The Journal of International Advanced Otology

J Int Adv Otol 2025; 21: 1–6 • DOI: 10.5152/iao.2025.241648

Case Report

A Case Report of Auditory Neuropathy Due to TWNK Gene Mutations

Tufatulin G.Sh[1,2,3], Garbaruk E.S[4,5], Lalayants M.R[6,7], Markova T.G[1,6,8], Mefodovskaya E.K[3], Koroleva I.V[1,3], Ryzhkova O.P[9], Orlova M.D[9], Shatokhina O.L[9], Sugarova S.B[1], Levin S.V[1,2]

[1]Saint Petersburg Scientific Research Institute of Ear, Throat, Nose and Speech, St. Petersburg, Russia
[2]North-Western State Medical University named after I.I. Mechnikov, St. Petersburg, Russia
[3]Saint Petersburg City Center of Pediatric Audiology, St. Petersburg, Russia
[4]Saint Petersburg State Pediatric Medical University, St. Petersburg, Russia
[5]Pavlov First Saint Petersburg State Medical University, St. Petersburg, Russia
[6]Russian Medical Academy of Continuing Professional Education, Moscow, Russia
[7]Russian Children's Clinical Hospital, Moscow, Russia
[8]Research Clinical Institute of Otorhinolaryngology named after L.I. Sverzhevsky, Moscow, Russia
[9]Research Center of Medical Genetics named after N.P. Bochkov, Moscow, Russia

ORCID iDs of the authors: T.G.S. 0000-0002-6809-7764, G.E.S. 0000-0002-9535-6063, L.M.R. 0000-0003-3975-7759, M.T.G. 0000-0002-1086-588X, M.E.K. 0000-0002-8453-2789, K.I.V. 0000-0001-8909-4602, R.O.P. 0000-0003-1285-9093, O.M.D. 0000-0002-3743-094X, S.O.L. 0000-0003-0351-1271, S.S.B. 0000-0003-0856-8680, L.S.V. 0000-0001-9770-7739.

Cite this article as: G.Sh T, E.S G, M.R L, et al. A case report of auditory neuropathy due to TWNK gene mutations. *J Int Adv Otol.* 2025, 21, 1648, doi: 10.5152/iao.2025.241648

Mutations in the TWNK gene were described in patients with Perrault syndrome—an autosomal-recessive disease that includes hearing loss, central auditory and speech disorders, cerebellar ataxia, motor and sensory neuropathy, and ovarian dysfunction. Only around 100 cases of Perrault syndrome have been described to date. Genetically, it caused by biallelic pathologic variants in 1 of 6 genes. A literature review and a case study of Perrault syndrome are given in the article. Two mutations in the TWNK gene were detected in a 13-year-old girl with the phenotype of auditory neuropathy spectrum disorder (ANSD). The nucleotide variant c.1523A>G (p.(Tyr508Cys), NM_021830.5) was previously described; another variant c.1199G>T (p.(Arg400Leu) NM_021830.5) is a new one with an unknown population frequency. The main value of this case is the combination of mutations in the TWNK gene with the phenotype of ANSD, as well as the manifestation of the disease with hearing impairment but without neurological symptoms, unlike what was described in the literature. Specifically, in this case, progression of hearing disorders, ineffective amplification, and limited CI effect were noted. Genetic testing results suggested endocrine system testing, which revealed ovarian dysfunction at a preclinical stage; cerebellar ataxia was also diagnosed. The patient requires further monitoring by a multidisciplinary team.

