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CLINICAL REPORT

Norrie Disease: Cochlear Enhancement and Cerebellar Signal Abnormalities

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ABSTRACT

Norrie Disease is a rare X-linked condition characterized by early childhood blindness and later onset sensorineural hearing loss. We report two male infants with genetically confirmed Norrie Disease and characteristic ocular abnormalities consisting of bilateral funnel retinal detachments, anterior segment dysgenesis, and/or buphthalmos and microphthalmia. MRI demonstrated enhancement of the cranial nerves, cochleae, and cerebellum with cerebellar restricted diffusion. Intracranial findings mimicked meningitis, labyrinthitis, and cerebellitis. Neither infant showed clinical signs of infection. Labyrinthine and cerebellar signal abnormalities have not been previously reported in the context of Norrie Disease. Clinicians should consider Norrie Disease when encountering such findings and be aware that the described intracranial features of Norrie Disease do not necessarily indicate central nervous system infection.

ABBREVIATIONS: ND, Norrie disease; NDP, Norrin Cystine Knot Growth Factor NDP; PFV, persistent fetal vasculature; FEVR, familial exudative vitreoretinopathy; ROP, retinopathy of prematurity

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INTRODUCTION

Norrie disease (ND; OMIM # 310600) is a rare, X-linked recessive condition that occurs primarily in male patients. Infants with ND are typically born blind or experience rapid vision loss soon after birth, while hearing is usually normal at birth but deteriorates to profound sensorineural hearing loss by an average age of 12 years in greater than one third of children.[1–4] Norrin, a growth factor encoded by the protein encoding gene NDP (Norrin Cystine Knot Growth Factor NDP), is required for angiogenesis in the eye, ear, brain, and female reproductive organs.[5] The Norrin protein is an activating ligand for the Frizzled-4 (Fzd4) receptor which activates the Wnt/β-catenin signaling pathway; this pathway regulates and maintains vascular development, including regression of hyaloid vessels, and promotes blood-brain barrier and blood-retina barrier integrity.[6] Pathogenic variants in *NDP* can result in a continuum of retinopathies including *NDP*-related persistent fetal vasculature (PFV), *NDP*-related familial exudative vitreoretinopathy (FEVR), *NDP*-related advanced retinopathy of prematurity (ROP), *NDP*-related Coats disease, and ND. In the spectrum of *NDP*-related retinopathies, ND is considered the most severe phenotype.[7] Herein we report two unrelated male infants with ND with typical eye findings, the presence of cranial nerve enhancement as well as previously unreported cerebellar and labyrinthine abnormalities.

Case Series

Our institution does not require IRB approval for retrospective cases series studies. The two cases presented here were referred by the Department of Ophthalmology to the Department of Radiology at Mayo Clinic, Rochester, MN for neuroimaging evaluation. Both patients underwent B-scan ocular ultrasound and MRI of the brain and orbits with and without contrast. Case 1 also underwent a head CT. All MRI examinations were performed on the same 3T system (GE Discovery MR750, GE Healthcare, Waukesha, WI). Brain imaging protocols included 3D T1-weighted MPRAGE, T2-weighted, T2 FLAIR, diffusion-weighted, susceptibility-weighted, postgadolinium T1-weighted, and postgadolinium T2 FLAIR sequences. Orbital imaging also included T2-weighted fat saturation, balanced steady-state free

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precession, and postgadolinium T1-weighted fat saturation sequences. All MR and CT imaging were retrospectively reviewed in consensus by 2 fellowship-trained pediatric neuroradiologists with 26 and 7 years of experience, respectively.

Case One

A five-week-old male infant was referred to our institution for a second opinion regarding bilateral leukocoria and anisocoria. He was born at term via spontaneous vaginal delivery. The pregnancy was complicated by COVID-19 infection during the second trimester. The mother was a primigravida with astigmatism and the family history was remarkable for high hyperopia without other notable ocular or medical conditions. The family reported an abnormal appearance of the infant's eyes shortly after birth. The pediatrician noted bilateral leukocoria prompting referral to ophthalmology. The infant showed no signs of infection, cranial nerve deficit, or cerebellar dysfunction. Ophthalmologic examination and neuroimaging were performed to assess for structural abnormalities and to evaluate for the possibility of retinoblastoma.

