

## CASE REPORT

### Evaluation and diagnostic approach in patient with Perrault Syndrome

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Article Info	ABSTRACT
<p>Received Apr 22, 2024 Revised May 18, 2024 Accepted May 31, 2024 Published Aug 1, 2024</p> <p><b>*Corresponding author:</b> Rachael Christin Nathania <a href="mailto:rachaelchristin4@gmail.com">rachaelchristin4@gmail.com</a></p> <p><b>Keywords:</b> Secondary amenorrhea Bilateral sensorineural hearing loss Perrault Syndrome Maternal health</p>	<p><b>Objective:</b> To report Perrault Syndrome identified in a patient with secondary amenorrhea and bilateral sensorineural hearing loss.</p> <p><b>Case Report:</b> A 16-year-old female presented to the obstetrics and gynecology clinic at a type B hospital with primary amenorrhea for one year. Menarche occurred at age 13, followed by regular menstrual cycles for two years, after which menstruation gradually ceased. She denied dysmenorrhea, constipation, leukorrhea, genital pruritus, growth retardation, and weight loss. The patient expressed concern about potential future infertility. At age 9, she was diagnosed with a viral infection by an ENT specialist due to bilateral hearing loss, leading to emotional disturbances. There was no history of prior medication, family illness, or chronic infections. Born at term via spontaneous vaginal delivery, the patient weighed 3,000 grams. Laboratory tests revealed normal T3 (1.51 ng/dl), FT4 (1.16 ng/dl), prolactin (18.25 ng/ml), estrogen (11 pg/ml), and progesterone (0.1 pg/ml) levels, but elevated FSH (66.46 mIU/ml) and LH (29.97 mIU/ml) levels. Symptomatic treatment included bone conduction hearing aids and estrogen replacement therapy.</p> <p><b>Conclusion:</b> Perrault Syndrome, a rare hereditary condition, manifests as sensorineural hearing loss (SNHL) and ovarian dysfunction, including primary ovarian insufficiency (POI) and gonadal dysgenesis, in individuals with a 46, XX karyotype. Molecular diagnosis remains challenging. Consultation with a pediatric endocrinologist can guide cyclic estrogen and progesterone therapy to induce withdrawal bleeding in adolescents with amenorrhea. Women at risk of ovarian failure should consider donor eggs or oocyte cryopreservation. Avoiding aminoglycosides and excessive noise is crucial for managing hearing loss.</p>

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#### Highlights:

1. The rare hereditary condition Perrault Syndrome is characterized by sensorineural hearing loss (SNHL) and ovarian dysfunction
2. Cyclic estrogens and progesterone may be given to adolescents with amenorrhea to induce withdrawal bleeding and mimic the menstrual cycle.



## INTRODUCTION

Perrault syndrome is a rare autosomal recessive genetic disease, which reported worldwide in about 40 families approximately with a 2:1 female-to-male ratio. There are two types of Perrault syndrome.<sup>1</sup> People with type 1 Perrault Syndrome characterized with symptoms of progressive sensorineural hearing loss, ovarian dysfunction, which usually begins at birth or in early childhood, and ovarian insufficiency in women with karyotype 46, XX, manifests as primary and secondary amenorrhea.<sup>1</sup> Additional neurologic symptoms and muscle or renal indications are present in type 2.<sup>1</sup>

Genetics are believed to be one of the factors causing ovarian dysfunction and hair cells abnormalities. One of eight causative genetic genes named LARS2, has biallelic mutations that support the diagnosis. LARS2 encodes mitochondrial amino acid protein, which is required in the cytoplasm and mitochondria for the translation of nuclear and mitochondrial encoded genes.<sup>1,2</sup>

Age of hearing loss onset and ovarian dysfunction can change depending on the frequency of delayed puberty in females with sensorineural hearing loss. Congenital hearing loss can start at birth or develop in infancy. Primary amenorrhea and primary ovarian insufficiency are two examples of ovarian dysfunction. In the literature, a diagnosis is made at a median age of 22.<sup>2</sup> Hearing impairment (mean age at diagnosis seven years) was noted in all but one reported case.<sup>2,3</sup> A multidisciplinary team with a reproductive endocrinologist and otolaryngologist is needed to prepare for puberty, mimicking the menstrual cycle and maintaining healthy bones.

The purpose of this case report was to provide an overview of Perrault syndrome because it is an uncommon genetic disorder with little existing literature. This case report highlighted the possibility that adolescents who have secondary amenorrhea may have genetic issues and explained how the family may be informed and what treatments are available.