KEYWORDS: Auditory neuropathy spectrum disorder, cochlear implantation, Perrault syndrome, TWNK gene

INTRODUCTION

Perrault syndrome was first described in 1951. The main symptoms include sensorineural hearing loss, central auditory and speech disorders, cerebellar ataxia, motor and sensory neuropathy in both men and women, and ovarian dysfunction in women.[1] This is an extremely rare disease with limited literature data, making it difficult to systematize gene–phenotype interactions in patients with Perrault syndrome.[2-5] To date, only around 100 cases of this disease have been reported in the literature. Its prevalence is less than 1:1 000 000, with females being affected more frequently.[6]

The autosomal-recessive type of inheritance with a normal karyotype is typical for Perrault syndrome. Perrault syndrome is genetically heterogeneous and is defined by biallelic pathologic variants in 1 of 6 genes (*CLPP*, *ERAL1*, *HARS2*, *HSD17B4*, *LARS2*, or *TWNK*), which explains the clinical diversity of this disease. Significant inter- and intra-familial phenotypic variability has been observed.[7]

The spectrum of ovarian dysfunction extends across a continuum from primary ovarian insufficiency to ovarian dysgenesis with increased gonadotropin levels and decreased estrogen levels. Most females with Perrault syndrome are infertile. Fertility in affected

Corresponding author: Ekaterina Garbaruk, e-mail: kgarbaruk@mail.ru
Received: July 31, 2024 • **Revision Requested:** September 9, 2024 • **Last Revision Received:** October 2, 2024 • **Accepted:** October 21, 2024 • **Publication Date:** January 27, 2025
Available online at www.advancedotology.org

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

males is usually reported as normal. Other endocrine disorders described in Perrault syndrome cases include Hashimoto's thyroiditis and autoimmune hypothyroidism.[8]

Neurological symptoms that are typically observed in patients with Perrault syndrome include cerebellar ataxia, nystagmus, ophthalmoplegia, hypotension, motor and sensory peripheral neuropathy, and sometimes learning difficulties and developmental delay. MRI findings can reveal demyelination and atrophic processes in the white matter of the cerebellum, medulla, cervical part of the spinal cord, and ventricular enlargement. According to the clinical features, Perrault syndrome has been classified as type I, which is static and without neurological disease, and type II, with progressive neurological disease. Meanwhile, it has been noted that symptoms manifest in different periods of life: hearing loss in childhood, later neurologic symptoms, and endocrine disorders in puberty.[4,7]

Bilateral sensorineural hearing loss is typical for patients with Perrault syndrome. Hearing loss is congenital in most cases or can manifest in early childhood. Hearing impairments range from profound with prelingual (congenital) onset to moderate with early-childhood onset. When onset is in early childhood, hearing loss can be progressive.[6,7] Cases of auditory neuropathy spectrum disorders (ANSDs) have also been reported. Italian authors described the case of ANSD in a girl with the homozygote variant c.425C>T/(p.Pro142Leu) in the CLPP gene. At the age of 3 years, after unsuccessful amplification, the child underwent cochlear implantation (CI). After a year of CI usage, the child detected low-intensity tones and phonemes, but speech-language abilities lagged beyond those expected despite consistent implant use.[9]

All reported cases of Perrault syndrome due to the *TWNK* gene mutation have included neurologic features such as nystagmus, a positive Romberg test, an ataxic gait, reduced deep tendon reflexes in the lower limbs, pes cavus, and axonal sensorimotor neuropathy. In most cases, the first signs of Perrault syndrome associated with the *TWNK* gene mutation are severe and progressive involvement of the nervous system. The onset of such symptoms may range from the first years of life (less than 3) through 48 years.[6-8]

