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Congenital NAD Deficiency Disorder

Synonym: Vertebral, Cardiac, Renal, and Limb Defects (VCRL)

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Summary

Clinical characteristics

Congenital NAD deficiency disorder (CNDD) is a multisystem condition in which cardiac, renal, vertebral, and limb anomalies are common, mimicking the clinical features described in VACTERL association. Congenital heart defects can include left-sided heart lesions, right-sided heart lesions, or both. Almost all surviving individuals have short stature, many with disproportionately shortened limbs. Vertebral anomalies, including hemivertebrae and vertebral fusion, occur frequently, often with rib anomalies. Renal anomalies may be severe, including dysplasia/hypoplasia and renal agenesis. Developmental delay / intellectual disability has been reported in more than half of affected individuals, although some affected individuals have had normal development, and some individuals succumbed to their congenital anomalies before developmental assessment could be performed. Other less common features may include cleft palate, eye anomalies, sensorineural hearing loss, tracheoesophageal fistula, polysplenia, anteriorly displaced anus, tethered spinal cord, cystic hygroma, epilepsy, hypothyroidism, and hypoparathyroidism.

Diagnosis/testing

The diagnosis of CNDD is established in a proband with suggestive findings and biallelic pathogenic variants in *HAAO*, *KYNU*, or *NADSYN1* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for CNDD. Supportive care includes standard treatment for congenital anomalies (congenital heart defects, cleft palate, limb anomalies, scoliosis, tethered spinal cord, renal anomalies, tracheoesophageal fistula / pyloric stenosis / laryngeal web, polysplenia, and strabismus/ptosis) and for functional/medical issues (hearing loss, developmental delay / intellectual disability, epilepsy, hypothyroidism, and hyperparathyroidism).

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Surveillance: At each visit: measurement of growth parameters; evaluation of nutrition status and safety of oral intake; assessment of mobility and self-help skills; monitoring of developmental progress and educational needs; monitoring of seizures; and assessment for new manifestations, such as changes in tone. At each visit until skeletal maturity: monitoring for scoliosis. Annually or as clinically indicated: audiology evaluation; ophthalmology evaluation; assessment of thyroid function; and serum calcium levels in those with hypoparathyroidism. For those with renal anomalies: measurement of blood pressure at each visit and renal function tests annually or as clinically indicated.

Agents/circumstances to avoid: Avoidance of medications that impair kidney function, in those with renal aplasia (solitary kidney) and/or known impaired kidney function.

Genetic counseling

CNDD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a CNDD-related 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 being unaffected and not a carrier. Once the CNDD-related 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

No consensus clinical diagnostic criteria for congenital NAD deficiency disorder (CNDD) have been published. However, the spectrum of congenital anomalies may overlap with the clinically described VACTERL association (*v*ertebral anomalies, *a*nal anomalies, *c*ardiac defects, *t*racheoesophageal fistula with *e*sophageal atresia, *r*enal anomalies, and *l*imb anomalies).

Suggestive Findings

CNDD **should be suspected** in individuals with the following imaging findings, further clinical features, and family history.

Imaging findings

- Congenital heart defects affecting:
  - Both the left- and right-sided structures (tetralogy of Fallot) OR
  - The left-sided structures (hypoplastic left heart, mitral valve defects, coarctation of the aorta, bicuspid aortic valve) OR
  - The right-sided structures (absent pulmonary trunk, double-outlet right ventricle)
- Renal anomalies, including renal aplasia, hypoplasia, and dysplasia
- Vertebral anomalies, including butterfly vertebra, hemivertebra, wedge-shaped vertebra, and fused vertebra, on spinal radiographs
- Shortened long bones, including rhizomelia and brachymelia, usually affecting both the arms and legs
- Short metacarpals with accessory ossicles on hand radiographs

