MINI REVIEW

Perrault syndrome: One, none or a thousand diseases?

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Objectives: Perrault syndrome is a rare, genetically heterogeneous, autosomal recessive disorder whose traditional hallmarks are sensorineural hearing loss and ovarian dysgenesis. Its phenotypic spectrum has recently been broadened due to patients' molecular characterisation. The aim of this review is to recapitulate the state-of-the-art knowledge about Perrault syndrome's clinical presentation and to give clinicians new diagnostic perspectives.

Methods: We have made a careful review of the literature, including the most recent case reports and original investigations that provide insight into the clinical and molecular characterization of the syndrome.

Results: We have collected data on 71 patients (18 males and 53 females) with clinical and molecular diagnosis of Perrault Syndrome. In particular's data on sensorineural hearing loss, ovarian dysgenesis, neurological symptoms and other features (as marfanoid habitus, hypotonia and scoliosis) have been taken into consideration.

Conclusion: This review provides clinicians an overview on Perrault syndrome clinical and molecular aspects and underlines the importance of WES analysis in patients with typical phenotype, also highlights the importance of testing PS-associated genes in non-syndromic SNHL in male and prepuberal female patients.

Key Words: *Perrault syndrome, Ovarian dysgenesis, Sensorineural hearing loss, Neuropathy, Ataxia, Marfanoid habitus.*

INTRODUCTION

Perrault Syndrome (PS) was classically defined as a genetic heterogeneous autosomal recessive disorder whose hallmarks are sensorineural hearing loss and ovarian dysgenesis with elevated FSH and LH. The first clinical description of this association was made by Perrault and colleagues in 1951 [1]. In female PS patients ovarian dysfunction can range from primary amenorrhea to premature ovarian failure due to ovarian dysgenesis [2]; little is known about the gonadic function in male PS patients probably due to an under diagnosis of the cases. Indeed, many of them have been recognised as PS patients only after the diagnosis in their sisters. Only one case of azoospermia in a patient with mutations in CLPP has been described so far [3], but further studies on fertility in male PS patients are needed.

Sensorineural hearing loss (SNHL), generally bilateral, has been reported in both sexes with different degrees, from a mild late-onset progressive loss to a congenital severe loss.

In the last years, PS patients' molecular analysis identified several genes associated to the syndrome demonstrating a significant genetic heterogeneity and broadening its clinical spectrum. Since 2010, six causative genes have been identified: HARS2 (MIM 600783), HSD17B4 (MIM 601860), CLPP (MIM 601119), ERAL1 (MIM 607435), TWNK (MIM 606075) and LARS2 (MIM 604544). Mutations in these genes explain only the 40% of the causes of PS [4]; therefore the genetic bases of more than half of the cases remain unclear. Recently PEX6 (MIM 601498), RMND1 (MIM 614917), YARS (MIM 608323), TFAM (MIM 617156) and GGPS1 (MIM 606982) have been investigated in patients with only clinical diagnosis [5].

Apart from HSD17B4 and PEX6, that encode peroxisomal proteins, and GGPS1 which encodes for geranylgeranyl diphosphate (GGPP) synthase, localized in the cytosol, all the other known genes encode mitochondrial proteins suggesting a relevant role of mitochondrial dysfunction in PS pathogenesis.

Based on the presence of neurological manifestations, including cerebellar and peripheral nervous system involvement and mild intellectual disability [6], PS patients are classified into type I, non-progressive and without neurological disease, and type II, with progressive neurological disease [7]. Many authors recommend regular lifetime follow up in patients with diagnosis of PS type I because neurological symptoms could present later and the disease could evolve to PS type II [8].

Another classification of PS patients has been made, instead, based on the molecular cause of the disease identifying 6 different subgroups of PS from PRLTS1 to PRLTS6. Moreover, different mutations in some of the six PS genes may result in other disorders with clinical features that could overlap PS. No specific genotype-phenotype correlation has been established so far (Table 1).

TABLE 1

Genes known to be involved in Perrault syndrome

Genetic type	MIM entry	Gene	MIM entry	Location
PRLTS1	233400	HSD17B4	601860	5q23.1
PRLTS2	614926	HARS2	600783	5q31.1
PRLTS3	614129	CLPP	601119	19p13.3
PRLTS4	615300	LARS2	604544	3p21.31
PRLTS5	616138	TWNK	606075	10q24.31
PRLTS6	617565	ERAL1	607435	17q11.2

LITERATURE REVIEW

A systematic review was conducted following a literature search of PubMed to identify publications on PS. Search terms included: "Perrault syndrome" AND "PRLTS". Titles and papers were retrieved and reviewed. Articles were included in the review if they reported one or more cases of PS and were in the English language. One paper in French language was considered as is the first description of the syndrome by Perrault and colleagues [9].