Currently, there are only a few published cases of ANSD in patients with Perrault syndrome associated with mutations in the *TWNK* gene.[10,11] Oldak et al[10] described 2 sisters who had normal psychomotor development during the first years of life. Initial neurological symptoms were observed at the age of 3 years for the older sister and at the age of 11 years for the younger sister. Neurological symptoms in the older sister included progressively deteriorating motor performance, horizontal nystagmus, imbalance, and gradually deteriorating walking. Sensorimotor polyneuropathy was noted in the younger sister. Binaural ANSD was identified at the ages of 5 and 12 years for the older and younger sisters, respectively. Hearing aids fitting for the older sister had limited benefits. Comprehensive audiological and vestibular evaluation revealed auditory neuropathy with a certain degree of cochlear dysfunction and partial atrophy of the vestibulocochlear nerves. Neuroimaging studies of both sisters showed diminished cervical enlargement of the spinal cord, partial atrophy of the vestibulocochlear nerves, and decreased gray and increased white matter volumes of the cerebellum. Genetic investigation revealed the compound heterozygous *TWNK* mutations: c.1196A>G (p.Asn399Ser) and c.1802G>A (p.Arg601Gln) in both patients.[10] Munson et al[11] reported a girl with normal psychomotor development during her first year of life, followed by early-onset ataxia and axonal polyneuropathy. The first neurological features of ataxia were demonstrated at 16 months of age. Bilateral ANSD with profound hearing thresholds was identified. She received bilateral CI and intensive auditory and spoken language rehabilitation. Sound detection thresholds improved to the normal range, but speech recognition and spoken language had limited development. Genetic testing identified a compound heterozygous state with 2 variants in the *TWNK* gene (NM_021830.4): c.561_563dupTGA, p.Asp188dup in exon 1 and c.1909C>T, p.Arg637Trp in exon 5.[11] Wu J et al. analyzed CI outcomes in 75 patients with ANSD in China, including 2 cases with *TWNK*-related Perrault syndrome. In the first case (with *TWNK* mutations: c.1172G>A and c.1844G>C), Perrault syndrome manifested with a neurological deficit, and was later followed by progressive hearing loss with high speech recognition after CI. That child also had a sibling with the same clinical and audiological phenotype. In the second case (with *TWNK* mutations c.1172G>A and c.1217G>A), hearing loss was congenital, and later ovarian dysfunction was diagnosed.

The diversity of the clinical picture of Perrault syndrome requires the accumulation of clinical cases for earlier diagnosis and appropriate intervention. The goal of this article is to describe the clinical case of Perrault syndrome associated with ANSD and caused by mutations in the *TWNK* gene, which has been proved by clinical and genetic investigations.

METHODS

Patient

The girl was born in a non-consanguineous marriage without pregnancy or delivery complications. There was no family history of hearing impairment. She passed the newborn hearing screening. During the first year of life, she had age-appropriate physical and pre-language development. At the age of 3 years, the girl demonstrated speech and language delay and attended speech therapy sessions. By the age of 8 years, her speech recognition deteriorated and was based mostly on lip reading. At that time, her speech and language development generally met age-appropriate norms. Audiological assessment identified ANSD. CT, MRI of the temporal bones, examinations by a neurologist and ophthalmologist did not reveal any pathology.

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of St. Petersburg Saint Petersburg State Pediatric Medical University (approval number: 177, date: 24 October 2022). Informed consent was obtained from the subjects' parents.

Audiological Evaluation

Audiological assessment consisted of pure-tone, speech, and impedance audiometry, otoacoustic emissions (OAEs), click-evoked auditory brainstem responses (ABR), electrocochleography, and electrically evoked ABR, cortical auditory evoked potentials (CAEPs) after CI. To evaluate auditory temporal resolution ability, the Random Gap Detection Test (RGDT) and the Duration Pattern Sequence test (DPST) were used.[1213] Electrocochleography was carried out using an

extratympanic electrode (TipTrode) with a click stimulus of 95 dB nHL. Electrically evoked ABR was performed through the trigger between the MedEl MAX interface (direct electrical stimulation) and the ABR recording system. Electrical currents were presented at the second, sixth, and tenth electrodes sequentially with 8-40 qu amplitude. Cortical auditory evoked potentials were recorded through free-field acoustic stimulation with a 2000 Hz tone at an intensity 70 dB HL.

Genetic Investigation

Clinical exome sequencing was performed on the proband's DNA using a paired-end (2×75 bp) sequencing method on an Illumina NextSeq 500 sequencer. Target enrichment was performed using a SeqCap EZ HyperCap Workflow solution capture array, which included the coding regions of 6010 genes.

Automated Sanger sequencing was carried out for the proband, parents, and the proband's sister to validate the *TWNK* candidate variants.