Further clinical features

- Short stature, frequently but not always with shortened long bones
- Microcephaly
- Nonspecific dysmorphic features, including cupped and/or low-set ears (See Clinical Description.)
- Sensorineural hearing loss
- Nuchal redundancy or cystic hygroma
- Cutaneous syndactyly of fingers and/or toes

- Other hand anomalies, including hyperphalangism, short phalanges, and/or short metacarpals
- Developmental delay / intellectual disability, ranging from mild to severe, although some affected individuals have no developmental issues
- Sacral dimple or other sacral stigmata, such as a sacral hair tuft
- Clubfeet

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 CNDD **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *HAAO*, *KYNU*, or *NADSYN1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include "likely pathogenic" variants. (2) Identification of biallelic *HAAO*, *KYNU*, or *NADSYN1* variants of uncertain significance (or of one known pathogenic variant in a given gene and one variant of uncertain significance in that same gene) 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 phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings may be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with multiple congenital anomalies are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of CNDD, the molecular genetic testing approach is use of a **multigene panel**.

A VACTERL association multigene panel that includes some or all of the genes listed in Table 1 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

When the phenotype is indistinguishable from many other inherited disorders characterized by multiple congenital anomalies, comprehensive genomic testing may be considered.

Comprehensive genomic testing does not require the clinician to determine which gene(s) are 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 Congenital NAD Deficiency Disorder

Gene [1, 2]	Proportion of Congenital NAD Deficiency Disorder Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
HAAO	~18% [6]	>99% [7]	Unknown [8]
KYNU	~41% [9]	>99% [7]	Rare [10]
NADSYN1	~41% [11]	>99% [7]	Unknown [8]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. 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.
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. Shi et al [2017], Szot et al [2021]
7. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
8. No data on detection rate of gene-targeted deletion/duplication analysis are available.
9. Shi et al [2017]; Ehmke et al [2020]; Schüle et al [2021]; Szot et al [2021]; Author, personal observation
10. One affected individual with a homozygous deletion of exon 5 of *KYNU* was identified using Sanger sequencing following manual inspection of trio exome analysis [Schüle et al 2021].
11. Szot et al [2020], Kortbawi et al [2022], Aubert-Mucca et al [2023], Erbs et al [2023]

Clinical Characteristics

Clinical Description

Congenital NAD deficiency disorder (CNDD) is a multisystem condition in which cardiac, renal, vertebral, and limb anomalies are common. Short stature with shortened long bones, developmental delay / intellectual disability, and other organ system involvement may also be present [Mark 2022]. The morbidity and mortality of these anomalies can be quite variable. To date, 27 individuals have been identified with biallelic pathogenic variants in *HAAO*, *KYNU*, or *NADSYN1*, of which 16 are still living [Shi et al 2017; Ehmke et al 2020; Szot et al 2020; Schüle et al 2021; Szot et al 2021; Kortbawi et al 2022; Aubert-Mucca et al 2023; Erbs et al 2023; Authors, personal observation]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Congenital NAD Deficiency Disorder: Frequency of Select Features

Feature	Proportion of Persons w/Feature [1]	Comment
Congenital heart defects	25/25 (100%)	Both left- & right-sided heart defects have been described.
Short stature	12/13 (92%)	
Vertebral anomalies	18/26 (69%)	
Developmental delay / intellectual disability	8/13 (62%)	

Table 2. continued from previous page.

Feature	Proportion of Persons w/Feature [1]	Comment
Renal anomalies	16/27 (59%)	
Facial dysmorphisms	12/26 (46%)	
Shortened limbs	10/27 (37%)	
Limb anomalies	7/24 (29%)	Hyperphalangism, short finger phalanges, absent toes, right terminal transverse upper limb reduction, radioulnar synostosis
Microcephaly	7/24 (29%)	Incl 2 persons w/small brain on autopsy
Neuromuscular anomalies	6/27 (22%)	Talipes, arthrogryposis, pterygia
Sensorineural hearing loss / inner ear abnormalities	4/27 (15%)	
Other brain findings	4/27 (15%)	
Syndactyly	4/26 (15%)	
Nuchal redundancy / cystic hygroma	4/26 (15%)	Noted either on prenatal imaging or postnatal physical exam