Ophthalmology. The initial ophthalmologic examination redemonstrated bilateral leukocoria. The infant's right globe was buphthalmic with increased intraocular pressure and neovascularization of the iris. The pupils were asymmetrically sized with corectopia and not reactive to light. The corneas were clear bilaterally and both eyes had shallow anterior chambers, left greater than right. Both eyes had clear lenses, posterior synechiae, retrolental plaques secondary to retinal detachments, elongated ciliary processes, and irregular retinal vasculature. Ultrasound (not shown) confirmed funnel retinal detachments in both eyes and a round hypoechoic cyst was observed in the right globe.

Imaging: Orbital Findings. Noncontrast head CT and contrast-enhanced MRI demonstrated hemorrhagic and/or proteinaceous exudates in both globes with no evidence of calcification or mass. MRI further delineated the bilateral funnel retinal detachments and compartmentalized fluid in the lateral aspect of the right globe, corresponding to the cyst observed on ultrasound. Linear midline structures within both globes extended from the retrolental region posteriorly to the optic discs, consistent with fibrous material from funnel retinal detachment and/or underlying PFV **(Figure 1)**.

Imaging: Intracranial Findings. On the contrast-enhanced MRI examination, the cerebellum demonstrated diffuse enhancement and restricted diffusion. Additionally, there was florid enhancement of the optic nerves, cisternal trigeminal, and intracanalicular facial and vestibulocochlear nerves; there was mild enhancement of the cisternal oculomotor nerves. Both cochleae showed avid enhancement with minimal enhancement of the vestibules.

Clinical Management. Given the mother's COVID-19 infection during pregnancy and the infant's brain enhancement pattern on MRI, the infant was initially treated for cerebellitis, meningitis, and labyrinthitis. A comprehensive infectious disease workup, including lumbar puncture and blood tests, was performed. Cerebral spinal fluid (CSF) cell counts, chemistry, and cultures for bacterial, viral, parasitic, and fungal etiologies were negative and antibiotic treatment was subsequently stopped. The follow-up MRI examination performed three weeks later was unchanged. The parents declined surgical intervention. At six months of age, the intraocular pressures in both eyes were decreased. The remainder of his examination was stable. Hearing was within normal limits at serial measurements by auditory brainstem response.

Genetic testing confirmed the diagnosis of ND with a maternally inherited hemizygous pathogenic frameshift variant c.388dupG (p.Met114HisfsX35) in *NDP*. The patient's mother was noted to be highly hyperopic and thought to have retinopathy of prematurity.

