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CASE REPORT

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Perrault syndrome: a forgotten presentation for infertile women

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Key clinical message

Perrault syndrome (PRLTS) is an uncommon hereditary condition distinguished by ovarian failure in females and sensorineural hearing loss. Infertility can be the presenting problem for a serious disease. History and physical examination is very essential among infertile couples.

Abstract

Perrault syndrome (PRLTS) is an uncommon hereditary condition distinguished by ovarian failure in females and sensorineural hearing loss. This case presentation describes a 22-year-old female from Saudi Arabia with PRLTS. The patient presented with progressive bilateral hearing loss since childhood, impacting her academic achievement. Additionally, she experienced amenorrhea since the age of 18 years, with previous investigations showing no hormonal imbalances. Other laboratory tests, including bone mineral density, kidney and liver function, electrolytes, and lipid profile, showed mostly normal results, except for a slightly abnormal lipid profile with low high-density lipoprotein and high low-density lipoprotein levels. This case highlights the challenges faced by individuals with PRLTS, specifically progressive hearing loss and gonadal dysfunction, leading to infertility. Further evaluation and management are warranted to address the patient's hearing impairment and fertility concerns, with a multidisciplinary approach involving audiology, endocrinology, and reproductive medicine.

KEYWORDS

deafness, ovarian dysgenesis, Perrault syndrome, primary amenorrhea, primary infertility, sensorineural hearing loss

1 | INTRODUCTION

Perrault syndrome (PRLTS) is an uncommon hereditary condition distinguished by ovarian failure in females and sensorineural hearing loss in both females and males.[1]

It is an autosomal recessive illness resulting from abnormalities in certain genes that regulate the function of the ovaries, mitochondria, and cochlea.[2,3]

Sensorineural hearing loss (SNHL) is a frequent early manifestation of PRLTS; subsequent neurological abnormalities include intellectual deficit, developmental delay,

seizures, motor and sensory neuropathy, muscle weakness and atrophy, cerebellar ataxia, restricted eye movements, nystagmus, and dyspraxia. Probable applications of magnetic resonance imaging (MRI) include the detection of cerebral leukodystrophy and cerebellar atrophy.[2,4,5]

PRLTS is characterized by the initial manifestation of auditory impairment in children or adolescents, which is subsequently followed by gonadal malfunction and female infertility.[6] Further characteristics could comprise neurological irregularities, such as intelligibility or cerebellar ataxia. In PRLTS, SNHL is generally reported to be due to a cochlear dysfunction, and only three cases due to a neural deficit (auditory neuropathy) are reported in the scientific literature, two cases with PRTLS5, associated with TWNK mutation[7] and a further case in PRTLS2, associated with HARS2 mutation.[8]

In this report, we describe a Saudi female diagnosed with PRLTS with symptoms of hearing loss, amenorrhea, and infertility.

2 | CASE HISTORY/ EXAMINATION

A 22-year-old female from the southern part of Saudi Arabia, who is a known case of PRLTS presented to reproductive endocrinology and infertility medicine department in 2023 with a history of infertility for 2 years; she had no period and has grown hair both in the pubic and axillary region; however, upon questioning the patient we have discovered that she has been following with the ear, nose, and throat (ENT) department for progressive bilateral SNHL.

Her hearing difficulties were first noticed by her mother when she was 9 years old, prompting a medical evaluation.

At the age of 12, she was diagnosed with mild hearing loss at King Khalid Hospital in Riyadh, Saudi Arabia. However, no further management or follow-up was provided at that time due to concerns about her underlying medical condition.

Over the years, hearing loss has progressively worsened, ranging from mild to profound in the right ear and slight to profound in the left ear. She had a unilateral cochlear implant. Despite her hearing impairment, she has developed coping strategies and was able to communicate with others by relying on raised voices and lip-reading. However, her hearing loss has significantly impacted her academic achievement, leading to her discontinuation of her high school education. The patient had a family history of hearing loss, as her sister and her paternal uncle were both diagnosed with the same medical diagnosis. The patient had some other concerns, including having symptoms previously of alternating nasal obstruction and facial pain, with no significant discharge, and no change in olfaction and was diagnosed in 2023 by an ENT physician with allergic rhinitis along with deviated nasal septum and was recommended to start on anti-allergic medications.

Upon examination, her weight was 63.5 kg, her height was 154 cm, and her blood pressure was 123/60 mm/hg. Her neck, chest, abdominal, and genital examination were normal. Her breast examination was Tanner II, and her pubic and axillary hair were Tanner III.