1. Not every individual was assessed for every feature.

Cardiovascular anomalies. Structural heart defects have been reported in all affected individuals thus far. Hypoplastic left heart (8 individuals) and tetralogy of Fallot (3 individuals) were the most common. However, coarctation of the aorta, aortic stenosis, bicuspid aortic valve, mitral valve defects, absent pulmonary trunk, double-outlet right ventricle, Shone complex (a combination of membranous or muscular subvalvular aortic stenosis, supravalvular mitral membrane, and parachute mitral valve), ventricular septal defect, atrial septal defect, anomalous left coronary artery from the pulmonary artery, and patent ductus arteriosus have also been reported. Two-vessel umbilical cord has also been described.

Growth issues

- Almost all surviving individuals have short stature, many with disproportionately shortened limbs, which is likely due to NAD deficiency. Height z scores range from +0.25 to −6.1.
- A minority of individuals have microcephaly, with z scores ranging from −2.3 to −6.4.

Musculoskeletal/neuromuscular findings. Vertebral anomalies, including hemivertebrae and vertebral fusion, occur frequently, often with rib anomalies. Disproportionately shortened long bones are common. Joint hypermobility, including hypermobile fingers, has also been described.

- Upper limb anomalies may include single palmar crease, hyperphalangism, short phalanges, and short metacarpals with accessory ossicles. A transverse terminal hand reduction with rudimentary fifth digit has also been observed.
- Lower limb anomalies may include shortened metatarsals, limb asymmetry, and absent toes.
- Syndactyly has been reported in both fingers and toes.
- Neuromuscular limb anomalies may include talipes, arthrogryposis, and pterygia.

Developmental delay / intellectual disability. Some affected individuals died from complications of their congenital anomalies before developmental assessment could be performed. Of those who were assessed, there was a range from normal to severe developmental delay / intellectual disability. One individual had isolated speech delay, and one had global developmental delay and autism spectrum disorder. The etiology of these delays is still uncertain. Four affected individuals have been reported with normal development.

Renal anomalies. Renal findings are common and frequently severe. Renal dysplasia/hypoplasia (8 individuals) is the most reported defect, along with unilateral renal agenesis (6 individuals). Bilateral renal agenesis, ureter agenesis, and hydronephrosis have occurred with less frequency.

Craniofacial features. A minority of affected individuals have a range of nonspecific dysmorphic features. Such features may include brachycephaly, low or high anterior hairline, narrow forehead, prominent supraorbital ridges, highly arched eyebrows, widely spaced eyes, narrow spaced eyes, upslanted and downslanted palpebral fissures, short palpebral fissures, epicanthal folds, depressed nasal bridge, broad nose, and thick nasal alae. Microretrognathia and cleft of the soft palate have also been reported. There does not appear to be a recognizable facial gestalt.

Neurologic

- One individual with seizures (Lenox-Gastaut syndrome) has been reported.
- Small brain on autopsy was recorded in two individuals. Five other individuals had documented microcephaly (see **Growth issues** above).
- Other findings on brain imaging include hydrocephalus and hypoplastic cerebellum.

Ears/hearing. Sensorineural hearing loss has been reported in four individuals, two of whom had documented inner ear abnormalities. Cupped ears and low-set ears are common, and posteriorly rotated ears have been reported.

Gastrointestinal findings. Tracheoesophageal fistula, polysplenia, hepatomegaly (from congestion), anteriorly displaced anus, and likely pyloric stenosis have all been identified.