The analyzed DNA samples were extracted from peripheral venous blood samples of the affected proband, her siblings, and healthy parents using standard methods. Clinical exome sequencing was performed on the proband's DNA using a paired-end (2 × 75 bp) reading method on an Illumina NextSeq 500 sequencer (Illumina, San Diego, CA, USA). Target enrichment was performed with a SeqCap EZ HyperCap Workflow solution capture array, including the coding regions of 6010 genes at that time described as clinically significant in The Human Gene Mutation Database (HGMD Professional, version 2018.1© 2013–2018 QIAGEN, Venlo, The Netherlands).

Sequencing data were processed using a standard computer-based algorithm from Illumina software, presented on the https://basespace.illumina.com website. Average coverage for this sample was 75.2×, coverage width (10×) was 99.25%.

Sequenced fragments were visualized with Integrative Genomics Viewer (IGV) software (©Broad Institute, and the Regents of the University of California, CA, USA). Filtering of the variants was based on their frequency of less than 1% in gnomAD and coding region sequence effects such as missense, nonsense, coding indels, and splice sites. The clinical significance of variants was evaluated according to the guidelines for massive parallel sequencing (MPS) data interpretation. Amplification and Sanger sequencing were performed to validate the exome variants in the *TWNK* gene in the proband and their presence in the patient's parents.

Automatic Sanger sequencing was carried out using an ABI Prism 3100xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's protocol, and the results were analyzed using Chromas (Technelysium Pty Ltd., South Brisbane, Australia). To amplify the fragment encompassing the candidate variants, custom primers were used (according to the NM_021830.5 reference sequence): TWNK_1F: GCTCGCAGTCTTGTCTTCCCT

TWNK_1R: TTGTCACCTGATCTTCTGCCCC

TWNK_3F: GTTCTTCTGCCTGGGGTGGT

TWNK_3R: ACACATGGGGGTGGTACGTG

RESULTS

At the age of 8 years, audiological assessment revealed ANSD with pure tone thresholds of 15-25 dB nHL (Figure 1). In contrast to hearing level, the child's speech discrimination was disproportionately poor: 10% for polysyllabic words in open-set format in quiet and 60% for close-set format. Both RGDT and DPST were failed. Amplification was not effective. Additional examination (neurologist, ophthalmologist, temporal bone imaging—computerized tomography, and magnetic resonance imaging) did not reveal pathological signs.

Over the next few months, hearing thresholds were unstable, fluctuating from 20 to 80 dB HL with a tendency to worsen. By the age of 9 years, the child's speech understanding became possible only through lip reading. A second attempt at amplification turned out to be ineffective. Cochlear implantation was recommended. Mild signs of motor awkwardness and increased fatigue appeared. Electrocochleography showed cochlear microphonics without compound action potential (Figure 2).

Cochlear implantation was performed at 11.5 years old, using a Concerto Mi1000 Pin+STANDARD implant and a Sonnet-2 sound processor from MedEl. One month later, the patient started to react to her name and to recognize sounds. Six months later, she could differentiate the main characteristics of sounds, and words and phrases by duration. Aided recognition of polysyllabic words was 50%. Electrically evoked ABRs have not been detected (Figure 3). Morphologically changed low-amplitude CAEPs were recorded at 18 months after CI. Further speech understanding gradually deteriorated. Reactions to sounds with CI became unstable. However, the child continued to use the sound processor. Due to the low benefit from the CI, sign language was implemented in the communication strategy.

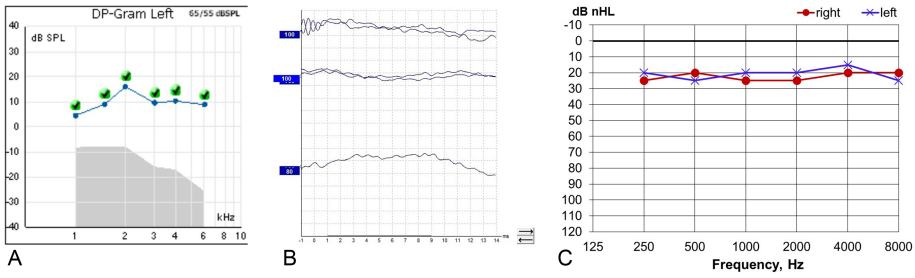

Figure 1. Initial audiological data (a) Distortion product otoacoustic emissions (DPOAEs), (b) click-auditory brainstem response on stimulus at the level of 100 dB nHL, and (c) pure tone audiogram at the age of 8 years old.