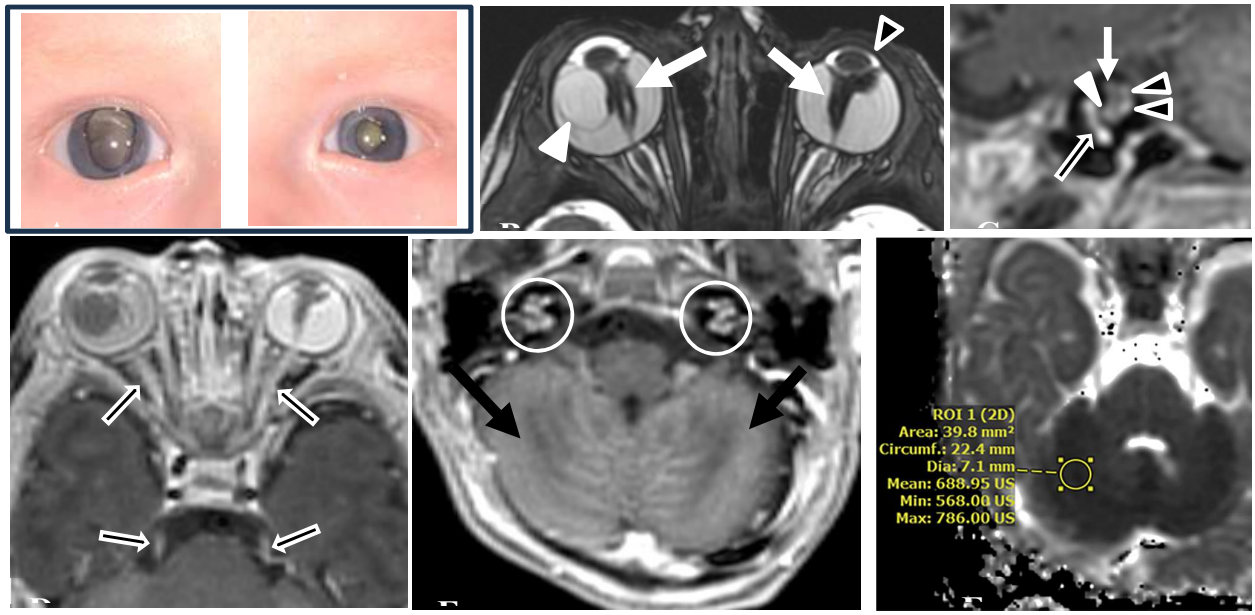

FIG 1. CASE I. MRI examination with and without IV gadolinium in a five-week-old male presenting with bilateral leukocoria. Clinical photograph of the eyes (A) demonstrates bilateral leukocoria. Axial bSSFP image (B) demonstrates bilateral funnel retinal detachments (white arrows). There is a loculated fluid collection in the right posterior segment (arrowhead) with mild buphthalmos of the right eye. The left anterior chamber is dysmorphic and shallow (black arrowhead). Sagittal oblique post-gadolinium T1W fat saturation image (C) of the right internal auditory canal demonstrates enhancement of the facial nerve (white arrow), cochlear nerve (white arrowhead), and vestibular nerves (black arrowheads). The cochlear basilar turn is enhancing (open arrow). These findings were also seen in the left internal auditory canal (not shown). Axial post-gadolinium T1W fat saturation images (D and E) show avid enhancement of the optic nerves, cisternal trigeminal nerves (open arrows in D), cochlea (circles in E), and cerebellum (black arrows in E). ADC map (F) demonstrates diffusion restriction of the cerebellum. All findings persisted on two follow-up MRI examinations, up to three weeks apart.

Case Two

A five-month-old male infant presented to his primary care provider with an enlarged right eye noted by his mother. He was the product of a diamniotic dichorionic twin gestation and was born at 34 weeks with no complications during pregnancy or delivery. His twin sister was healthy with normal eyes. The family history was notable for two maternal uncles who were blind as children, had progressive hearing loss, and died before adulthood. The infant had no signs of infection, cranial nerve deficit, or cerebellar dysfunction. Ophthalmologic examination and neuroimaging were performed to assess for structural abnormalities and to evaluate for the possibility of retinoblastoma.

Ophthalmology. Ophthalmologic assessment was obtained to further evaluate the enlarged right eye. On ophthalmologic examination, there was bilateral leukocoria. The right eye was buphthalmic with elevated intraocular pressure, no light perception, and exposure keratopathy. Ocular ultrasonography demonstrated bilateral funnel retinal detachments (images not shown).

Imaging: Orbital Findings. The contrast-enhanced MRI demonstrated bilateral mixed signal retinal detachments with hemorrhagic fluid-fluid levels and additional proteinaceous components **(Figure 2).** Linear midline structures extended from the retrolental regions posteriorly to the optic discs in both globes, consistent with fibrous material from funnel retinal detachments and/or underlying PFV. No intraocular mass or calcifications were observed to suggest tumor or retinoblastoma, with calcifications excluded on susceptibility-weighted imaging and the corresponding phase map. The right globe was mildly enlarged, while the left globe was shrunken. The anterior chambers were shallow bilaterally.