Other findings

- **Eyes.** Strabismus and ptosis were noted in one affected individual, while ocular crystals and hypopigmented iris with nodules were reported in another affected individual.
- **Respiratory** findings include hypoplastic right lung and laryngeal web.
- **Endocrine** findings include hypothyroidism identified at birth in two affected individuals and hypoparathyroidism identified at birth in one affected individual.
- **Lymphatic** findings include cystic hygroma and nuchal redundancy or thickening.

Prognosis. The life span for individuals with this condition is not known, although it is likely dependent on the severity and type of congenital anomalies in any given affected individual. Of the nine known individuals who did not survive, five were either terminated or did not survive pregnancy due to their anomalies, while four did not survive the first year of life due to severe birth defects. The current oldest known living person is age 30 years [Erbs et al 2023].

Phenotype Correlations by Gene

The phenotype does not differ by the associated gene.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *HAAO*, *KYNU*, or *NADSYN1* have been identified.

Prevalence

To date, there are 27 reported individuals from 25 families with CNDD, of whom 16 are still living.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *HAAO*.

KYNU. Biallelic pathogenic variants in *KYNU* can lead to hydroxykynureninuria (also known as xanthurenic aciduria) [Christensen et al 2007]. Affected individuals excrete large amounts of 3-hydroxykynurenine, xanthurenic acid, and kynurenine in the urine. The phenotypic affects, aside from the urinary findings, are difficult to define, as most individuals identified with this are from consanguineous families, in which there could be more than one autosomal recessive condition segregating in the family. Elevated levels of urinary 3-hydroxykynurenine, xanthurenic acid or xanthurenate, and kynurenine in individuals with congenital NAD deficiency disorder have been reported on a research basis [Ehmke et al 2020, Schüle et al 2021].

NADSYN1. There is preliminary evidence that a single pathogenic variant in *NADSYN1* can cause vertebral, heart, kidney, limb, liver, and intraspinal deformities [Lin et al 2021]. This will require further data to confirm.

Differential Diagnosis

Many of the congenital anomalies seen in congenital NAD deficiency disorder (CNDD) can be seen as isolated anomalies in an otherwise unaffected individual.

VACTERL association (*v*ertebral defects, *a*nal atresia, *c*ardiac malformation, *t*racheoesophageal fistula with *e*sophageal atresia, *r*enal anomalies, and *l*imb anomalies). Vertebral, cardiac, renal, and limb anomalies are common in both CNDD and VACTERL association [van de Putte et al 2020]. However, anal anomalies and tracheoesophageal fistula are rarely reported in CNDD. In addition, CNDD is frequently associated with disproportionate short stature, and developmental delays / intellectual disability and facial dysmorphisms are more common in CNDD than in VACTERL association.

Disorders of known genetic cause in the differential diagnosis of CNDD are summarized in Table 3.

Table 3. Genetic Disorders in the Differential Diagnosis of Congenital NAD Deficiency Disorder

Gene / Genetic Mechanism	Disorder	MOI	Overlapping Features	Distinguishing Features
SALL1	Townes-Brocks syndrome (TBS)	AD	TBS is assoc w/dysplastic ears w/ frequent hearing loss & thumb malformations &, less frequently, renal impairment (42%), congenital heart defects (25%), & vertebral anomalies (9%).	The frequency of imperforate anus (84%) & dysplastic ears (87%) is much higher in TBS than in CNDD.
TGDS [1]	Catel-Manzke syndrome (OMIM 616145)	AR	Catel-Manzke syndrome is characterized by unique hand malformations, incl accessory ossification center, w/shortening & clinodactyly of index fingers, which can be seen in CNDD. [2]	• Pierre Robin sequence is more common in Catel-Manzke syndrome than in CNDD. • Cardiac, vertebral, & renal anomalies & multiple other features occur much more frequently in CNDD than in Catel-Manzke syndrome.

