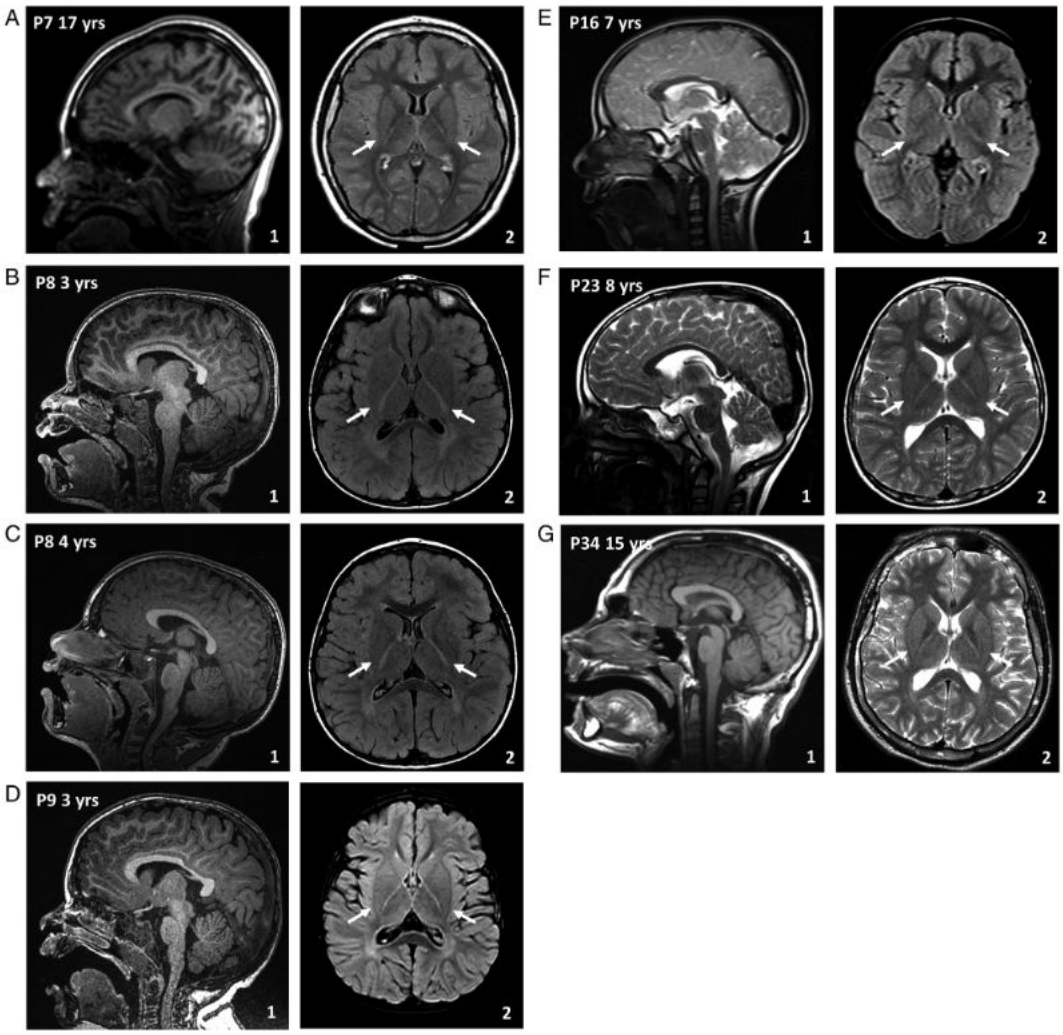

Figure 1. Individuals with biallelic pathogenic *ENTPD1* variants show white matter abnormalities, thinning of the corpus callosum, cerebellar atrophy, and signal abnormalities in the posterior limb of the internal capsule. Representative MRI of the brain of affected individuals from different families at different ages is shown. Arrows in the axial images highlight abnormal signal hyperintensity of the posterior limb of the internal capsule.

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A. Sagittal T_1-weighted imaging (1) and axial T_2-fluid-attenuated inversion recovery (FLAIR) (2) of P7 at age 17 years.

B, C. Sagittal T_1-weighted imaging (1) and axial T_2-FLAIR (2) of P8 at age 3 and 4 years, respectively.

