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Research Article

PERRAULT SYNDROME: THE GENETIC PUZZLE

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ABSTRACT:

Perrault syndrome (PS) is a rare and complex hereditary disorder characterized by sensorineural hearing loss (SNHL) and ovarian dysfunction, affecting both males and females. Named after French physician Louis-Charles Perrault, who first described it in 1951, PS manifests through many symptoms. Key genetic contributors include mutations in HSD17B4, HARS2, CLPP, LARS2, ERAL1, and TWNK, all associated with mitochondrial dysfunction. These genetic anomalies impact mitochondrial energy production, DNA maintenance, and cellular homeostasis, leading to symptoms of SNHL, ovarian dysfunction, and neurological abnormalities. This literature review explores the clinical presentations, genetic pathways, diagnostic challenges, and current treatment approaches for PS.

Methods: We conducted a comprehensive literature search for this literature review from April to June 2024 using PubMed and Google Scholar. Keywords included: Perrault syndrome, sensorineural hearing loss, ovarian dysfunction, primary ovarian insufficiency, HSD17B4, HARS2, CLPP, LARS2, ERAL1, and TWNK.

Conclusion: PS remains poorly understood due to its rarity and heterogeneity. This review highlights the importance of multidisciplinary approaches in diagnosis and management, considering the physical and psychological impacts on patients and their families. The necessity for increased research efforts, improved clinical awareness, and comprehensive care strategies is emphasized to better understand and treat this enigmatic condition.

Keywords: Perrault disorder, Perrault disease, HSD17B4, HARS2, CLPP, LARS2, ERAL1, TWNK

INTRODUCTION

Perrault syndrome (PS) is a rare and complex hereditary disorder that affects both men and women. This disorder was named after the French physician Louis-Charles Perrault, who first described it in 1951. It exhibits various symptoms, making it difficult for medical professionals to understand and assess fully. PS deserves great attention due to its substantial effects on physical, mental, and overall welfare. There exists a need to enhance diagnostic tools and investigate beneficial therapies for PS.[1]

Two of the major symptoms of PS include sensorineural hearing loss and ovarian dysgenesis. The hearing loss manifests in late childhood or early adulthood while ovarian dysgenesis manifests as premature menopause, amenorrhea, or barrenness.[2] Genetic variables play a critical part in the etiology of PS and anomalies in different qualities related to mitochondrial work have been distinguished as major supporters.[3] The basic aspects highlight the centrality of mitochondrial breakdown in the etiology of the disorder as these qualities play a role in mitochondrial vitality and cellular homeostasis. It is still unclear how these hereditary anomalies cause the clinical phenomenology of PS.

METHODS

We conducted a comprehensive literature search for this literature review from April to June 2024 using PubMed and Google Scholar. Keywords included Perrault syndrome, sensorineural hearing loss, ovarian

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dysfunction, primary ovarian insufficiency, HSD17B4, HARS2, CLPP, LARS2, ERAL1, and TWNK. The inclusion criteria were peer-reviewed articles, studies involving human subjects with confirmed diagnoses of PS, and research focusing on gene mutations, clinical manifestations, and management of these conditions.

EPIDEMIOLOGY

Studies involving the prevalence for PS are difficult to obtain the rarity of the syndrome. An estimated 100 individuals have been reported in literature.[4] Although reports come from many countries, the incidence is less than one in million. Accurately determining prevalence estimates is complicated by the possibility of under diagnosis due to the heterogeneity in clinical presentation and the rarity of PS.

DIAGNOSIS

Sensory Neural Hearing Loss (SNHL)

Both males and females with PS experience sensorineural hearing loss (SNHL), which can vary in severity (Table 1). Although hearing loss usually first appears in early childhood, it can progress and get worse over time. Pure tone audiometry and auditory brainstem response (ABR) testing are essential diagnostic methods for determining the degree of hearing impairment. The SNHL can vary in severity.[5]

Ovarian Dysgenesis

Primary amenorrhea is characterized by deficiency in secondary sexual traits and infertility because of streak gonads in females with PS.[6] Hormonal assessments usually show low estrogen and increased gonadotropin levels.