Table 3. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Overlapping Features	Distinguishing Features
~23 genes incl: *FANCA* *FANCC* *FANCG*	Fanconi anemia (FA)	AR AD XL [3]	Short stature & variable birth defects are common.	• Only ~75% of persons w/FA have physical abnormalities &, of these persons, renal (20%), cardiac (6%), & spine anomalies (2%) are far less common than in CNDD. • Bone marrow failure & cancer susceptibility have not been reported in CNDD.
Chromosome 22q11.2 deletion	22q11.2 deletion syndrome (22q11.2DS)	AD	Congenital heart defects are common in 22q11.2DS (64%); renal anomalies (16%) & vertebral anomalies may also be seen.	22q11.2DS can be assoc w/immune deficiency (77%) & palatal abnormalities (67%), which are much less commonly reported in CNDD.

AD = autosomal dominant; AR = autosomal recessive; CNDD = congenital NAD deficiency disorder; MOI = mode of inheritance
1. Biallelic pathogenic variants in *TGDS* have been reported in individuals with Catel-Manzke syndrome.
2. Ehmke et al [2020]
3. Fanconi anemia (FA) can be inherited in an autosomal recessive manner, an autosomal dominant manner (*RAD51*-related FA), or an X-linked manner (*FANCB*-related FA).

Teratogen exposure

- **Diabetic embryopathy.** Cardiac defects and renal anomalies are common in both diabetic embryopathy and CNDD. Neural tube defects, cleft lip, cleft palate, anorectal anomalies, and anotia/microtia are more frequent in diabetic embryopathy [Castori 2013]. Developmental delay / intellectual disability and short stature with shortened long bones are more common in CNDD.
- **Thalidomide** exposure in pregnancy places the fetus at risk for severe upper- and lower-limb defects, cardiac defects, and malformations in other systems (e.g., renal defects). However, renal and cardiac defects are much less common in individuals exposed to thalidomide in pregnancy than in individuals with CNDD [Vargesson 2015]. In addition, the common limb defects seen with thalidomide exposure (phocomelia and amelia) are very rare in CNDD.
- **Valproate** exposure places the fetus at increased risk for congenital heart defects (e.g., atrial septal defects), microcephaly, and cleft palate, features that have been reported in CNDD. However, the risk of spina bifida is much higher with valproate exposure, and vertebral and renal anomalies are not commonly reported in association with valproate exposure [Jentink et al 2010].

Management

No clinical practice guidelines for congenital NAD deficiency disorder (CNDD) have been published.

Evaluations Following Initial Diagnosis

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

Table 4. Congenital NAD Deficiency Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length/height, & head circumference	To assess for short stature &/or microcephaly

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Craniofacial	Physical exam for evidence of cleft palate or other craniofacial findings	Referral to craniofacial clinic, ENT, or plastic surgeon as appropriate
Hearing	Audiology eval	To assess for hearing loss
Musculoskeletal	AP & lateral radiographs of entire spine	• To assess for vertebral & rib anomalies • Consider CT of spine, particularly if cervical spine anomalies are suspected.
	Assessment for clubfoot, arthrogryposis, pterygia, limb reduction defects, & syndactyly	Referral to orthopedist as needed
	Clinical assessment for external sacral anomalies	If present, consider spinal ultrasound (if < age 3 mo) or spinal MRI (if > age 3 mo) to evaluate for spinal dysraphism &/or tethered spinal cord
Cardiovascular	Echocardiogram	To assess for congenital heart defects
Renal	Renal/bladder ultrasound	• To assess for renal &/or bladder anomalies • Consider referral to urologist &/or nephrologist as appropriate
Gastrointestinal	Assessment for feeding issues &/or coughing w/feeding	Consider eval for tracheoesophageal fistula, pyloric stenosis, or laryngeal web.
	Consider abdominal ultrasound	To assess for polysplenia & hepatomegaly
Hematologic/ Immunologic	If polysplenia is identified, consider referral to hematologist/immunologist for assessment of splenic function.	
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	Neurologic eval	• To incl brain MRI if seizures, microcephaly, or neuromuscular findings are present • Consider EEG if seizures are a concern.
Endocrinologic	Consider obtaining thyroid studies, such as TSH & free T_4.	To assess for hypothyroidism in those w/growth issues
	Consider obtaining total calcium level for hypocalcemia.	W/reflex to obtaining intact PTH for hypoparathyroidism in those w/low serum calcium level
Eyes	Consider baseline ophthalmology eval.	To assess for strabismus, ptosis, ocular crystals, & nodules on iris
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of CNDD 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.	