D. Sagittal T_1-weighted imaging (1) and axial T_2-FLAIR (2) of P9 at age 3 years.

E. Sagittal T_2-weighted imaging (1) and axial T_2-FLAIR (2) of P16 at age 7 years.

F. Sagittal (1) and axial (2) T_2-weighted imaging of P23 at age 8 years.

G. Sagittal T_1-weighted imaging (1) and axial T_2-weighted imaging of P34 at age 15 years.

of affected individuals. Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

A hereditary spastic paraplegia, leukodystrophy and leukoencephalopathy, cerebral palsy spectrum disorder, or **developmental delay / intellectual disability multigene panel** that includes *ENTPD1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while

limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *ENTPD1*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ENTPD1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None identified to date [6, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Travaglini et al [2018], Mamelona et al [2019], Pashaei et al [2021], Calame et al [2022]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020].
7. Although no intragenic deletions or duplications have been identified to date, given that loss of function is a mechanism of disease causation, identification of an intragenic deletion or duplication may warrant further investigation and clinical correlation.

Clinical Characteristics

Clinical Description

To date, 40 individuals from 22 families have been identified with biallelic *ENTPD1* pathogenic variants [Novarino et al 2014, Travaglini et al 2018, Mamelona et al 2019, Pashaei et al 2021, Calame et al 2022, Ölmez et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

All individuals reported to date had onset younger than age five years. All individuals had developmental delay and intellectual disability, and progressive spastic paraplegia with gait impairment as well as abnormal deep tendon reflexes (hypereflexia, hyporeflexia, and/or areflexia). Additional neuromuscular findings can include weakness, neuropathy, and epilepsy. Other common findings are dysarthria, behavior abnormalities, and neurocognitive regression. Less commonly observed clinical findings include scoliosis and cataracts. At the time

of this writing, *ENTPD1*-related neurodevelopmental disorder (*ENTPD1*-NDD) does not seem to affect life spa,n as affected individuals are known to have reached adulthood.

Table 2. *ENTPD1*-Related Neurodevelopmental Disorder: Frequency of Select Features

Feature		Proportion of Persons w/Feature [1]
Developmental delay / intellectual disability		38/38
Neuromuscular	Progressive spastic paraparesis	40/40
	Abnormal deep tendon reflexes	28/36
	Muscle weakness	27/36
	Peripheral neuropathy	18/36
	Epilepsy	7/36
Dysarthria and dysphagia		27/36
Behavior abnormalities		22/36
Neurocognitive regression		21/36

1. Because limited clinical details are available for some reported individuals included in this table, the denominator represents the total number of individuals in whom the corresponding finding was reported.

Onset. All affected individuals to date had onset before age five years. A common first manifestation is delayed walking or other motor and speech delays. First steps typically occur later than the average (i.e., age one year).

Intellectual disability ranges from borderline/mild to moderate/severe with impaired ability to engage independently in activities of daily living, which is not solely related to progressive spastic paraplegia.

Speech and language development are variable. Some individuals never achieve independent expressive language, whereas others communicate expressively with dysarthric speech.

Ability to engage in activities of daily living varies and depends on the level of intellectual disability, with some individuals requiring around-the-clock care.

Progressive spastic paraparesis manifests as weakness and spasticity of the lower extremities. Although individuals with this disorder learn to walk, albeit oftentimes delayed, progressive spastic paraplegia during childhood leads to progressive gait impairment, described as spastic, unsteady, toe walking, and ataxic. Issues with balance and frequent falling are common, potentially resulting in loss of independent ambulation and wheelchair dependence. Wheelchair dependence typically occurs in the teenage to young adult years.

Abnormal deep tendon reflexes include hyperreflexia, hyporeflexia, and areflexia. In the individuals reported to date, areflexia/hyporeflexia is more common than hyperreflexia. Although it is unclear why some individuals develop hyperreflexia and others develop hyporeflexia or areflexia, it could be a combination of uniform upper motor neuron disease with variable lower motor neuron disease (likely resulting from excitotoxicity due to impaired ATP metabolism). Even within the same individual, abnormal reflexes can vary between upper and lower extremities. Additionally, it is unclear if reflexes become progressively more hyperreflexic or hyporeflexic.

Muscle weakness varies. While the proximal lower extremities are most commonly involved, the upper extremities can also be involved. Amyotrophy was noted in some individuals.

Peripheral neuropathy, which can affect upper and lower limbs, manifests as hyporeflexia or areflexia, impaired sensation, and neuropathic pain. Neuropathic findings, including abnormal reflexes, tend to occur in advance of progressive spasticity.