We considered articles describing patients with a definite molecular diagnosis but not excluding articles where only a clinical characterization has been

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given. Due to the small number of patients already diagnosed with PS, we considered several case reports. Through this research we selected 39 papers; of them 26 were case reports.

RESULTS

From the review of the literature, we have collected data on 71 patients (18 males and 53 females) with clinical and molecular diagnosis of PS. The data are shown in. All the signs and symptoms presented in the table have been described at least in two unrelated patients. Of note, in some cases the molecular diagnosis was before the onset of the hallmarks clinical features, so hearing and ovarian function may not being assessed in some patients. For this reason, the total number of patients with SNHL does not correspond to the total number of patients; despite SNHL is a hallmark of the disease. Similarly, the total number of patients with ovarian dysgenesis does not represent the whole female cohort (Table 2).

TABLE 2

Clinical features of patients with molecular diagnosis of Perrault syndrome described in the literature. For each symptom, the number of affected patients and their percentage have been reported in bold on the total number of patients and not in bold on the total number of patients with a mutation in that gene. For the ovarian dysgenesis, only the female cohort has been considered. SNHL: sensorineural hearing loss; POF: premature ovarian failure.

			HSD17B4 3 patients		HARS2 19 patients		CLPP 13 patients		LARS2 18 patients		TWNK 16 patients		ERAL1 2 patients		Tot. affected 71 patients	
SNHL	Onset	Prelingual	0	-	3	(16%)	1	(8%)	5	(28%)	0	-	0	-	**9/71**	**(13%)**
		Postlingual	3	(100%)	15	(79%)	11	(85%)	13	(72%)	16	(100%)	2	(100%)	**60/71**	**(85%)**
	Course	Progressive	3	(100%)	17	(89%)	11	(85%)	17	(94%)	16	(100%)	2	(100%)	**68/71**	**(96%)**
		Non progressive	0	-	0	-	0	-	1	(5%)	0	-	0	-	**1/71**	**(1%)**
Ovarian dysgenesis	Primary amenorrhea		1	(33%)	3	(16%)	4	(31%)	8	(44%)	11	(69%)	0	-	**27/53**	**(51%)**
	Secondary amenorrhea		0	-	0	-	0	-	2	(11%)	2	(12%)	0	-	**4/53**	**(8%)**
	Oligomenorrhea/POF		0	-	4	(21%)	7	(54%)	2	(11%)	0	-	1	(50%)	**14/53**	**(26%)**
	Hypotrophic uterus		1	(33%)	0	-	0	-	7	(39%)	3	(19%)	1	(50%)	**12/53**	**(23%)**
Neurological symptoms	Peripheral neuropathy		1	(33%)	0	-	1	(8%)	1	(5%)	6	(37%)	0	-	**19/71**	**(27%)**
	Primary amenorrhea		2	(67%)	0	-	1	(8%)	0	-	14	(87%)	0	-	**17/71**	**(24%)**
	Nystagmus		0	-	0	-	0	-	0	-	10	(62%)	0	-	**10/71**	**(14%)**
	Cognitive impairment		2	(67%)	0	-	0	-	2	(11%)	1	(6%)	0	-	**5/71**	**(7%)**
	Spasticity		0	-	0	-	2	(15%)	0	-	1	(6%)	0	-	**3/71**	**(4%)**
	Dysarthrya		1	(33%)	0	-	0	-	0	-	6	(37%)	0	-	**7/71**	**(10%)**
	Epilepsy		0	-	0	-	1	(8%)	0	-	1	(6%)	0	-	**2/71**	**(3%)**
	Ophtalmoplegia		0	-	0	-	0	-	0	-	5	(31%)	0	-	**5/71**	**(7%)**
Other features	Hypotonia		0	-	0	-	0	-	0	-	3	(19%)	0	-	**3/71**	**(4%)**
	Marfanoid habitus		1	(33%)	0	-	0	-	3	(17%)	0	-	0	-	**4/71**	**(6%)**
	Scoliosis		0	-	0	-	0	-	1	(5%)	1	(6%)	0	-	**2/71**	**(3%)**
	References		[7], [9]		[7], [10]–[13]		[3], [5], [11], [14], [15]		[3], [8], [11], [16]–[21]		[3], [11], [22]–[27]		[28]			

assessed (data not shown in table 2). Only Kume and colleagues described the case of a female patient, carrier of mutations in TWNK, presented ataxia and SNHL with adult onset and no confirmation of gonadal dysfunction [10].