Other Symptoms

Although ovarian dysgenesis and hearing loss are the two primary symptoms of PS, some patients also experience other clinical symptoms. These could include ataxia, intellectual disability, and peripheral neuropathy, among other neurological symptoms. Those who are affected can vary widely in the presence and severity of these symptoms.[7]

Table 1: Clinical Features and Diagnostic Methods

Clinical Feature	Description	Diagnostic Method
Sensorineural Hearing Loss (SNHL)	Progressive hearing loss starting in early childhood	Pure tone audiometry, Auditory Brainstem Response (ABR)
Ovarian Dysfunction	Premature ovarian insufficiency, primary amenorrhea, infertility in females	Hormonal assessments, Ovarian ultrasound imaging
Neurological Symptoms	Ataxia, intellectual disability, peripheral neuropathy	Neurological assessments, MRI

GENETICS

ERAL1

Changes in ERAL1, which encodes a mitochondrial GTPase, have been ensnared in PS. ERAL1 is involved in mitochondrial ribosome assembly and its mutations result in impaired mitochondrial function (Table 2).[8]

HARS2

This gene encodes histidyl-tRNA synthetase which is fundamental for mitochondrial proteins. Changes in HARS2 are connected to PS with disconnected hearing issues and ovarian dysgenesis without noteworthy neurological association.

CLPP Gene

CLPP gene is located on located on chromosome 19 [19p13.3]. It encodes a mitochondrial peptidase which is involved in protein quality control. Changes in CLPP are related to PS and neurological manifestations such as ataxia and mental incapacity. Computational structural insight about CLPP and single-cell RNA sequence data for eight reported PS genes suggest a common cellular pathophysiology for this disorder, although there is some variance between every single gene. The pathophysiology of Perrault syndrome related to CLPP gene mutations involves mitochondrial dysfunction. The role of the CLPP gene is to encode the mitochondrial matrix ATP-dependent CLPP protease, a critical enzyme in the mitochondrial quality control system. This protease forms a part of a proteolytic complex that degrades misfolded or damaged proteins within the mitochondria. The mutations in this CLPP gene lead to three main effects First being the loss of function of the protease. As a result, the enzyme cannot properly degrade misfolded or damaged proteins. Second, the inability to degrade damaged proteins leads to their accumulation within the mitochondrial matrix. This change in mitochondria affects mitochondrial function, including energy production, oxidative phosphorylation, and regulation of apoptosis Third, cellular and molecular changes result in oxidative stress, energy deficiency and apoptosis. Mitochondrial dysfunction leads to reduced ATP production and increased production of reactive oxygen species which can cause cellular damage and apoptosis. This particularly affects cells with high energy demands, such as those in the ovaries, inner ear, and nervous system.[9]

HSD17B4 Gene

Mutations in the HSD17B4 gene located on chromosome 5 have been identified as one of the genetic causes of Perrault syndrome. This gene encodes an enzyme critical for peroxisomal beta-oxidation of fatty acids, a process essential for maintaining cellular lipid homeostasis and energy production. The peroxisomal enzyme known as multifunctional enzyme type 2 possesses three enzymatic activities: dehydrogenase activity, hydratase activity, and enoyl-CoA hydratase activity. Dehydrogenase converts hydroxysteroids to ketosteroids. Hydratase catalyzes the hydration of 2-enoyl-CoA to 3-hydroxyacyl-CoA. Enoyl-CoA hydratase is essential in the breakdown of very long-chain fatty acids. Mutations in this enzyme lead to accumulation of VLCFAs due to the failure to breakdown VLCFAs. Also, there will be defective steroid metabolism. Disruption in the conversion of hydroxysteroids to ketosteroids affects hormonal balance and steroid synthesis.[10]

TWNK Gene

The TWNK gene encodes for the "helicase protein twinkle". This protein is responsible for unwinding the double-stranded mtDNA and also for proper mitochondrial function. It is essential for the mitochondrial DNA replication and stability and copy number of mtDNA. Compound heterozygous missense mutations of the TWNK gene lead to mitochondrial dysfunction and multiple mtDNA deletion. The effects of impaired twinkle helicase function due to missense mutations in the TWNK gene include mitochondrial DNA depletion or deletions. Abnormal replication can lead to a decrease in mtDNA copy number or there will be an accumulation of large-scale deletions in mtDNA. This affects the cells, mainly those with high energy demands such as those of the auditory system, ovaries, and nervous system, experience mitochondrial dysfunction. Mitochondrial dysfunction produces more reactive oxygen species which leads to increased oxidative stress damaging cellular components by producing free radicals. Cellular energy deficiency results from decreased ATP production which can affect multiple tissues thus leading to the wide variety of symptoms.[11]