Electromyography / nerve conduction studies revealed findings consistent with motor axonal neuropathy.

Epilepsy. Epilepsy, occurring in some affected individuals, typically starts in early childhood. Seizures are convulsive and respond well to standard anti-seizure medication such as valproic acid. EEG reveals generalized epileptiform activity.

Dysarthria ranges from nasal speech with mild dysarthria to anarthria (i.e., total inability to articulate speech). Individuals with dysarthria often also have dysphagia.

Dysphagia. Difficulty swallowing liquids and solid food with resultant coughing, choking, and aspiration can occur and tends to progress. Rarely, dysphagia requires gastrostomy tube placement.

Behavior abnormalities include attention-deficit/hyperactivity disorder, aggression, anger, impulsivity, and autism spectrum disorder. Behavior abnormalities range from mild/moderate to severe and can affect early childhood school performance if left untreated. Additionally, aggression, anger, impulsivity, and autistic behaviors affect interpersonal relationships and can be disabling.

Neurocognitive regression can manifest as progressively impaired ability to engage independently in activities of daily living, worsening academic performance, and speech and language impairment. Regression was observed in childhood with progressive difficulties with school performance, followed by slow progression into early adulthood. Longitudinal data are currently insufficient to determine if neurocognitive regression continues throughout the life span of affected individuals.

Other findings

- **Hand and foot deformities** most commonly included camptodactyly of the hands and feet and spatulated digits. These deformities can affect day-to-day functioning, including fine and gross motor function.

  Pes cavus can be evident early in the disease course and has been reported in young children.

- **Scoliosis.** At this time it is unclear if scoliosis, present in five of 36 individuals, is progressive. Because scoliosis may be a late finding in neuromuscular disorders and because the individuals with *ENTPD1*-NDD reported to date are mostly children or adolescents, its frequency may be underestimated. There were no known vertebral anomalies. No individuals are known to have undergone surgical intervention.

- **Cataracts**. While seen in approximately 10% of affected individuals, no information is available on cataract type or whether surgical intervention was necessary for any of these individuals.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

Pure and complex hereditary spastic paraplegia. Hereditary spastic paraplegia (HSP) has traditionally been classified into "pure" and "complex," each of which constitutes a large group of disorders with diverse molecular etiologies.

- Pure HSP is characterized by progressive spastic paraplegia with gait impairment, corticospinal tract axonopathy, and axonal length-dependent neuropathy [Harding 1993, Blackstone 2018].
- Complex HSP, the HSP category that encompasses *ENTPD1*-NDD, shares the features of pure HSP in addition to developmental delay / intellectual disability, behavior abnormalities, structural brain abnormalities, ataxia, and epilepsy, among others [Fink 2013, Elsayed et al 2021].

ENTPD1-NDD and other complex HSPs have significant overlap with a vast range of neurodevelopmental disorders, and it is increasingly difficult to assign predominant phenotypic designations. As individuals with *ENTPD1*-NDD may be diagnosed by general pediatricians, developmental and behavioral pediatricians, child neurologists, physiatrists, and/or neuromuscular specialists, it is reasonable to continue using movement disorder designations (SPG64 and HSP-*ENTPD1* [Lange et al 2022]) as well as *ENTPD1*-NDD to maximize clinical recognition of the condition.

Prevalence

ENTPD1-NDD is rare. Its prevalence is unknown. To date, 40 affected individuals have been reported (see Clinical Description).

Affected individuals have been reported throughout the world. However, it appears that this disorder is more common in populations with elevated rates of consanguinity.

Additionally, the following recurrent *ENTPD1* variants have been identified (see Table 7):

- The variants c.574-6_574-3delTTTC and c.770_771delGG (p.Gly257GlufsTer18) were found in the homozygous state in unrelated consanguineous families from countries with substantial Portuguese ancestry (Brazil and Portugal), which suggests that these variants represent founder variants from the Iberian Peninsula [Calame et al 2022].
- The variants c.1041delG (p.Ile348PhefsTer19) and c.1109T>A (p.Leu370Ter), identified in several Iranian families, may represent founder variants in this population [Calame et al 2022].

Genetically Related (Allelic) Disorders

As of the writing of this chapter, no phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ENTPD1*.