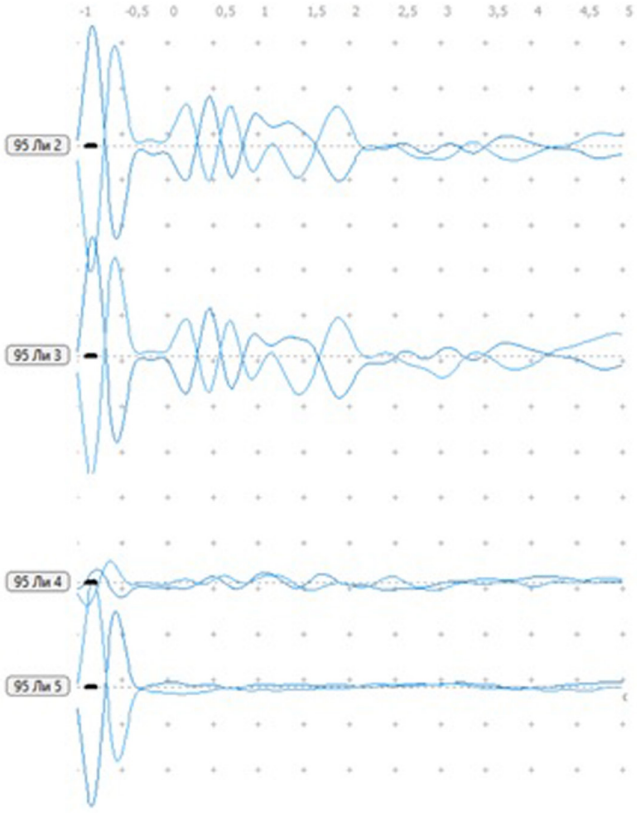

Figure 2. Electrocochleography results: upper curves—rarefaction and condensation polarities, clear response (cochlear microphonics); lower curves—clamped tube (no response).

At this time, exome sequencing was performed. Two mutations in the *TWNK* gene were detected. The nucleotide variant c.1523A>G (p.(Tyr508Cys), NM_021830.5) was previously described with a population frequency of 0.0002687 (The Genome Aggregation Database (v.2.1.1)). Another variant, c.1199G>T (p.(Arg400Leu), NM_021830.5) is a new one with an unknown population frequency. The presence of these variants was confirmed in parents whose hearing was normal (Figure 4).

Absence of electrically evoked ABRs with poor speech perception after CI reflects a neuropathy type of ANSD. Based on the results of the genetic testing and clinical symptoms, it was assumed that the child might have Perrault syndrome type II due to *TWNK* gene mutations.

The endocrinologist concluded that the puberty development of the child corresponds to Tanner stage 2. However, profound hormonal testing revealed that luteinizing hormone was 4 times higher than the normal value, follicle-stimulating hormone was 10 times higher than the normal value, estradiol level was decreased, which could suggest ovarian hypofunction. Neurological evaluation revealed mild signs of possible cerebellar ataxia debut. The psychiatric evaluation concluded that the child had an organic emotional-labile disorder.

DISCUSSION

TWNK gene codes for the twinkle protein (NP_068602), which is a helicase necessary for mitochondrial DNA replication. Mutations in this gene reduce the activity of the enzyme, which leads to the slow accumulation of large mitochondrial DNA deletions.[14,15] This may explain the slow progression of the disease and the involvement of the neural and endocrine systems in our patient.