3 | METHODS

The patient was further evaluated for hormonal changes earlier, where FISH analysis in 2015 showed normal results with two copies of the X chromosome. In addition, in 2016, an MRI of her brain and pituitary was performed, revealing no abnormalities. A follow-up MRI in 2022 also showed no abnormalities as well. A pelvic ultrasound was done, and it was difficult to assess both the uterus and ovaries and recommended MRI be done.

MRI of the pelvis revealed a uterine size of $4.29 \times 1.09 \times 1.93$ cm, and the ovaries were not visualized.

In 2021, the patient visited the fertility clinic and was assessed for the response after hormonal replacement therapy which was associated with withdrawal bleeding; however, the patient stopped her medication for 3 months for unknown social reasons and had no period since. Additional investigations were requested and showed low level of Vitamin D, Insulin-like GF-1, normal range of TSH, testosterone, free T3, PTH, prolactin serum, and growth hormone (GH); however, her FSH (72 IU/L) and LH (25 IU/L) were high suggesting an apparent hormonal disturbance contributing to her infertility (Table 1).

Other laboratory tests were performed for the patient over time; however, no abnormalities were observed with bone mineral density measurement, kidney function tests, or liver function tests. Furthermore, electrolyte and mineral assessments were performed to evaluate any abnormalities in calcium, phosphorus, and other relevant elements. These tests consistently showed normal levels over time, indicating no significant disturbances in her electrolyte and mineral balance. However, slight abnormality was found in lipid profile tests with low HDL, high LDL (in2018 and became normal in 2021), low cholesterol, and normal triglycerides. Furthermore, genetic testing was performed by the geneticist, and a pathogenic variant in one of the genes, HSD17B4 was identified. Dual-energy x-ray absorptiometry scan was performed for both the lumbar spine and the right and left femur. Normal BMD for patient's age and gender-matched reference (within

TABLE 1 Hormonal laboratory tests.

Test name	Unit	Results	Reference range	Date of the exam
Vitamin D	Nmol/l	52.2	75–350.0	2021
TSH	MIU/L	1.669	0.35–4.94	2021
TSH	MIU/L	1.605	0.35–4.94	2022
Testosterone	Nmol/l	0.96	0.38–1.97	2021
T3. Free	Pmol/L	4.90	2.627–5.699	2021
Prolactin serum	Ug/L	18.7	5.18–26.53	2021
PTH	Pmol/L	6.0	1.60–7.20	2021
Insulin-like GF-1	Nmol/l	9.43	14.17–48.36	2021
Growth hormone (GH)	mIU/L	1.58	0.18–20.70	2021
FSH	IU/L	33.8	3.03–8.08	2021

two standard deviations for matched age and gender) was reported.

In view of her high FSH, and the very low fertility potential, the patient was informed about the result and that in vitro fertilization would not be a valid option. The patient was advised to continue on her hormonal replacement therapy, calcium, and Vitamin D supplements.

4 | DISCUSSION

Sensorineural hearing impairment is a defining characteristic of PRLTS.[9] It commonly presents itself in the period of childhood or adolescence and deteriorates gradually as time passes. Both ears are affected by hearing loss, which can range in severity from modest to profound. Our patient had one ear affected in her early childhood and the other ear was being assessed periodically. Differentiating this hearing loss from other types of congenital or early-onset hearing loss is its progressive nature. Patients may have issues in the areas of speech perception, communication, and education, which can have adverse effects on their social lives.[10] As an adjustment to the hearing impairment, coping mechanisms such as lip-reading and speaking with an elevated voice may be utilized and this is what we have seen with our patient.[11]

Additionally, she had primary amenorrhea. Females afflicted with PRLTS frequently manifest ovarian dysfunction in addition to hearing loss.[6] The absence of menstrual cycles, or primary amenorrhea, is a frequent sign. At the commencement of puberty or a later stage in life, amenorrhea might manifest. Ovarian dysfunction is a condition that manifests in PRLTS through hormone abnormalities, poor ovulation, and possible infertility.[12,13]