CNDD = congenital NAD deficiency disorder; MOI = mode of inheritance; PTH = parathyroid hormone; T_4 = thyroxine; TSH = thyroid-stimulating hormone

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for congenital NAD deficiency disorder.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Congenital NAD Deficiency Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Cleft palate	Standard treatment per craniofacial team	
Hearing	Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district
Scoliosis, clubfeet, & limb anomalies	Standard treatment per orthopedist	
Tethered spinal cord	Standard treatment per neurosurgeon	
Congenital heart defects	Standard treatment per cardiologist	
Renal aplasia, hypoplasia, & dysplasia	Standard treatment per nephrologist	This typically incl routine monitoring of kidney function & blood pressure (See Table 6.)
Tracheoesophageal fistula, pyloric stenosis, &/or laryngeal web	Standard treatment per gastroenterologist &/or otolaryngologist	
Polysplenia	Standard treatment per hematologist &/or immunologist	
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Hypothyroidism or hypoparathyroidism	Standard treatment per endocrinologist	
Strabismus & ptosis	Standard treatment per 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 adaptive sports or Special Olympics.

ASM = anti-seizure medication

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 are provided.

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.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve

coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

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. Congenital NAD Deficiency Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each clinic visit
Hearing	Audiology eval	Annually in childhood or as clinically indicated
Musculoskeletal	Clinical assessment for scoliosis	At each visit until skeletal maturity
	Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit
Renal	Measurement of blood pressure	At each visit for those w/known renal anomalies
	Renal function tests incl serum BUN/creatinine & urinalysis	Annually or as clinically indicated in those w/ known renal anomalies
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations such as seizures or changes in tone.	
Endocrinologic	Assessment of thyroid function [1]	As clinically indicated
	Assessment of serum calcium levels	As clinically indicated for monitoring of hypoparathyroidism
Eyes	Ophthalmology eval	Annually or as clinically indicated

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
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

BUN = blood urea nitrogen; OT = occupational therapy; PT = physical therapy
1. Which may include obtaining thyroid-stimulating hormone and free thyroxine levels.

Agents/Circumstances to Avoid

Avoidance of medications that impair kidney function, in those with renal aplasia (solitary kidney) and/or known impaired kidney function.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from more in-depth evaluation for occult congenital malformations.

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

Congenital NAD deficiency disorder (CNDD) 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 a *HAAO*, *KYNU*, or *NADSYN1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a causative 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 that 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. Maternal isodisomy of chromosome 2 has been reported in a proband with *KYNU*-related CNDD [Schüle et al 2021].

- 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 a CNDD-related 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 being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has CNDD or is a carrier, offspring will be obligate heterozygotes (carriers) for a CNDD-related pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a CNDD-related pathogenic variant.

Carrier Detection

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

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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 affected, are carriers, or are at risk of being carriers.
- It is appropriate to offer carrier testing for reproductive partners of known carriers, particularly if consanguinity is likely.