Sporadic tumors occurring as single tumors in the absence of any other findings of *ENTPD1*-NDD can contain a somatic pathogenic variant in *ENTPD1* that is **not** present in the germline. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

Table 3. Selected Genes of Interest in the Differential Diagnosis of *ENTPD1*-Related Neurodevelopmental Disorder

Gene	Disorder(s)	MOI	Clinical Findings	Features of Disorder(s) Overlapping w/*ENTPD1*-NDD
ALDH18A1	SPG9A [1] & SPG9B [2]	AD AR	• Cataracts • Gastroesophageal reflux • Motor neuronopathy • Dysarthria • Ataxia • Cognitive impairment	• Cataracts • Motor neuropathy • Dysarthria • Ataxia • Cognitive impairment
ALDH3A2	Sjogren-Larrson syndrome (OMIM 270200)	AR	• Congenital ichthyosis • Macular dystrophy • Leukodystrophy • Seizures	• White matter abnormalities in brain • Seizures
AMPD2	SPG63 [2] & pontocerebellar hypoplasia type 9 (OMIM 615809)	AR	• Short stature • Thin corpus callosum • White matter changes • Seizures • Variable neurocognitive symptoms	• Brain abnormalities • Seizures • Variable neurocognitive findings

Table 3. continued from previous page.

Gene	Disorder(s)	MOI	Clinical Findings	Features of Disorder(s) Overlapping w/*ENTPD1*-NDD
AP5Z1	SPG48 [2]	AR	• Urinary incontinence • Parkinsonism • Dystonia • Thin corpus callosum • Leukodystrophy • Severe DD in infantile onset	• Brain abnormalities • DD
B4GALNT1	SPG26 [2]	AR	• Amyotrophy • Dysarthria • Ataxia • DD • Dystonia	• Dysarthria • Amyotrophy • DD
BICD2	Spinal muscular atrophy 2A (OMIM 615290)	AD	• Amyotrophy • Contractures • Weakness • Gait abnormalities	• Amyotrophy • Weakness • Gait abnormalities
CYP2U1	SPG56 [2]	AR	• Severe DD • Dystonia • Polyneuropathy • Calcification of basal ganglia	• DD/ID • Neuropathy • Brain abnormalities
CYP7B1	SPG5A [2]	AR	• Ataxia • Polyneuropathy • Extrapyramidal signs • MRI signs of leukodystrophy	• White matter abnormalities • Neuropathy
DDHD2	SPG54 [2]	AR	• Severe DD • Optic atrophy • Thin corpus callosum • Leukodystrophy	• DD/ID • Brain abnormalities
ITPA	Developmental & epileptic encephalopathy 35 (OMIM 616647)	AR	• Cataracts • Feeding difficulties • Encephalopathy • Seizures • Delayed myelination • Abnormal T_2-weighted signal intensity in posterior limb of internal capsule	• Cataracts • Seizures • White matter abnormalities • Abnormal signal intensity in posterior limb of internal capsule
KIF1A	SPG30 [2, 3]	AD AR	• Spastic ataxia • Polyneuropathy	• Spasticity • Gait abnormalities • Neuropathy
PGAP1	SPG67 (NDD w/ dysmorphic features, spasticity, & brain abnormalities) (OMIM 615802)	AR	• Severe DD • Tremor • Agenesis of corpus callosum • Hypomyelination	• DD/ID • Brain abnormalities
SPG21 (*ACP33*)	Mast syndrome (SPG21) [2]	AR	• Ataxia • Adult-onset dementia & parkinsonism • Polyneuropathy • Akinetic mutism seen in advanced cases	Neuropathy

Table 3. continued from previous page.

Gene	Disorder(s)	MOI	Clinical Findings	Features of Disorder(s) Overlapping w/*ENTPD1*-NDD
SPG7	SPG7 [2]	AR AD	• Dysarthria • Ataxia • Optic atrophy • Supranuclear palsy • Mitochondrial abnormalities on skeletal muscle biopsy	• Gait abnormalities • Dysarthria
SPG11	SPG11	AR	• Obesity [4] • Nystagmus • Dysarthria • Gait abnormalities • ID • Brain abnormalities	• Dysarthria • ID • Gait abnormalities • Brain abnormalities
TECPR2	*TECPR2*-related hereditary sensory & autonomic neuropathy w/ID	AR	• Central apnea • Severe DD • Microcephaly • Dysmorphic features • Abnormal reflexes	• DD/ID • Dysmorphic features • Abnormal reflexes
ZFYVE26	SPG15 [5]	AR	• DD • Optic atrophy • Ataxia • Central retinal degeneration • Polyneuropathy	• DD/ID • Abnormal gait • Neuropathy