Uncertainty surrounds the precise mechanism by which PRLTS-associated hearing loss occurs.[6,14] It is believed, nonetheless, that compromised mitochondrial function in the cochlea is the cause.[2] The process by which cells produce energy is mediated by mitochondria, which are vital for the health and function of sensory cells in the inner ear. PRLTS has been linked to genetic mutations in transcripts HSD17B4 and HARS2, which are implicated in mitochondrial function, as seen with our patient.[3,15] As a result of these mutations interfering with mitochondrial activities, sensory cells degenerate, and hearing loss ensues. PRLTS individuals exhibit extensive neurological involvement, which includes sensorineural deafness. Luckily, our patient had a normal brain MRI. Neurological involvement has been reported by Nishi et al. and has been identified with ataxic gait, pes equinovarus, nystagmus, and restricted extraocular movements in a study of the literature concerning PRLTS in 21 patients.[16] The link between PRLTS and Leber's hereditary optic neuropathy was recently established by Stronka et al.[17] MRI revealed cerebral leucodystrophy, cerebellar hypoplasia, and other abnormalities in patients with PS. The early diagnosis of growing central nerve involvement associated with PRLTS is facilitated by PET scans. According to a study by Fiumara et al., PRLTS is categorized into two types: type I, which is static and lacks neurologic characteristics, and type II, which is characterized by progressive neurologic disease.[4]

The diagnosis of PRLTS necessitates a thorough assessment that includes genetic tests, hormone exams, and audiological evaluations.[4,6,7] In order to ensure multidisciplinary care, our patient had been referred to a geneticist to assess other family members and perform the required genetic tests, ENT physician to follow-up and offer different audiological assessment tests such as pure-tone audiometry and other auditory examinations can ascertain the nature and degree of hearing impairment. The aforementioned assessments are critical in the ongoing monitoring of hearing loss progression. Additionally, the function of the auditory system connecting the ear and the brain can be evaluated with the use of auditory brainstem response (ABR) testing,[10,11] and a reproductive endocrinologist

for evaluation of hormone levels such as anti-Müllerian hormone (AMH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol can offer valuable information regarding the degree of ovarian dysfunction. These reproductive hormones are essential for establishing the cause of primary amenorrhea and measuring ovarian function.[18,19] Utilizing imaging modalities, such as pelvic ultrasonography, one can evaluate the uterine and ovarian structures. Estrogen replacement therapy is usually prescribed in order reduce the risk of osteoporosis and cardiovascular disease. Assisted reproduction using donor eggs for in vitro fertilization (IVF) can be offered to patients with premature ovarian insufficiency; however, this is not a valid option in our community and culture.

We have previously reported a 27-year-old female patient with Perrault's syndrome who was deaf and mute along with primary amenorrhea. Her hormonal assay revealed hypergonadotropic hypogonadism and the karyotype was 46 XX. She had a hypoplastic uterus and streak ovaries confirmed by pelvic ultrasound and MRI in addition to degenerative discs and Tarlov cysts in the spine. *LARS2* mutation was diagnosed when whole-exome sequencing was performed.[20] It is also interesting to note that when Perrault first described the case in 1951, it was about two sisters with sensorineural hearing loss and infertility.[21]

Genetic testing may be advised in certain instances to validate the diagnosis of PRLTS and detect certain mutations in genes that are linked to the condition. A crucial component of the care of PRLTS is genetic counseling. Individuals and families can obtain information from genetic counselors regarding the inheritance patterns of the disorder, the probability of transmitting it to subsequent generations, and the reproductive alternatives that are accessible.[1,2,5] In addition, they have the capacity to streamline genetic testing and result interpretation, providing valuable information regarding the likelihood of recurrence and implications for family planning choices. To further comprehend the underlying mechanisms and create specific therapeutics for this rare condition, additional research is required.

5 | CONCLUSION

A multidisciplinary approach, early detection, early referral to related specialties, and thorough assessment are critical components in the effective management and assistance of patients diagnosed with PRLTS. This includes attending to their hormone concerns, fertility challenges, and hearing impairment. Genetic counseling, hormonal replacement therapy, and audiological therapies are essential components of the therapeutic strategy for patients with PRLTS.

AUTHOR CONTRIBUTIONS

Manal Alkhonezan: Conceptualization; data curation; methodology; project administration; writing – original draft; writing – review and editing. **Shahad Alkhonezan:** Investigation; methodology; resources; validation; writing – original draft; writing – review and editing. **Dania Al-Jaroudi:** Conceptualization; formal analysis; methodology; supervision; validation; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have declared that they don't have any conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was reviewed and approved by the King Fahad Medical City Institutional Review Board (IRB Number: 24-025).

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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