Imaging: Intracranial Findings. Intracranially, on the contrast-enhanced MRI examination, there was striking symmetric enhancement of the optic nerves, cisternal oculomotor nerves, cisternal trigeminal nerves, cisternal and intracanalicular vestibulocochlear nerves, and both cochleae. The cerebellum exhibited diffuse enhancement and mild restricted diffusion, primarily involving gray matter and pial surfaces.

Clinical Management. Based on the infant's clinical presentation and the pattern of MRI abnormalities, ND was suspected. As there was no clinical suspicion for cerebellitis or meningitis, the infant did not undergo an infectious disease workup. The patient underwent iridectomy, lensectomy, and vitrectomy of the left eye, which was bare light perception, as per parental decision. At surgery, the retina

exhibited ischemic and atrophic features, which prompted the decision to halt further surgical intervention to avoid the risk of causing iatrogenic retinal breaks. At the one-month follow-up visit, the right intraocular pressure was improved, and the left eye showed possible light perception vision. Repeat ocular surgery was performed two months later to remove scar tissue, but retinal salvage was unsuccessful given the disorganized nature of the intraocular contents. After two months, the infant continued to demonstrate bare light perception in the left eye. On two separate speech awareness threshold testing sessions, mild hearing loss was suspected. The parents have declined sedated auditory brainstem response to date.

Genetic testing confirmed the ND diagnosis with a maternally inherited hemizygous deletion of the entire *NDP* coding region. Further genetic testing of family members revealed the infant's sister was hemizygous for the deletion with a normal eye examination, and the patient's mother was found to have an ocular phenotype consistent with familial exudative vitreoretinopathy (FEVR).

