

## Case Reports

### Perrault Syndrome with Marfanoid Habitus in Two Siblings

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**Abstract.** *Background:* Familial pure gonadal dysgenesis with 46 XX karyotype and sensorineural deafness constitutes a rare autosomal recessive syndrome described initially by Perrault in 1951. The spectrum of the disease remains undetermined. Families with additional newer findings are regularly reported.

*Case:* We report two siblings with gonadal dysgenesis, progressive sensorineural deafness, Marfanoid body proportions and skeletal features, and a normal female karyotype. The diagnosis of Perrault syndrome was made. Abnormal body proportions including a longer arm span, shorter trunk, high arched palate, long slender fingers and positive thumb and wrist sign were observed. The siblings did not have any cardiac or ocular features of Marfan's syndrome.

*Conclusion:* The report of the siblings adds to the expanding spectrum of findings in Perrault syndrome.

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**Key Words.** Perrault syndrome—Primary amenorrhea—Sensorineural deafness—Familial gonadal dysgenesis

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#### Introduction

The finding of sensorineural deafness and ovarian dysgenesis in two sisters formed the basis of the initial description of the Perrault Syndrome by Perrault in 1951. The initial family described included a cousin with isolated sensorineural deafness without gonadal dysgenesis.<sup>1</sup> Subsequently Pallister and Opitz<sup>2</sup> reviewed the 14 known cases and concluded that the syndrome was an uncommon autosomal recessive trait with gonadal dysgenesis in female homozygotes and facultative deafness in male and female homozygotes.

We report two adolescent siblings born to non-consanguineous parents with Perrault syndrome. Additionally, both sisters had Marfanoid features.

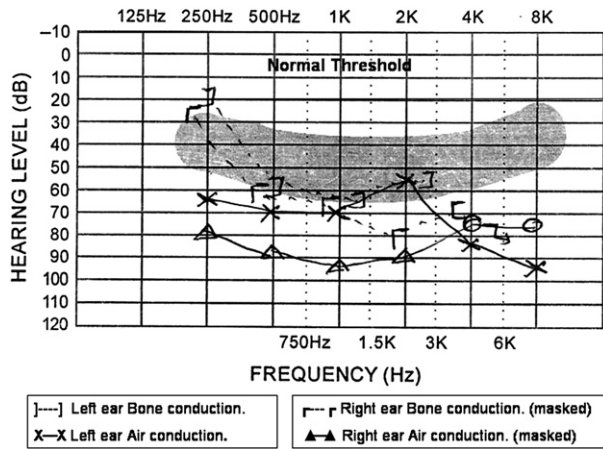
#### Case 1 (Born 1986)

The older sibling presented to the Ear, Nose and Throat (ENT) department in our hospital with complaints of progressive decline in hearing over the last 2 years. Her assessment in the ENT department which included a pure tone audiometry (Fig. 1) was suggestive of a severe bilateral sensorineural hearing loss. She was advised to use a hearing aid. At the age of 16 years she was brought to the gynecology clinic with complaints of primary amenorrhea and failure to develop any secondary sexual characteristics. At that point she underwent blood investigation which revealed elevated gonadotropins. Ultrasound of the abdomen did not visualize the ovaries. A karyotype done revealed a normal female (46XX) karyotype. She was initiated on estrogen replacement and developed withdrawal bleeding after 9 months of therapy. Later she was switched over to a low dose oral contraceptive containing both estrogens and progesterone. At the age of 19, when she was first seen in our clinic, she was 169 cm tall and weighed 56 kg. Her body proportions were Marfanoid with an arm span of 182 cm and an upper segment:lower segment (US:LS) ratio of 0.78:1. She had long slender fingers with a positive wrist and thumb signs. Her breast development was Tanner stage 3 and had pubic hair of Tanner stage 3. She had no somatic features of Turner's syndrome. The eye, neurological, and cardiovascular systems were normal. The thyroid gland was diffusely enlarged.