The uniqueness of the present clinical case is the type and the time of manifestation of hearing loss—ANSD was the first sign of *TWNK*-associated Perrault syndrome. Previously, mostly peripheral sensorineural hearing loss due to mutations in the *TWNK* gene was described in the literature.[1,2,5-7] Perrault syndrome could not be suspected in the present case until genetic testing was conducted, as the only symptom initially observed was hearing impairment, with no neurological signs or ovarian dysfunction present. This underscores the diverse manifestations of Perrault syndrome; literature has documented cases where ANSD was identified only after significant neurological symptoms emerged.[10,11] In our case, the child began to exhibit a combination of signs typical of Perrault syndrome—ovarian, neurological, and hearing disorders—only after the age of 10. Due to genetic testing and early revealed TWNK gene mutations, ovarian hypofunction was identified at a preclinical stage at the age of 11 years; otherwise, ovarian dysfunction would have been diagnosed only after a menarche delay. Early ovarian hypofunction identification provides timely hormonal correction, which might secure fertility in this girl, unlike it was in previously described late-diagnosed Perrault syndrome cases with infertility.

The differential diagnosis of *TWNK*-related ANSD should be based on symptoms, audiological, radiological, and genetic investigations. Many cases of ANSD (both of genetic and non-genetic origin) manifest at birth. Children with ANSD who are not identified through newborn hearing screening may exhibit delayed speech and language development and poor reactions to sounds. In this case, the first symptoms emerged at age 8 years with normal speech, language,

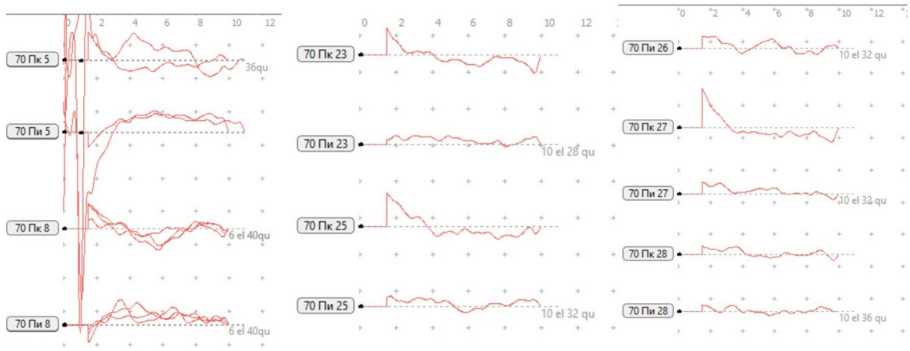

Figure 3. Electrically evoked auditory brainstem response results.