Prenatal Testing and Preimplantation Genetic Testing

Once the CNDD-related 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
- **MedlinePlus**
  Intellectual Disability

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. Congenital NAD Deficiency Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HAAO	2p21	3-hydroxyanthranilate 3,4-dioxygenase		HAAO	HAAO
KYNU	2q22.2	Kynureninase	KYNU database	KYNU	KYNU
NADSYN1	11q13.4	Glutamine-dependent NAD(+) synthetase		NADSYN1	NADSYN1

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 Congenital NAD Deficiency Disorder (View All in OMIM)

604521	3-@HYDROXYANTHRANILATE 3,4-DIOXYGENASE; HAAO
605197	KYNURENINASE; KYNU
608285	NAD SYNTHETASE 1; NADSYN1
617660	VERTEBRAL, CARDIAC, RENAL, AND LIMB DEFECTS SYNDROME 1; VCRL1
617661	VERTEBRAL, CARDIAC, RENAL, AND LIMB DEFECTS SYNDROME 2; VCRL2
618845	VERTEBRAL, CARDIAC, RENAL, AND LIMB DEFECTS SYNDROME 3; VCRL3

Molecular Pathogenesis

Nicotinamide adenine dinucleotide in the oxidized form (known as NAD^+) plays critical cellular functions, including as an electron acceptor required for ATP synthesis. NAD^+ can be synthesized *de novo* biologically via one of the following three mechanisms: from tryptophan through the NAD^+ *de novo* synthesis pathway; from the deaminated precursor nicotinic acid (NA) through the Preiss-Handler pathway; and from NA derivatives (NAD^+ precursors nicotinamide mononucleotide [NMN] and nicotinamide riboside [NR]) using a salvage pathway [Zapata-Pérez et al 2021]. Individuals with biallelic pathogenic variants in the NAD^+ *de novo* synthesis pathway demonstrate decreased production of NAD, either through measurement of human NAD levels, or in mouse and yeast models of specific pathogenic variants that have been identified in individuals with Congenital NAD deficiency disorder [Shi et al 2017, Szot et al 2020, Szot et al 2021].

Mechanism of disease causation. Loss of function

Chapter Notes

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References

Literature Cited

Aubert-Mucca M, Janel C, Porquet-Bordes V, Patat O, Touraine R, Edouard T, Michot C, Tessier A, Cormier-Daire V, Attie-Bitach T, Baujat G. Clinical heterogeneity of NADSYN1-associated VCRL syndrome. Clin Genet. 2023;104:114-20. PubMed PMID: 36951206.

Castori, M. Diabetic embryopathy: a developmental perspective from fertilization to adulthood. Mol Syndromol. 2013;4:74-86. PubMed PMID: 23653578.

Christensen M, Duno M, Lund AM, Skovby F, Christensen E. Xanthurenic aciduria due to a mutation in KYNU encoding kynureninase. J Inherit Metab Dis. 2007;30:248-55. PubMed PMID: 17334708.

Ehmke N, Cusmano-Ozog K, Koenig R, Holtgrewe M, Nur B, Mihci E, Babcock H, Gonzaga-Jauregui C, Overton JD, Xiao J, Martinez AF, Muenke M, Balzer A, Jochim J, El Choubassi N, Fischer-Zirnsak B, Huber C, Kornak U, Elsea SH, Cormier-Daire V, Ferreira CR. Biallelic variants in KYNU cause a multisystemic syndrome with hand hyperphalangism. Bone. 2020;133:115219. PubMed PMID: 31923704.

Erbs E, Brasen CL, Lund AM, Rasmussen M. Adult patient diagnosed with NADSYN1 associated congenital NAD deficiency and analysis of NAD levels to be published in: European Journal of Medical Genetics. Eur J Med Genet. 2023;66:104698. PubMed PMID: 36649848.

Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, de Jong-van den Berg LT, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med. 2010;362:2185-93. PubMed PMID: 20558369.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Kortbawi H, Ames E, Pritchard A, Devine P, van Ziffle J, Slavotinek A. Further description of two patients with biallelic variants in NADSYN1 in association with cardiac and vertebral anomalies. Am J Med Genet A. 2022;188:2479-84. PubMed PMID: 35491967.

Lin J, Zhao L, Zhao S, Li S, Zhao Z, Chen Z, Zheng Z, Shao J, Niu Y, Li X, Zhang JT, Wu Z, Wu N. Disruptive NADSYN1 variants implicated in congenital vertebral malformations. Genes (Basel). 2021;12:1615. PubMed PMID: 34681008.