## CASE REPORT

A 16-year-old female came to the obstetrics and gynecology clinic at a type B hospital with the main complaint of not having her period since one year ago. The patient first menstruated at the age of 13 years, then for two years, the patient experienced regular menstruation every month, but in the last year, the patient felt that her menstruation had decreased until it stopped. Complaints of abdominal pain during

menstruation were denied. Other complaints, such as difficulty defecating, vaginal discharge, genital itch, stunted growth, and weight loss, were rejected by the patient. The patient also worried about not being able to get pregnant in the future other than this problem.

According to the patient's mother, at the age of 9 years, the patient was brought to the ENT doctor because hearing in both ears felt reduced and was diagnosed by the doctor as a disease caused by a virus. The patient could not hear using both her ears, and emotional changes occurred because of the patient's reduced hearing. There was no history of previous drug use, family illness, and chronic infections. The patient is the second of two children, born when the patient's mother was 20 years old through spontaneous vaginal delivery without complications at term, with a birth weight of 3,000 grams.

Laboratory results showed normal Triiodothyronine (T3) levels (1.51 ng/dl), free thyroxine (FT4) levels (1.16 ng/dl), prolactin (18.25 ng/ml), estrogen (11 pg/mL), and progesterone test (0.1pg/mL). However, there was an increase in follicle-stimulating hormone (FSH) levels (66.46 mIU/mL) and luteinizing hormone (LH) levels (29.97 mIU/mL). Symptomatic treatments were given, such as bone hearing aids and estrogen replacement therapy.

## DISCUSSION

Sensorineural hearing loss (SNHL) and ovarian dysfunction are hallmarks of a rare autosomal recessive genetic disorder known as Perrault Syndrome.<sup>2,3,4</sup> SNHL is bilateral and can be severe in the congenital stage or mild in early childhood. Hearing loss can get worse over time, even if it started in infancy. Ovarian dysfunction includes primary ovarian insufficiency (POI) and gonadal dysgenesis, characterized by absence or dysplasia of the gonads and manifests as primary and secondary amenorrhea.<sup>2,3</sup> There are two types; type I is Perrault Syndrome, which is static without neurological disease. At the same time, progressive neurological disorders accompany type 2. Type 2 symptoms include absent tendon reflexes, nystagmic dysarthria, cognitive impairment, scoliosis, cerebellar atrophy, and seizure.<sup>2,5</sup>

The clinical features of SNHL in both men and women, as well as ovarian dysfunction in women, along with a karyotype that is typically normal in affected persons, support the diagnosis of Perrault Syndrome 46, XX.<sup>2,6</sup> Additional tests such as a karyotype test and anti-Mullerian hormone (AMH) test can be performed. The eight causative genes (HARS2, HSD17B4, CLLP, C10orf, ERAL1, TWNK, LARS2, and RMND1), all

have biallelic pathogenic mutations that support the diagnosis.<sup>1,7-9</sup> At this time, 18 people with LARS2-Perrault have reported 19 variations.<sup>8</sup> LARS2 mutations usually manifest as Perrault syndrome type 1.<sup>10</sup> There were only 15 cases with mutations in this gene as of 2018, and one of those cases had Perrault syndrome type 2.<sup>10</sup> There is the presence of neuropathic spectrum disorder (ANSD) with bilateral progressive SNHL caused by a CLPP homozygous mutation. On chromosome 19, the mitochondrial protease CLPP is encoded. By decreasing misfolded or damaged proteins, this protease regulates the integrity of mitochondrial proteins, preserving the cell's regular metabolic process. In Perrault Syndrome, CLPP peptidase activity is suppressed, resulting in mitochondrial dysfunction.<sup>4,11,12</sup> It is this dysfunction of mitochondrial protein homeostasis that causes Perrault Syndrome.<sup>13</sup> According to another study, people with TWNK mutation-caused Perrault Syndrome exhibit adult neurologic symptoms.<sup>14</sup>

However, about 60% of people with Perrault syndrome identified so far cannot be diagnosed at the molecular level.<sup>3,7,15</sup> Other literature says that the differential diagnosis of Perrault syndrome is Turner syndrome; about half of Turner patients have some degree of hearing disorders. Karyotype analysis can rule out this diagnosis.<sup>2</sup> According to a study of the literature, amenorrhea, elevated gonadotropin levels, and sensorineural hearing loss are prevalent symptoms of Perrault Syndrome despite its clinically significant degree of variability.<sup>16</sup> Uncertainty exists regarding the general pathogenetic link between sensorineural hearing loss and ovarian dysgenesis.<sup>6</sup> A small portion of the broad neurological involvement observed is sensorineural hearing loss in patients with Perrault Syndrome. Magnetic resonance imaging in Perrault Syndrome patients shows cerebral leukodystrophy, cerebellar hypoplasia, etc.<sup>6</sup>