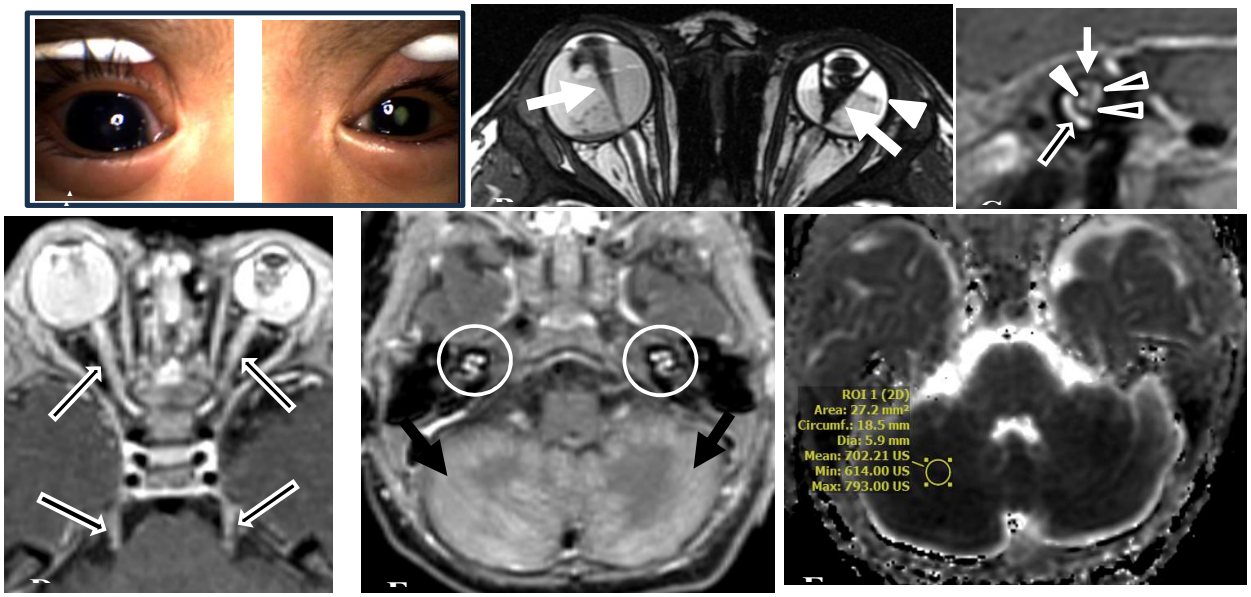

FIG 2. CASE 2. MRI examination with and without IV gadolinium in five-month-old male presenting with bilateral leukocoria. Clinical photograph of the eyes (A) best demonstrates leukocoria in the left eye. Axial bSSFP image (B) demonstrates bilateral funnel retinal detachments (white arrows) with hemorrhagic exudates, debris, and fluid-fluid levels (white arrowhead). There is mild buphthalmos of the right eye. Sagittal oblique post-gadolinium T1W fat saturation image (C) of the right internal auditory canal demonstrates enhancement of the facial nerve (white arrow), cochlear nerve (arrowhead), and vestibular nerves (black arrowheads). The cochlear basilar turn is enhancing (open arrow). These findings were also seen in the left internal auditory canal (not shown). Axial post-gadolinium T1W fat saturation images (D and E) show avid enhancement of the optic nerves and cisternal trigeminal nerves (open arrows in D) and avid enhancement of the cochlea (circles in E) and cerebellum (black arrows in E). ADC map (F) demonstrates diffusion restriction within the cerebellum.

DISCUSSION

The novel imaging findings presented in this study, labyrinthine enhancement and cerebellar enhancement with restricted diffusion, represent new contributions to the understanding of ND. These findings expand the scope of CNS abnormalities in ND beyond the known ocular manifestations and cranial nerve enhancement.

The ocular manifestations of ND are well documented and include congenital blindness, retinal detachment, persistent fetal vasculature, and cataracts. These eye problems lead to severe vision impairment and blindness in the newborn period of affected individuals. Also well documented in the context of ND is profound postlingual sensorineural hearing loss. Less frequently reported is associated cranial nerve enhancement. Although a few case reports have noted cerebellar atrophy in ND patients, none have described cerebellar signal abnormalities or enhancement.[8,9] Additionally, endolymphatic hydrops has been reported in ND patients though without post-gadolinium enhancement described.[10] To the best of our knowledge, the identification of labyrinthine enhancement and cerebellar enhancement and restricted diffusion, as observed in both our patients, constitute novel imaging findings in the context of ND.

ND can present with a range of syndromic features. Most infants with ND come to medical attention because of their ocular abnormalities. The course of disease has been described as having a vascularly active phase early in development during which vascular endothelial

growth factor (VEGF) is upregulated, with subsequent retinal neovascularization and persistent fetal vasculature. A stalk of fibrous tissue along the course of the hyaloid vasculature results in secondary tractional retinal detachments which are frequently exudative and hemorrhagic. Iris atrophy, glaucoma, cataract, optic nerve atrophy, and eventual phthisis bulbi ensues.[3,11,12] Visual acuity in patients with ND is expected to decline leading to a loss of light perception early in the postnatal period. As such, the visual potential is characteristically poor. Surgery may be considered to retain some degree of light perception for the purposes of ambulation, maintenance of a normal sleep-wake cycle, and prevention of phthisis bulbi. However, even for the most skilled surgeons, performing ocular surgery in patients with ND is extremely challenging and success rates are low.[13]