She was the older of two siblings born to non-consanguineous parents. Her mother was 161cm tall and had attained menarche at the age of 16. Her mother had six female siblings, all of whom had a delay in the age of menarche (16–18 years). Her father

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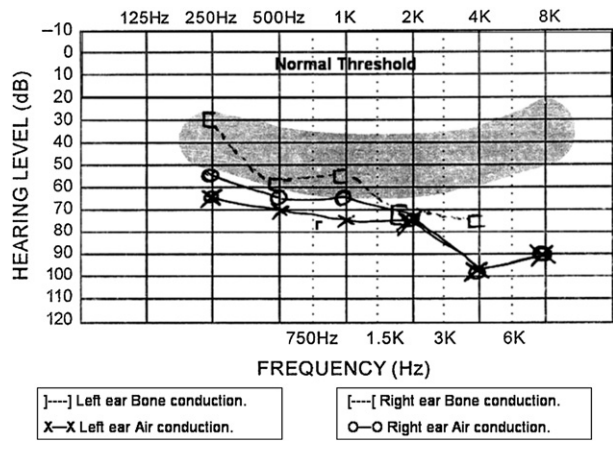


**Fig. 1.** Audiogram of Patient 1 revealed decreased thresholds for both air conduction (AC) and bone conduction (BC) suggestive of bilateral severe sensorineural deafness. The upper shaded area represents normal thresholds. The lower ovoid shaded area is the “speech banana,” which represents the spectrum of speech frequency of a normal conversation.

was 168 cm tall and started shaving at the age of 18 years. Mid parental height was 164.5cm. Results of the laboratory tests are detailed in Table 1.

**Case 2 (Born 1990)**

The younger sibling was born by normal vaginal delivery at a local hospital. She had no perinatal or childhood illnesses. She had been brought to our clinic at the age of 16 years with complaints of primary amenorrhea and lack of secondary sexual development. She also complained of a progressive decline in hearing over the last 2 years. She was 162 cm tall (mother’s height: 161cm, and mid parental height: 164.5cm) and weighed 40 kg. She also had an arm span which was 10 cm longer than her standing height and an US:LS ratio of 0.78:1. She had long slender fingers with high arched palate, positive thumb and wrist signs. She had no secondary sexual



**Fig. 2.** Audiogram of Patient 2 revealed decreased thresholds for both air conduction (AC) and bone conduction (BC) suggesting a moderately severe to profound bilateral sensorineural deafness. Description of the shaded areas is same as in the previous figure.

development, with a breast staging of Tanner 1 and no pubic or axillary hair. Her gonadotropin levels were elevated (FSH: 34.8 IU/L and LH: 18.0 IU/L) with a normal karyotype. Results of her investigation are given in Table 1. Ultrasound of the pelvis could not detect the ovaries on both sides; otherwise she had normal female internal organs. ENT evaluation was done and pure tone audiometry suggested bilateral moderately severe to profound sensorineural deafness (Fig. 2) and she was advised to use a hearing aid. For initiation of pubertal changes we started her on small doses of ethinyl estradiol.

**Discussion**

The presentation of the siblings with primary amenorrhea, infantile female phenotype, underdeveloped genitalia, normal female karyotype, and significant sensorineural deafness was consistent with the diagnosis of Perrault syndrome as described by Pallister and Opitz.<sup>2</sup>

Nishi et al<sup>3</sup> reviewed 21 patients from the literature, including two of their own, in eight families and documented 16 females with ovarian dysgenesis and severe sensorineural deafness. The other three were male family members with normal testicular functions and deafness. One woman had isolated gonadal dysgenesis and a 4-year-old girl had deafness. Her ovarian functions were not evaluated. All patients had a normal karyotype.