Mark PR. NAD+ deficiency in human congenital malformations and miscarriage: a new model of pleiotropy. Am J Med Genet A. 2022;188:2834-49. PubMed PMID: 35484986.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Schüle I, Berger U, Matysiak U, Ruzaike G, Stiller B, Pohl M, Spiekerkoetter U, Lausch E, Grünert SC, Schmidts M. A homozygous deletion of exon 5 of KYNU resulting from a maternal chromosome 2 isodisomy (UPD2) causes Catel-Manzke-syndrome/VCRL syndrome. Genes (Basel). 2021;12:879. PubMed PMID: 34200361.

Shi H, Enriquez A, Rapadas M, Martin EMMA, Wang R, Moreau J, Lim CK, Szot JO, Ip E, Hughes JN, Sugimoto K, Humphreys DT, McInerney-Leo AM, Leo PJ, Maghzal GJ, Halliday J, Smith J, Colley A, Mark PR, Collins F, Sillence DO, Winlaw DS, Ho JWK, Guillemin GJ, Brown MA, Kikuchi K, Thomas PQ, Stocker R, Giannoulatou E, Chapman G, Duncan EL, Sparrow DB, Dunwoodie SL. NAD deficiency, congenital malformations, and niacin supplementation. N Engl J Med. 2017;377:544-52. PubMed PMID: 28792876.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Szot JO, Campagnolo C, Cao Y, Iyer KR, Cuny H, Drysdale T, Flores-Daboub JA, Bi W, Westerfield L, Liu P, Leung TN, Choy KW, Chapman G, Xiao R, Siu VM, Dunwoodie SL. Bi-allelic mutations in NADSYN1 cause multiple organ defects and expand the genotypic spectrum of congenital NAD deficiency disorders. Am J Hum Genet. 2020;106:129-36. PubMed PMID: 31883644.

Szot JO, Slavotinek A, Chong K, Brandau O, Nezarati M, Cueto-González AM, Patel MS, Devine WP, Rego S, Acyinena AP, Shannon P, Myles-Reid D, Blaser S, Mieghem TV, Yavuz-Kienle H, Skladny H, Miller K, Riera MDT, Martínez SA, Tizzano EF, Dupuis L, James Stavropoulos D, McNiven V, Mendoza-Londono R, Elliott AM, Phillips RS, Chapman G, Dunwoodie SL, et al. New cases that expand the genotypic and phenotypic spectrum of congenital NAD deficiency disorder. Hum Mutat. 2021;42:862-76. PubMed PMID: 33942433.

van de Putte R, van Rooij IALM, Haanappel CP, Marcelis CLM, Brunner HG, Addor MC, Cavero-Carbonell C, Dias CM, Draper ES, Etxebarriarteun L, Gatt M, Khoshnood B, Kinsner-Ovaskainen A, Klungsoyr K, Kurinczuk JJ, Latos-Bielenska A, Luyt K, O'Mahony MT, Miller N, Mullaney C, Nelen V, Neville AJ, Perthus I, Pierini A, Randrianaivo H, Rankin J, Rissmann A, Rouget F, Schaub B, Tucker D, Wellesley D, Wiesel A, Zymak-Zakutnia N, Loane M, Barisic I, de Walle HEK, Bergman JEH, Roeleveld N. Maternal risk factors for the VACTERL association: a EUROCAT case-control study. Birth Defects Res. 2020;112:688-98. PubMed PMID: 32319733.

Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today. 2015;105:140-56. PubMed PMID: 26043938.

Zapata-Pérez R, Wanders RJA, van Karnebeek CDM, Houtkooper RH. NAD+ homeostasis in human health and disease. EMBO Mol Med. 2021;13:e13943. PubMed PMID: 34041853.

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