Both our patients showed strikingly similar ocular features on MRI. Both demonstrated bilateral funnel retinal detachments with hemorrhagic exudates and linear midline fibrotic structures extending from the optic discs to the lenses. Total funnel-shaped retinal detachment is a retinal configuration described in ND;[14,15] this occurs with severe retinal detachments where the retinal folds are markedly uplifted and fixed centrally in a funnel shape.[13] Retinal "macrocysts" develop as secondary findings in patients with chronic retinal detachments.[16] Both patients exhibited shallow anterior chambers and no appreciable ocular calcifications, findings consistent with prior reports of ND.[14,17–19] Shallow anterior chambers can be observed on MRI and serve as indicators of anterior segment dysgenesis, which is typically accompanied by incomplete formation of the angle of the eye and reduced drainage of ocular fluid. In ND, abnormal fluid production and decreased drainage of ocular fluid can result in increased intraocular pressure and glaucoma, which, in turn, can cause buphthalmos. Both infants reported herein had unilateral buphthalmos and increased intraocular pressures. In addition, the Case 2 infant had unilateral microphthalmia. Typically, microphthalmic globes will progress to phthisis bulbi. The absence of intraocular calcifications in ND is a useful indicator that retinoblastoma is absent. There are however rare case reports of ND with ocular calcifications.[10] Cataracts were not present in either of our patients but are a common occurrence in ND. The cause of cataracts in ND includes retinal detachment, the presence of other retrolental structures, anterior segment dysgenesis, and proliferative vitreoretinopathy, which can interfere with the normal diffusion of nutrients to the lens and subsequent cataract formation.

Profound sensorineural hearing loss is also a common feature in ND, reported in 33-100% of patients.[4,20,21] The age of onset of hearing loss is widely variable though many patients experience hearing loss beginning in early adolescence.[4] A study evaluating histopathological differences between knock-out mouse models with an Ndp gene disruption and control mouse models found abnormalities of the cochlea in ND localized to the stria vascularis which accounts for the primary cochlear vasculature.[22] An early cadaveric study of a patient with ND investigated the cochlea under light and electron microscopy and described severe degeneration of the Organ of Corti, spiral ganglion, and stria vascularis with marked loss of hair cells.[3] A more recent analysis confirms that *NDP* is required for maturation and maintenance of cochlear hair cells.[23] Early pathology of cochlear microvasculature leads to loss in vessel integrity, diminished endocochlear potential, eventual hair cell death, and subsequent sensorineural hearing loss. Due to the delayed onset of hearing loss, there may be a therapeutic window in which early intervention could be employed, potentially by using advancing gene therapy and small-molecule technologies.[24]

Cranial nerve abnormalities have rarely been reported in ND. In one report of an adult patient with ND, congenital blindness, progressive hearing loss, epilepsy, enhancement of several cranial nerves (CN III; V, VII, VIII, IX, X, and X) was reported.[25] Another case involving an infant with ND described enhancement of the intraorbital optic nerves, oculomotor nerves, and trigeminal nerves.[14] A recent imaging report of a patient with ND described thickened acoustic nerves (CN VIII) but no cranial nerve enhancement. None of these reports describe any corresponding cranial nerve deficits.

The Norrin protein is an activating ligand for the Frizzled-4 (Fzd4) receptor which activates the Wnt/β-catenin signaling pathway.[6] Considering the essential role that the Wnt pathway plays in vascular development and maintenance of the blood brain barrier of the retina and inner ear, it is plausible that the abnormal enhancement of these structures is indicative of compromised blood-brain barrier integrity. It is important to note that in both our patients, the enhancement of multiple cranial nerves was considered concerning for acute CNS infection even though there were no clinical or laboratory parameters indicating such. Both our patients showed florid enhancement of the cochleae and, in Case 2, mild enhancement of the vestibules. Labyrinthine enhancement in ND has not been previously reported and we hypothesize the enhancement is a result of a faulty blood brain barrier. The presence of cerebellar enhancement and restricted diffusion in patients with ND has also not been previously reported. Analogous to cranial nerve enhancement, cerebellar enhancement may indicate disruption of the integrity of the blood-brain barrier. High expression of Norrin and frizzled-4 have been found in the cerebellum of wild-type mice with correlating vascular changes noted in the cerebellum of Norrin/Ndph knockout mice.[26] Furthermore, the restricted diffusion observed of the cerebellum may be attributed to ischemic changes, potentially clarifying the observed cerebellar atrophy observed in some patients with ND, and/or intramyelinic edema.[27]

Based on the ophthalmic examinations and imaging findings in our two patients, genetic analysis was performed which demonstrated loss of function variants and similar phenotypes. One patient had a complete deletion of the *NDP* gene, while the other had a frameshift mutation. Genetic testing and counseling are essential for patients suspected of having ND. A timely and precise genetic diagnosis can facilitate proper screening for syndromic features of ND, surveillance, and guide family planning for unaffected carriers. Ophthalmologic evaluation of carrier mothers provides care for previously unidentified eye disease, specifically FEVR, that may require treatment (e.g., retinal laser) to prevent retinal detachment.