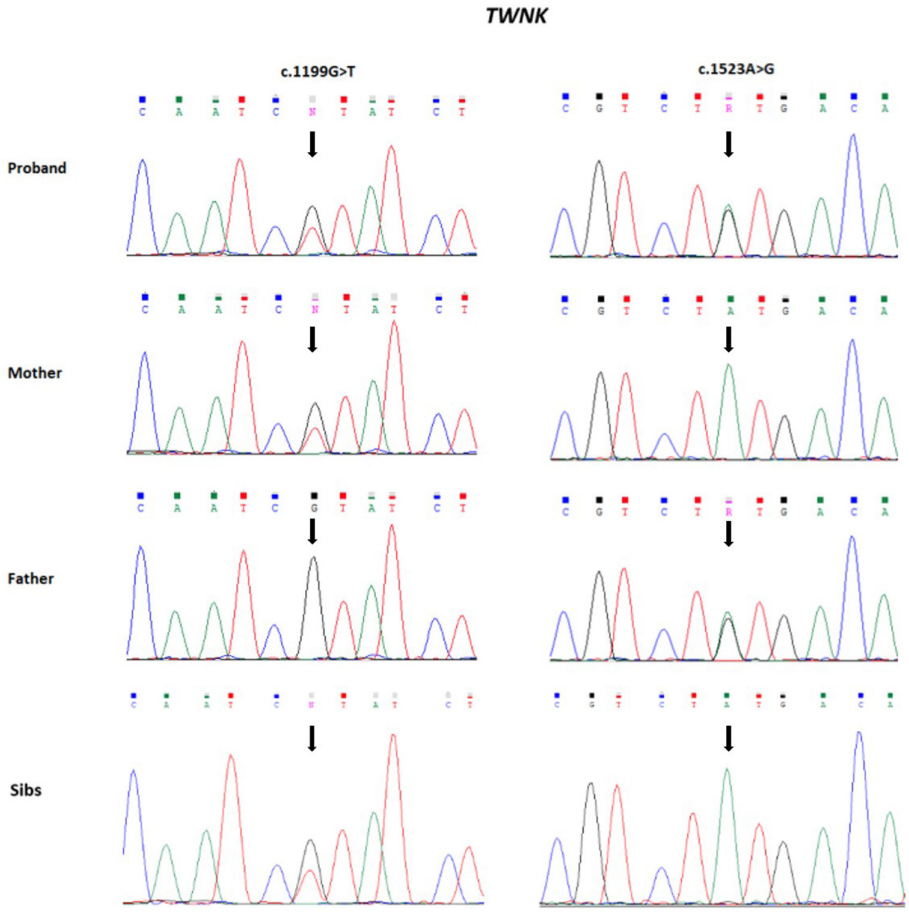

Figure 4. Sanger sequencing results demonstrating *TWNK* variants in the compound-heterozygous state in the proband and in the heterozygous state in parents and siblings (marked with arrows).

and hearing development prior to that point. This suggests a late onset or progressive development of ANSD.

Specific electrophysiological findings—such as a cochlear microphonic potential without a compound action potential and absent CAEP peaks—indicate a postsynaptic type of disorder (neuropathy rather than synaptopathy). This is confirmed by the lack of amplification effects and very limited benefits from CI. Cochlear implantation and MRI data ruled out an organic origin for ANSD. Therefore, genetic testing is a main method for differential diagnosis in such cases. Targeted gene testing or gene panel testing for ANSD may be ineffective; thus, exome of genome sequencing increases the likelihood of identifying the underlying etiology.

Diagnosing the exact genetic cause and pathophysiology of a hearing deficit allows for identifying optimal auditory rehabilitation approaches. Timely intervention using hormone therapy and assistive reproductive technologies might help to increase fertility in women with Perrault syndrome. A multidisciplinary team should provide observation, treatment, and rehabilitation for patients with Perrault syndrome.

CONCLUSION

Literature review and case study of Perrault syndrome are given in the article. The main value of this case is the combination of mutations in the *TWNK* gene with a phenotype of ANSD, and that hearing impairment was the first symptom of Perrault syndrome. A specific clinical and electrophysiological picture and low CI efficiency suggest a neuropathy type of *TWNK*-related ANSD.

Genetic testing carried out to verify the etiology indicated that additional investigation of the nervous and endocrine systems was warranted. Further tests revealed ovarian dysfunction at a preclinical stage and the debut of cerebellar ataxia in the child. The patient needs future monitoring by a multidisciplinary team.

Limitations of the Study

The only case of *TWNK*-related ANSD was described in the article, making it impossible to identify any patterns based on this data. More cases of ANSD in patients with mutations in the *TWNK* gene should be analyzed. Further investigations and literature reviews on this topic will help to systematize information regarding the symptoms and potential management options.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by the Ethics Committee of St. Petersburg Saint Petersburg State Pediatric Medical University (approval number: 177, date: 24 October 2022).