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; NDD = neurodevelopmental; SPG = spastic paraplegia
1. Panza et al [2016]
2. See Hereditary Spastic Paraplegia Overview.
3. Citterio et al [2015]
4. Cardozo-Hernández et al [2020]
5. Saffari et al [2023]

Management

No clinical practice guidelines for *ENTPD1*-related neurodevelopmental disorder (*ENTPD1*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ENTPD1*-NDD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *ENTPD1*-Related Neurodevelopmental Disorder: Recommended Evaluations

System/Concern	Evaluation	Comment
Developmental delay / Intellectual disability	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education

Table 4. continued from previous page.

System/Concern		Evaluation	Comment
Neuromuscular	**Progressive spastic paraparesis**	Neurologic eval	• To incl baseline brain MRI (if not already performed) [1] • Consider EMG/NCS [2] • To incl assessment of strength, gait, deep tendon reflexes, spasticity
	Neuropathy		
	Epilepsy		Consider EEG if seizures are a concern.
Musculoskeletal / Activities of daily living		Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, scoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve or maintain gross motor skills) &/or OT (to improve or maintain fine motor skills)
Dysarthria		Speech & language assessment	
Behavioral findings		Health care professional / developmental pediatrician	Consider psychological &/or psychiatric evals if issues are severe.
Neurocognitive regression		Psychological assessment	
Cataracts		Ophthalmologic eval	To assess for reduced vision, best corrected visual acuity, refractive errors, strabismus, & cataracts, which may require referral for subspecialty care &/or low vision services
Genetic counseling		By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of *ENTPD1*-NDD to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADL = activities of daily living; MOI = mode of inheritance; NCS = nerve conduction studies
1. Brain MRI is essential for comparison in the event of neurocognitive regression.
2. EMG/NCS may help identify and/or determine the severity of neuropathy, especially in individuals with impaired cognition who cannot report their symptoms or follow directions during a complicated neurologic examination.
3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *ENTPD1*-NDD.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists (see Table 5).

Table 5. *ENTPD1*-Related Neurodevelopmental Disorder: Supportive Care

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Spastic paraparesis / Neuropathy	Physical medicine & rehab / PT & OT	• Incl stretching to help avoid contractures & falls • Consider need for positioning & mobility devices, disability parking placard.
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; suggest use of broad-spectrum ASM (e.g., valproic acid). • Education of parents/caregivers [1]
Dysarthria	Per treating speech-language pathologist	Consider alternative means of communication.
Dysphagia	Swallow study & speech therapy	Consider dietary modifications, alternative means of providing nutrition & hydration if necessary, w/ consideration of gastrostomy tube placement if necessary.
Behavioral findings	Treatment of behavioral findings incl combination of therapy & pharmacologic treatment	Mgmt by psychologists, behavioral therapists, &/or psychiatrists w/behavioral interventions &/or medications as needed
Neurocognitive regression	Psychological assessment	
Scoliosis	Orthopedics	Per treating orthopedist
Cataracts	Per treating ophthalmologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in Special Olympics and/or adaptive sports.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services may be available.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *ENTPD1*-Related Neurodevelopmental Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Developmental delay / Intellectual disability	Monitor developmental progress & educational needs.	At each visit
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for: • New manifestations such as seizures & neurocognitive regression; • Changes in existing issues w/tone & neurocognitive regression.	

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	Per treating clinicians
	Scoliosis	For those w/scoliosis: per treating orthopedist
		For those w/o scoliosis; evaluate yearly
Dysarthria	Per treating speech-language pathologist	Per treating speech-language pathologist
Dysphagia	Swallow study & speech eval	If clinical concerns for new findings
Neurobehavioral/ Psychiatric	Per treating mental health professional	Per treating mental health professional
Neurocognitive	Monitor developmental progress & educational needs.	At each visit
Ophthalmologic involvement	Per treating ophthalmologist	Per treating ophthalmologist
	Per treating low vision services	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

Agents/Circumstances to Avoid

While mild-to-moderate physical activity is highly recommended, affected individuals should avoid activity that significantly worsens their symptoms (e.g., worsening weakness, muscle cramps).