While ND can present with a range of syndromic features, our study highlights remarkable similarities on MRI between two infants with ND. In addition to the expected ocular abnormalities associated with ND and the rarely described cranial nerve enhancement, our findings reveal novel imaging abnormalities not previously associated with this disease. Specifically, it was striking and noteworthy that labyrinthine enhancement and cerebellar enhancement and restricted diffusion were seen in both infants. It is important for clinicians to be aware of these abnormalities can be associated with ND and recognize that CNS infection may not be the underlying cause of intracranial imaging abnormalities in infants with ND. Furthermore, while many of these patients undergo orbital imaging, it may be advisable to also include brain MR imaging to evaluate the cranial nerves and cerebellum in cases where ND is suspected.

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REFERENCES

1. Warburg M. Norrie's Disease. *Acta Ophthalmol (Copenh)*. 1961;39(5):757-772. doi:10.1111/j.1755-3768.1961.tb07740.x
2. Holmes LB. Norrie's disease--an x-linked syndrome of retinal malformation, mental retardation and deafness. *N Engl J Med*. 1971;284(7):367-368. doi:10.1056/NEJM197102182840707
3. Nadol JB, Eavey RD, Liberfarb RM, et al. Histopathology of the ears, eyes, and brain in Norrie's disease (oculoacousticocerebral degeneration). *Am J Otolaryngol*. 1990;11(2):112-124. doi:10.1016/0196-0709(90)90007-i
4. Smith SE, Mullen TE, Graham D, Sims KB, Rehm HL. Norrie disease: extraocular clinical manifestations in 56 patients. *Am J Med Genet A*. 2012;158A(8):1909-1917. doi:10.1002/ajmg.a.35469
5. Ke J, Harikumar KG, Erice C, et al. Structure and function of Norrin in assembly and activation of a Frizzled 4-Lrp5/6 complex. *Genes Dev*. 2013;27(21):2305-2319. doi:10.1101/gad.228544.113
6. Ye X, Smallwood P, Nathans J. Expression of the Norrie disease gene (Ndp) in developing and adult mouse eye, ear, and brain. *Gene Expr Patterns GEP*. 2011;11(1-2):151-155. doi:10.1016/j.gep.2010.10.007
7. Scruggs BA, Reding MQ, Schimmenti LA. NDP-Related Retinopathies. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed October 28, 2022. http://www.ncbi.nlm.nih.gov/books/NBK1331/
8. Liu D, Hu Z, Peng Y, et al. A novel nonsense mutation in the NDP gene in a Chinese family with Norrie disease. *Mol Vis*. 2010;16:2653-2658.
9. Rodríguez-Muñoz A, García-García G, Menor F, Millán JM, Tomás-Vila M, Jaijo T. The importance of biochemical and genetic findings in the diagnosis of atypical Norrie disease. *Clin Chem Lab Med*. 2018;56(2):229-235. doi:10.1515/cclm-2017-0226
10. Gong Y, Liu Z, Zhang X, et al. Endolymphatic Hydrop Phenotype in Familial Norrie Disease Caused by Large Fragment Deletion of NDP. *Front Aging Neurosci*. 2022;14. doi:10.3389/fnagi.2022.771328
11. Wawrzynski J, Patel A, Badran A, Dowell I, Henderson R, Sowden JC. Spectrum of Mutations in NDP Resulting in Ocular Disease; a Systematic Review. *Front Genet*. 2022;13:884722. doi:10.3389/fgene.2022.884722