The onset of deafness was noted from 10 months to 31 years. Though all patients except one had deafness by the age of 10 years the onset of deafness in one patient was in the early thirties. The absence of deafness

**Table 1.** Laboratory Values in Both Patients

	Case 1	Case 2	Normal Values
Serum FSH (in IU/L)	45.6	34.8	Follicular -2.8–11.3 IU/L Luteal -1.2–9.0 IU/L Midcycle -5.8–21.0 IU/L
Serum LH (in IU/L)	25.3	18.0	Follicular -1.1–11.6IU/L Luteal 0.0–14.7IU/L Midcycle -17.0–77.0IU/L
Serum TSH (in IU/L)	1.84	3.25	0.3–4.5 IU/L
Serum Prolactin (in pmol/L)	734.7	839.1	82.6–1086 pmol/L
Karyotype	46 XX	46 XX	—

in a given patient with 46 XX gonadal dysgenesis at presentation does not rule out Perrault syndrome because the patients could develop deafness much later at an older age. Most patients had moderate to severe sensorineural deafness with mutism among patients with early onset of deafness. Ear, nose, and throat examination were reported as normal with pure tone audiometry showing a flat configuration.<sup>4</sup>

The common pathogenetic relationship between ovarian dysgenesis and sensorineural deafness is unclear. Sensorineural deafness appears to be a part of a more widespread neurological involvement seen in a subset of patients with Perrault syndrome. Gottschalk et al<sup>5</sup> reviewed neurological data from 28 patients from literature with Perrault syndrome. In eight of them more extensive neurological involvement was reported. The involvement included mental retardation, ataxia, hypotonia, weakness, spastic diplegia, and epilepsy. Cerebellar involvement confirmed by CT scan was seen in one 18-year-old patient. Linssen et al<sup>6</sup> reported distal sensory neuropathy in three patients with Perrault syndrome. The patients had additionally mild mental retardation, dyspraxia and fine choreotic movements. Fiumara et al<sup>7</sup> reported four (two sets of siblings) patients with PS and severe peripheral nervous involvement. Both sets of siblings had clinical, neurophysiological and pathological data consistent with hereditary sensorimotor neuropathy Type 1. It does appear that neurological involvement appears later and may be age related. Sensorineural deafness may represent the first step of a more widespread degeneration of the peripheral and central nervous system.

However, it does become apparent from literature that a subset of patients may not develop any further neurological involvement. The first patient with the disease followed up to the age of 35 did not show any evidence of additional neurological involvement. Fiumara et al<sup>7</sup> proposed that two different forms of PS might exist, both being autosomal recessive. Type 1, the original form, appears static and non-progressive. The type 2 form of PS is associated with progressive neurodegeneration. Both our patients have no additional features of neurological involvement except for involvement of the eighth cranial nerve. However, it may be prudent to observe development of further neurodegeneration before classifying them.

In the initial description of 21 patients by Nishi et al,<sup>3</sup> the height of the patients varied from 99cm (at age 19) to 183 cm. Seven of the twenty for whom the height was available were below the 5th percentile for age. Patients with more advanced neurological disease appear to be shorter than the patients with non-progressive PS. Our patients were taller than the expected height based on the mid parental height. Growth hormone status has not been systematically evaluated in patients with PS.

An assessment of growth hormone (GH) levels would require that the patients to be primed with gonadal steroids before a GH stimulation test is performed. The widespread neurological involvement may include hypothalamic dysfunction, accounting for short stature in a subset of patients.

The findings of abnormal body proportions noted in our patients have not been previously reported. In a report by Bosze et al,<sup>8</sup> body proportions was reported in two siblings. The heights were 160 and 162 cm, arm spans were 162 and 164 cm and US:LS ratios were 0.76:1 and 0.78:1 respectively. Nishi et al,<sup>3</sup> in their description of 21 patients, noted that two patients had high arched palate. Both our siblings had abnormal body proportions with high arched palate and long fingers with positive wrist and thumb sign.

The genetic basis of PS is still unclear. The disease may represent a heterogeneous group of genetic disorders with multiple gene defects. The mapping studies were done by Lipovich et al<sup>9</sup> on the patients family first described by Pallister and Opitz<sup>2</sup> which has mapped the defect to the long arm of chromosome 5. Further studies on other families are awaited to confirm the homogeneity of the genetic defect and the underlying molecular defect.

## Conclusion

Perrault syndrome represents a spectrum of disorders characterized by 46 XX gonadal dysgenesis and neurological involvement. The earliest neurological involvement is the detection of sensorineural deafness. Features of Marfan's syndrome may be part of the extended phenotype or may represent a coincidence.

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