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

ENTPD1-related neurodevelopmental disorder (*ENTPD1*-NDD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *ENTPD1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ENTPD1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *ENTPD1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Intrafamilial variability has been reported in *ENTPD1*-NDD. Affected family members with the same biallelic pathogenic variants in *ENTPD1* have been reported to have variable ages at disease onset, rate of progression, and clinical features (gait abnormalities, speech impairment, and developmental delay / intellectual disability) [Calame et al 2022].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *ENTPD1*-NDD are obligate heterozygotes (carriers) for a pathogenic variant in *ENTPD1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ENTPD1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ENTPD1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.
- Carrier testing should be considered for the reproductive partners of individuals known to be carriers, particularly if consanguinity is likely and/or if both partners are of the same ethnic background (see Prevalence).

Prenatal Testing and Preimplantation Genetic Testing

Once the *ENTPD1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **HSP Research Foundation**
  Australia
  Email: inquiries@hspersunite.org.au
  www.hspersunite.org.au
- **MedlinePlus**
  Intellectual Disability
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Hereditary Spastic Paraplegia Information Page
- **Spastic Paraplegia Foundation, Inc.**
  Phone: 877-773-4483
  sp-foundation.org
- **Tom Wahlig-Foundation**
  Tom Wahlig Stiftung
  Germany
  www.hsp-info.de/en/foundation.htm

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. ENTPD1-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ENTPD1	10q24.1	Ectonucleoside triphosphate diphosphohydrolase 1	ENTPD1	ENTPD1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for ENTPD1-Related Neurodevelopmental Disorder (View All in OMIM)

601752	ECTONUCLEOSIDE TRIPHOSPHATE DIPHOSPHOHYDROLASE 1; ENTPD1
615683	SPASTIC PARAPLEGIA 64, AUTOSOMAL RECESSIVE; SPG64

Molecular Pathogenesis

ENTPD1 encodes ectonucleoside triphosphate diphosphohydralase 1 (ENTPD1), a hydralase protein involved in the hydrolysis of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to adenosine monophosphate (AMP). ENTPD1 is ubiquitously expressed and has important functions in energy metabolism in many tissues throughout the body [Jackson et al 2007, Nardi-Schreiber et al 2017]. Recent evidence suggests that impairment of energy metabolism in individuals with *ENTPD1*-related neurodevelopmental disorder (*ENTPD1*-NDD). Affected pathways include amino acid, lipid, carbohydrate, and heme metabolism [Calame et al 2022]. Although ATP is an important neuronal signaling molecule, excess ATP can cause neurotoxicity. Given the wide expression of ENTPD1 and evidence of extraneurologic involvement, the reason why *ENTPD1*-NDD predominantly causes neurologic symptoms is unknown.

Mechanism of disease causation. All genetic and functional evidence supports loss of function as the mechanism of action in *ENTPD1*-NDD [Calame et al 2022].

***ENTPD1*-specific laboratory technical considerations.** Assays that may help confirm variants of uncertain significance as pathogenic loss-of-function variants, performed largely on a research basis, include the following [Calame et al 2022]:

- Anti-CD39/ENTPD1 flow cytometry of peripheral blood mononuclear cells
- ATP or ADPase assays using lymphoblastoid cell lines
- Anti-CD39/ENTPD1 immunohistochemistry of sural nerve biopsy

Table 7. Notable *ENTPD1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001776.6	c.574-6_574-3delTTTC	--	Possible founder variants in persons of Portuguese ancestry (from Brazil & Portugal) [Calame et al 2022]
NM_001776.6 NP_001767.3	c.770_771delGG	p.Gly257GlufsTer18	
	c.1041delG	p.Ile348PhefsTer19	Possible founder variant in Iranian population [Calame et al 2022]
	c.1109T>A	p.Leu370Ter	

Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Lupski Laboratory

Daniel Calame, MD, PhD (daniel.calame@bcm.edu), and Isabella Herman, MD, PhD (isabellg@bcm.edu), are actively involved in basic, translational, and clinical research regarding individuals with *ENTPD1*-related neurodevelopmental disorder (*ENTPD1*-NDD). They would be happy to communicate with persons who have any questions regarding diagnosis of *ENTPD1*-NDD or other considerations.

Dr Calame and Dr Herman are also interested in hearing from clinicians treating families affected by disorders associated with progressive or non-progressive spastic paraplegia or abnormal neurodevelopment in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Calame and Dr Herman to inquire about review of *ENTPD1* variants of uncertain significance.

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