12. Sisk RA, Hufnagel RB, Bandi S, Polzin WJ, Ahmed ZM. Planned preterm delivery and treatment of retinal neovascularization in Norrie disease. *Ophthalmology*. 2014;121(6):1312-1313. doi:10.1016/j.ophtha.2014.01.001
13. Ozdemir Zeydanli E, Ozdek S, Acar B, et al. Surgical outcomes of posterior persistent fetal vasculature syndrome: cases with tent-shaped and closed funnel-shaped retinal detachment. *Eye Lond Engl*. Published online June 23, 2022. doi:10.1038/s41433-022-02140-0
14. Zhou Y, Shapiro MJ, Burton BK, Mets MB, Kurup SP. Case report: A case of Norrie disease due to deletion of the entire coding region of NDP gene. *Am J Ophthalmol Case Rep*. 2021;23:101151. doi:10.1016/j.ajoc.2021.101151
15. Huang L, Zhang L, Li X, et al. Ocular manifestations of Chinese patients with copy number variants in the NDP gene. *Mol Vis*. 2022;28:29-38.
16. Verdaguer P, Nadal J. Intraretinal cyst secondary to longstanding retinal detachment. *Eur J Ophthalmol*. 2012;22(3):506-508. doi:10.5301/ejo.5000034
17. Payabvash S, Anderson JS, Nascene DR. Bilateral persistent fetal vasculature due to a mutation in the Norrie disease protein gene. *Neuroradiol J*. 2015;28(6):623-627. doi:10.1177/1971400915609350
18. Dhingra S, Shears DJ, Blake V, Stewart H, Patel CK. Advanced bilateral persistent fetal vasculature associated with a novel mutation in the Norrie gene. *Br J Ophthalmol*. 2006;90(10):1324-1325. doi:10.1136/bjo.2005.088625
19. Li H, Li Z, Wang D, et al. Next-generation sequencing reveals a case of Norrie disease in a child with bilateral ocular malformation. *Front Genet*. 2022;13. Accessed October 30, 2022. https://www.frontiersin.org/articles/10.3389/fgene.2022.870232
20. Halpin C, Owen G, Gutiérrez-Espeleta GA, Sims K, Rehm HL. Audiologic features of Norrie disease. *Ann Otol Rhinol Laryngol*. 2005;114(7):533-538. doi:10.1177/000348940511400707
21. Parving A, Warburg M. Audiological findings in Norrie's disease. *Audiol Off Organ Int Soc Audiol*. 1977;16(2):124-131.
22. Rehm HL, Zhang DS, Brown MC, et al. Vascular defects and sensorineural deafness in a mouse model of Norrie disease. *J Neurosci Off J Soc Neurosci*. 2002;22(11):4286-4292. doi:2002
23. Hayashi Y, Chiang H, Tian C, Indzhykulian AA, Edge ASB. Norrie disease protein is essential for cochlear hair cell maturation. *Proc Natl Acad Sci U S A*. 2021;118(39):e2106369118. doi:10.1073/pnas.2106369118
24. Bryant D, Pauzuolyte V, Ingham NJ, et al. The timing of auditory sensory deficits in Norrie disease has implications for therapeutic intervention. *JCI Insight*. 2022;7(3):e148586. doi:10.1172/jci.insight.148586
25. Jokela M, Karhu J, Nurminen J, Martikainen MH. Multiple Cranial Nerve Gadolinium Enhancement in Norrie Disease. *Ann Neurol*. 2022;91(1):158-159. doi:10.1002/ana.26274
26. Luhmann UFO, Neidhardt J, Kloeckener-Gruissem B, et al. Vascular changes in the cerebellum of Norrin /Ndph knockout mice correlate with high expression of Norrin and Frizzled-4. *Eur J Neurosci*. 2008;27(10):2619-2628. doi:10.1111/j.1460-9568.2008.06237.x
27. Meyers SP. Intracranial Abnormalities with Diffusion Restriction. *Magn Reson Imaging Clin N Am*. 2021;29(2):137-161. doi:10.1016/j.mric.2021.02.004