Informed Consent: Written informed consent was obtained from the subject's parents who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – T.G., K.I.; Design – G.E., K.I.; Supervision – M.T., K.I.; Resources – T.G., S.S.; Materials – T.G., L.M., R.O., O.M., S.O., S.S., L.V.; Data Collection and/or Processing – T.G., G.E., M.E., R.O., O.M., S.O.; Analysis and/or Interpretation – G.E., L.M. M.T., M.E., L.V.; Literature Search – G.E., M.T.; Writing – T.G., G.E., L.M., M.T.; Critical Review – K.I.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

REFERENCES

1. Perrault M, Klotz B, Housset E. Two cases of Turner syndrome with deaf-mutism in two sisters. *Bull Mem Soc Med Hop Paris*. 1951;67(3-4):79-84. (In French).
2. Pierce SB, Chisholm KM, Lynch ED, et al. Mutations in mitochondrial histidyl tRNA synthetase HARS2 cause ovarian dysgenesis and sensorineural hearing loss of Perrault syndrome. *Proc Natl Acad Sci U S A*. 2011;108(16):6543-6548. [CrossRef]
3. Jenkinson EM, Rehman AU, Walsh T, et al. Perrault syndrome is caused by recessive mutations in CLPP, encoding a mitochondrial ATP-dependent chambered protease. *Am J Hum Genet*. 2013;92(4):605-613. [CrossRef]
4. Chatzispyrou IA, Alders M, Guerrero-Castillo S, et al. A homozygous missense mutation in ERAL1, encoding a mitochondrial rRNA chaperone, causes Perrault syndrome. *Hum Mol Genet*. 2017;26(13):2541-2550. [CrossRef]
5. Pierce SB, Gersak K, Michaelson-Cohen R, et al. Mutations in LARS2, encoding mitochondrial leucyl-tRNA synthetase, lead to premature ovarian failure and hearing loss in Perrault syndrome. *Am J Hum Genet*. 2013;92(4):614-620. [CrossRef]
6. Lerat J, Jonard L, Loundon N, et al. An application of NGS for molecular investigations in Perrault syndrome: study of 14 families and review of the literature. *Hum Mutat*. 2016;37(12):1354-1362. [CrossRef]
7. Newman WG, Friedman TB, Conway GS, Demain LAM. Perrault syndrome. In: *GeneReviews® [Internet]*. Adam MP, Ardinger HH, Pagon RA, et al. eds. [Updated 2018]. Seattle (WA): University of Washington, Seattle; 2014. Available at: https://www.ncbi.nlm.nih.gov/books/NBK242617/.
8. Domínguez-Ruiz M, García-Martínez A, Corral-Juan M, et al. Perrault syndrome with neurological features in a compound heterozygote for two TWNK mutations: overlap of TWNK-related recessive disorders. *J Transl Med*. 2019;17(1):290. [CrossRef]
9. Forli F, Bruschini L, Franciosi B, et al. A Rare Case of Perrault syndrome with auditory neuropathy spectrum disorder: cochlear implantation treatment and literature review. *Audiol Res*. 2021;11(4):609-617. [CrossRef]
10. Ołdak M, Oziębło D, Pollak A, et al. Novel neuro-audiological findings and further evidence for TWNK involvement in Perrault syndrome. *J Transl Med*. 2017;15(1):25. [CrossRef]
11. Munson HE, De Simone L, Schwaede A, et al. Axonal polyneuropathy and ataxia in children: consider Perrault Syndrome, a case report. *BMC Med Genomics*. 2023;16(1):278. [CrossRef]
12. Keith RW. *Random Gap Detection Test*. St Louis, MO: Auditec; 2002.
13. Ogorodnikova EA, Stolyarova EI, Balyakova AA. Auditory segmentation in schoolchildren with normal hearing and with hearing and speech impairments. *Sens Syst*. 2012;26:20-31 (In Russian).
14. Milenkovic D, Matic S, Kühl I, et al. TWINKLE is an essential mitochondrial helicase required for synthesis of nascent D-loop strands and complete mtDNA replication. *Hum Mol Genet*. 2013;22(10):1983-1993. [CrossRef]
15. Peter B, Farge G, Pardo-Hernandez C, Tångefjord S, Falkenberg M. Structural basis for adPEO-causing mutations in the mitochondrial TWINKLE helicase. *Hum Mol Genet*. 2019;28(7):1090-1099. [CrossRef]