Anti-mullerian hormone (AMH) levels increase between ages 4 and 8 but remain stable through early adulthood. However, throughout childhood, AMH levels are either undetectable or very low. It is unclear whether this indicates early follicular loss or impaired pre- or postnatal folliculogenesis. Despite low AMH levels, all girls go through puberty on their own. This means that although if it only contains a small number of follicles, there are probably enough of them to cause the partial development of secondary sexual characteristics and enable the expansion of the uterus.<sup>7</sup>

People with the 46, XX karyotype for Perrault Syndrome should be diagnosed if they have the following clinical symptoms and family history. There is a spectrum of ovarian dysfunction, from primary ovarian insufficiency (POI) to ovarian dysgenesis. POI

is the absence of menstruation before age 40, accompanied by an increase in follicle-stimulating hormone (FSH) levels and a decrease in serum estrogen concentration.<sup>3,17,18</sup>

A developmental disorder known as ovarian dysgenesis is characterized by loss of gonads and supporting cells (granulosa and theca cells, respectively), dysplastic, streaked, or no ovaries. With hypogonadotropic hypogonadism, the serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) increase along with a decrease in the concentration of estrogen in the blood. Upon ultrasound examination, the uterus appears primitive and prepubescent. Autosomal recessive inheritance is supported by family history, including possible parental relatives.<sup>3,17</sup>

From menarche through menopause, when endogenous production starts to diminish, ovarian hormones have a crucial role in regulating bone, cardiovascular, and hormonal health in women.<sup>19</sup> One percent of women have hypogonadotropic hypogonadism, either primary or secondary. In consultation with a pediatric endocrinologist, cyclic estrogen and progesterone may be given to adolescents with amenorrhea to induce withdrawal bleeding and mimic the menstrual cycle after the end of puberty as a treatment for POI.

The age of diagnosis and the level of function loss affect how an ovarian disorder is treated. If the patient has not hit puberty yet, estrogen replacement therapy can be administered to speed up the process. If the patient has entered puberty, oral contraceptive pills should be used to maintain bone health.<sup>2</sup> Estrogen replacement therapy is given until age 50, if there are no contraindications, to reduce the risk of osteoporosis and cardiovascular disease. If the patient intends to become pregnant in the future, she should think about assisted reproduction using donor eggs for in vitro fertilization (IVF) for POI. Before considering conception, women at risk for ovarian failure should investigate donor egg oocyte cryopreservation and measure their uterus.<sup>20</sup> In addition to employing donor eggs, gestational surrogacy can also be used due to premature ovarian failure and frequently underdeveloped uteruses.<sup>2,20</sup>

Treatment for hearing loss can range from more educational materials to cochlear implantation, depending on the severity of the loss and age at the time of loss. This is usually done in close collaboration with otolaryngologists, audiologists, and the child's school system. Regular monitoring for the development of hearing loss is essential. Opioid drugs, such as aminoglycosides and excessive noise, can exacerbate hearing loss. Family education is also needed by informing them that the hearing loss they experience

will be progressive. Perrault syndrome can cause fertility problems. It is essential to screen the proband's siblings so that early identification of the disease might help in timely intervention<sup>6</sup>.

The limitation of this study was that the diagnosis was only made based on the results of anamnesis and laboratory examination. We did not perform karyotype testing, so in this case, the transmissibility of the pathogen was not known to support the diagnosis. This case report provides an overview of the evaluation and how to diagnose patients with Perrault Syndrome. The fact that this case involved a rare hereditary ailment is advantageous. According to the literature, Perrault syndrome is a rare autosomal recessive genetic disorder that affects only about 40 families worldwide, so there is still little existing research related to this syndrome.

## CONCLUSION

An uncommon autosomal recessive hereditary condition called Perrault Syndrome is characterized by sensorineural hearing loss (SNHL) and ovarian dysfunction. Ovarian dysfunction includes primary ovarian insufficiency (POI) and gonadal dysgenesis. Perrault Syndrome has a 46, XX karyotype. Additional tests such as karyotyping and anti-mullerian hormone (AMH) tests are not recommended because 60% of people with Perrault Syndrome identified so far cannot be diagnosed at the molecular level. In consultation with a pediatric endocrinologist, cyclic estrogens and progesterone may be given to adolescents with amenorrhea to induce withdrawal bleeding and mimic the menstrual cycle. Before considering pregnancy, women at risk for ovarian failure should consider donor eggs, oocyte cryopreservation, and uterine size. Opioid drugs such as aminoglycosides and excessive noise, which can exacerbate hearing loss, are situations and agents that people with hearing loss should avoid.

## DISCLOSURES

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### Conflict of interest

There is no conflict of interest.

### Patient consent for publication

The patient agreed that her case is published in the report.

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### Author contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting, and approval for publication of this manuscript.

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