Our review of the literature shows that the severity of the organ involvement can be linked to the causative gene. SNHL due to mutations in HARS2, LARS2 and CLPP can present also as pre-lingual, even congenital, and profound. Ovarian dysgenesis can present as primary amenorrhea but mutations in genes such as ERAL1 and CLPP may mostly determine premature ovarian failure or irregular menses. Neurological features that are common and a hallmark for the diagnosis of PS type II are a characteristic of TWNK-PS. In the cohort of 16 patients with mutations in TWNK herein collected, 87% presented peripheral neuropathy, about 60% presented nystagmus and about 30% presented dysarthria, ataxia and/or ophtalmoplegia. These findings strongly support the search for TWNK mutations in type II PS patients.

When patients fulfill all the clinical criteria for PS, it is likely to detect a pathogenic variant in one of the known genes, most frequently LARS2 (19%), CLPP (16%) and TWNK (12%) [11]. However, in approximately 60% of patients with a clinical diagnosis of PS it is impossible to obtain a molecular diagnosis [12]. Therefore, Whole Exome Sequencing (WES) can be considered in patients lacking a genetic diagnosis, especially when the clinical presentation is atypical, in order to provide patients and their families streamlined care, prognostic information and accurate recurrence risk advice.

DISCUSSION

Perrault syndrome has significant clinical heterogeneity and the most recent findings have shown the involvement of different tissues, organs or systems. Both SNHL and ovarian dysgenesis, the typical hallmarks of the syndrome, can present different degrees of severity.

Due to this heterogeneity, there may be many undiagnosed cases, especially when the clinical picture is not straightaway suggestive of the syndrome. For example, a non-syndromic sensorineural hearing loss in a male patient is difficult to correlate to PS. Another issue is represented by SNHL in prepuberal females or in females who do not present primary amenorrhea. Among the 53 female patients reported in our cohort, 45 had primary or secondary amenorrhea or premature ovarian failure. The remaining patients without signs of ovarian dysgenesis are familial cases who received the diagnosis of PS during the childhood when only hearing function could be

WES has also led to the identification of new variants both in known and new candidate genes. For example, a homozygous pathogenic variant in YARS, encoding a tyrosyl-tRNA synthetase and previously related to Charcot-Marie-Tooth neuropathy, has been found in a patient with profound congenital hearing impairment, primary amenorrhea, progressive retinal degeneration, agenesis of the corpus callosum and liver disease [13-15]. Other genes that have recently been candidate as causative of Perrault syndrome are TFAM and GGPS1. The former encodes a cofactor of the mitochondrial transcriptase and it has been associated to PS with cognitive impairment. The latter encodes an enzyme required for protein prenylation and it has been associated to PS with slowly progressive SNHL, moderate myopathy, oligomenorrhea and premature ovarian failure [14]. The role of mitochondria is particularly interesting, given the amount of energy required by neurons and cells with sensory and endocrine activities that are likely to be significantly damaged by mitochondrial dysfunction [16]. Moreover, mitochondrial diseases often involve the same tissues affected in PS, usually in a more severe and diffuse form. All these findings may suggest a possible interpretation of Perrault syndrome as a milder phenotype caused by genes previously associated to very different, often mitochondrial, syndromes [17].

For instance, LARS2 is known as causative of a lethal multisystem metabolic

disorder characterized by severe lactic acidosis, hydrops and sideroblastic anemia, impaired coagulation and cardiac, pulmonary and renal involvement [18-21]. Moreover, two new genes recently associated to PS, RMND1 and PEX6, are respectively responsible for a severe multisystem disorder called Combined Oxidative Phosphorylation Deficiency (COXPD11) [22-26] and Zellweger syndrome, characterized by severe neurologic dysfunction, craniofacial abnormalities and liver dysfunction [27,30].

The definition of the role of mitochondrial disfunction is important for the eventual future application in Perrault syndrome of therapeutic strategies acting on mitochondrial pathways and already currently used for the therapy of mitochondrial diseases such as Leber's Hereditary Optic Neuropathy (MIM 535000) [31].

CONCLUSION

In conclusion Perrault syndrome is an often undiagnosed syndrome characterized by large heterogeneity in clinical features and genetic loci. Clinical suspicion can lead to diagnosis and molecular definition, important for both clinical management of patients and accurate assessment of recurrence risk within a family. The precise diagnosis could be reached in more cases if clinicians take in account PS also in atypical cases where the hallmarks clinical features are missed and by including PS-associated genes in the molecular analysis for non-syndromic post-lingual SNHL.

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DISCLOSURES

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