HARS2 Gene

Biallelic variants of HARS2 are associated with PS. It is a heterozygous missense mutation in HARS2. HARS2 encodes for a mitochondrial histidyl t-RNA synthetase which is important for mitochondrial protein synthesis. It links histidine to its cognate t-RNA in the mitochondrial matrix, which is an important step in translating mitochondrial DNA-encoding proteins. This gene mutation impairs normal mitochondrial protein synthesis leading to disrupted function of mitochondria. Mitochondria provide energy to demanding tissues like the inner ear and ovaries and due to the mutation, the process is disrupted, causing bilateral sensorineural hearing loss and ovarian dysgenesis. Hearing loss is due to dysfunctional mitochondria which leads to degeneration of cochlear structures. Ovaries need energy for oocyte maturation and HARS2 gene mutation leads to dysfunctional mitochondria leading to underdeveloped ovaries, primary amenorrhea, and infertility in females. The nucleotide substitution creates HARS p.L200V and alternate splicing leads to the deletion of 12 codons leading the affected members to carry 3 mutant transcripts. The aminoacylation activity of HARS2 P.V368L and HARS2 P.L200V is decreased, and the deletion mutant is not properly expressed in mammalian mitochondria.[12]

LARS2 Gene

Table 2: Gene Mutations and Their Impact on Perrault Syndrome

Gene	Location	Type of Mutation	Impact on Mitochondrial Function	Clinical Manifestations
TWNK	Chromosome 10 (10q24.31)	Missense, Nonsense	Mitochondrial DNA replication and stability	Progressive SNHL, ovarian dysfunction, neurological symptoms
CLPP	Chromosome 19 (19p13.3)	Missense, Frameshift	Protein quality control in mitochondria	SNHL, ataxia, intellectual disability, peripheral neuropathy
ERAL1	Chromosome 17 (17q11.2)	Missense	Mitochondrial ribosome assembly	SNHL, ovarian dysfunction, varied neurological symptoms
HARS2	Chromosome 5 (5q31.3)	Missense mutation	Mitochondrial protein synthesis	Bilateral SNHL, ovarian dysgenesis, primary amenorrhea
HSD17B4	Chromosome 5 (5q23.1)	Missense, Nonsense	Peroxisomal beta-oxidation of fatty acids	VLCFA accumulation, oxidative stress, SNHL, ovarian dysfunction
LARS2	Chromosome 3 (3p21.31)	Missense	Mitochondrial protein synthesis	SNHL, ovarian dysfunction, learning disabilities, cerebellar ataxia
SGO2[i]	Information Not Available	Missense, Nonsense, Splice site, Frameshift	Not well understood	Varied neurological and reproductive symptoms
CLDN14[ii]	Chromosome 21 (21q22.13)	Missense	Not well understood	SNHL, possibly other undetermined symptoms

LARS2 encodes leucyl-tRNA synthetase, another protein vital for mitochondrial function. Changes in LARS2 result in PS with changing degrees of hearing and ovarian issues. Some patients with PS exhibit neurologic features such as learning disability, cerebellar ataxia, and peripheral neuropathy. LARS2 C.1077delT leads to a frameshift at codon 360 of the 901-residue protein.[13] After HARS2, LARS2 is the second gene encoding mitochondrial tRNA synthetase. LARS2 encoded mitochondrial leucyl t-RNA synthetase attaches leucine to t-RNA for protein synthesis in mitochondria.[14]

MANAGEMENT

Hearing Loss

This requires a multidisciplinary team including an audiologist and otolaryngologist (Table 3). Also, interventions such as special educational resources, devices to amplify sound used in hearing aids, vibrotactile devices that translate sound into vibrations, and cochlear implantation, which is suitable for children older than 12 months with severe to profound hearing loss.[17] For mild to moderate hearing loss, routine audiological assessments should be done. No follow-up is needed for profound hearing loss.

Primary Amenorrhea

The treatment option for this involves a pediatric endocrinologist and treatment involves puberty induction and menstrual cycle mimicry to establish regular cycles and maintain bone health by adjustment of estrogen dose. In vitro fertilization is a consideration for women with gonadal dysgenesis. Puberty induction should be monitored every three months, and staging of pubertal development and estrogen dose adjustment is important. If estrogen replacement therapy is given, annual follow-up and bone density assessment for every five years approximately should be done. Oocyte cryopreservation can be an option as well.

Agents and Circumstances to Avoid

Avoid medications such as aminoglycosides due to ototoxicity. Avoid loud noise exposure to prevent worsening of hearing loss.

Evaluation of relatives at risk

It is important to evaluate siblings to identify early those who would benefit from intervention. Patients who benefit early are young children with profound hearing loss, and estrogen replacement to facilitate pubertal development in females with ovarian involvement and potential oocyte cryopreservation in primary ovarian insufficiency.[18]

Table 3: Management and Treatment Approaches

Manifestation	Management Approach
Hearing Loss	Audio logical assessments, hearing aids, vibrotactile devices, cochlear implants
Primary Amenorrhea	Pediatric endocrinologist consultation, puberty induction, estrogen dose adjustment, assisted reproduction techniques
Surveillance	Routine audiological assessments, monitoring pubertal development, annual follow-ups, bone density assessments
Relatives at Risk	Evaluation of siblings for early intervention, genetic counseling
Agents and Circumstances to Avoid	Avoid ototoxic medications like aminoglycosides, avoid loud noise exposure

FUTURE DIRECTIONS

A summary of recommendation for future studies is provided (Table 4).

Table 4: Future Directions in Research and Clinical Practice

Area	Potential Direction
Genetic Research	Next-Generation Sequencing (NGS) for novel gene mutation identification, gene mapping, and functional studies
Pathophysiology Studies	Investigating molecular mechanisms, developing animal models
Diagnostic Approaches	Improved diagnostic tools for early detection, enhanced genetic testing protocols
Therapeutic Strategies	Exploring gene therapy, identifying pharmacological interventions
Clinical Management and Support	Establishing multidisciplinary care teams, improving access to hearing aids and cochlear implants, fertility preservation techniques
Patient Registries and Databases	Creating registries for data collection, encouraging collaboration between researchers and healthcare providers
Awareness and Education	Increasing awareness among healthcare providers and the public, developing educational programs for patients and families

CONCLUSION

Because of its infrequency, complexity, and range of presentations, PS poses a substantial clinical challenge. PS is largely characterized by sensorineural hearing loss and ovarian dysfunction. First identified by the French physician Louis-Charles Perrault in 1951, the illness is worth studying for its effects on specific patients as well

as for the insights it might bring into the more general relationships between human health, mitochondrial function, and heredity. Mutations in several genes are linked to mitochondrial function, such as HARS2, LARS2, CLPP, TWNK, ERAL1, and HSD17B4 which are the genetic basis of PS. The clinical symptoms of PS are caused by a series of cellular dysfunctions that arise from the disruption of vital mitochondrial processes caused by these mutations. There are still a lot of unanswered questions about the precise biological mechanisms behind the syndrome and the development of targeted medicines, despite progress in understanding its genetic underpinnings.

To support early identification and intervention, improved diagnostic methods and increased clinical knowledge are desperately needed given the substantial negative effects of PS on health. To treat the wide-ranging impacts of the condition, multidisciplinary techniques involving audiologists, endocrinologists, geneticists, and other specialists are essential. The use of hormone therapies, auditory aids, and even assisted reproductive technologies as management measures highlight the importance of individualized and thorough care planning.

Furthermore, attention needs to be paid to the social and psychological aspects of having Perrault Syndrome. Communication difficulties, problems with infertility, and general quality of life are problems that patients and their families must deal with. Providing care that is integrated medically, psychologically, and socially is crucial to improving the quality of life and results for PS patients.

To sum up, even though Perrault Syndrome is uncommon, there is a great deal of clinical and research interest in this disorder. Prospective endeavors ought to center around the progression of genetic investigations to unearth the intricate pathophysiological mechanisms, and the creation of efficacious treatments, and guarantee that patients obtain prompt and all-encompassing care. In addition to helping those who are directly impacted, more knowledge and comprehension of PS will progress genetic and medical research.

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