

PERRAULT'S SYNDROME: A CLINICAL AND GENETIC INVESTIGATION OF THREE SISTERS

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Abstract - Perrault's syndrome (P.S.) is rare. The combination of gonadal dysgenesis and hearing loss was accompanied by 46,XX karyotype in three sisters with parental consanguineous marriage. Genetic investigation revealed normal female karyotype, positive Barr and negative fluorescence (F)-bodies, which was confirmed by molecular study on the basis of fluorescence in situ hybridization (FISH), with application of Xcen probe, showing the presence of two signals in 95% of the cells of these 3 Iranian sisters. The pedigree showed parental consanguinity (first cousin) with an autosomal mode of inheritance for both Perrault's syndrome and hearing loss. These findings together with normal thyroid function, serum prolactin, high level of serum gonadotropins is similar to the menopausal period in all 3 sisters. Estrogen and progesterone were recommended for all 3 sisters. This combined therapy led to menstruation and after a few months their breasts were normally developed. For further management cochlear implantation, speech therapy and training courses were suggested in order to improve hearing and intellectual abilities.

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presenting with the same pattern of clinical manifestations, including ovarian dysgenesis and sensorineural deafness, has also been published (4). A case of 2 sisters lacking pubertal development and hearing impairment was also reported as an uncommon syndrome in 1985 (5). Other reports in the literature include: (a) the case of 2 Oriental sisters with XX- chromosome complement and bilateral sensorineural hearing loss and (b) the case of 2 Japanese girls, (6, 7, 8). With sensorineural deafness, ovarian dysgenesis and Perrault's syndrome (6, 7, 8), altogether, 24 cases of Perrault's syndrome have been reported in the literature (3, 10, 13) so far.

The purpose of present investigation was to perform genetic investigation, including cytogenetics and molecular cytogenetics (FISH), together with clinical and paraclinical studies in 3 Iranian sisters with gonadal dysgenesis and hearing loss.

INTRODUCTION

The importance of gonadal dysgenesis prompted Perrault and his colleagues in 1951 to publish the first report on two sisters with and additional sensorinerural deafness (1). Further studies and chromosomal investigations revealed normal female karyotype (46,XX) and deaf mutism (2). So far 3 cases with ovarian dysgenesis and sensorineural deafness, having an autosomal recessive mode of inheritance, have been reported (3). A report on the case of two other sisters,

MATERIALS AND METHODS

The karyotyping of 3 sisters with Perrault's syndrome was performed on the lymphocytes stimulated with phytohaemagglutinin (PHA) and by adding colchicine. Harvesting was followed by hypotonic treatment and preparation of slides, and staining was carried out on the basis of giemsa banding technique (GTG). The karyogram was prepared according to the chromosome nomenclature (ISCN) (11). The analysis of sex chromatin, including Barr-body and fluorescence

body, was performed on the hair root cells. For performance of fluorescence in situ hybridization (FISH), on peripheral blood the standard protocol was used with biotin-lated DNA-Probes including Xcen (12). Slides were denatured with 70% formamide and dehydrated in 70, 90 and 100% ethanol. Cells were hybridized with probes and incubated. Then slides were rinsed in 50% formamide. Detection and amplification of hybridization signals was performed with Avidin/FITC and goat anti-Avidin-antibodies. The chromosomes were stained with Propidiumiodide/DAPI, the slides examined with a fluorescence microscope (Leitz) and the cells were analysed and photographed.

The audiometric examination was performed on both ears with the use of ACS-A 27 and OBA 22-822 Medsen audiometer. The patients were three sisters whose parents and maternal grandparents were first cousins. The patients included a 26 year old girl as the proband and two sisters 20 and 18 years old, their heights being 155, 166 and 166 centimeters respectively (Table 1).

RESULTS

Three sisters, all with primary amenorrhea, lacking secondary sexual manifestations, but with normal height and skeletal system were clinically and genetically investigated (Tables 1-4).

Case 1

Case 1 was the proposita for the Perrault's syndrome in the pedigree; she had hypoplastic uterus, streak and small ovaries, with normal X-ray of sella turcica. Audiometry showed bilateral sensorineural hearing loss (Table 4, Fig 1, 4).

Psychological investigation showed a mild mental retardation with IQ=64 (Table 1). The routine laboratory tests revealed stage zero for the thyroid size, with a normal function. Serum gonadotropin level was found to be 42 and 59.2

IU/ml for FSH and LH, respectively; serum prolactin was normal. Progesterone challenge was negative and the combined therapy of estrogen and progesterone led to menstruation and development of both breasts (Table 2). On the other hand, genetic investigation revealed an apparently normal female karyotype, positive Barr body, negative F-body, and the two hybridized signals of both X-chromosomes on FISH (Table 3).

Table 1. Clinical finding in 3 sisters with perrault's syndrome

Case No	Age (Yr.)	Height (cm)	Ultra Sonography (uterus & ovaries)	X-Ray (sella turcica)	Type of hearing loss	Status of IO/ mental retardation
1	26	155	U: hypoplastic O: streak with Dysgenesis	Normal	Bilateral Sensorineural	IQ = 64 Mild retarded
2	20	166	U: hypoplastic O: streak with Dysgenesis	Normal	Bilateral Sensorineural	IQ = 102 Normal
3	18	160	U: hypoplastic O: streak with Dysgenesis	Normal	Bilateral Sensorineural	IQ = 74 border line

U: uterus; O: ovaries

Table 2. Para - Clinacal finding in 3 sisters with perrault's syndrome

Case No	status of thyroid	Throid function (T.F.T)	Serum - gonadotropin's level (IU/ml)		Progesterons challenge
			FSH	LH	
1	Stage 0	Normal	42	59.2	Negative
2	Stage 1 _A	Normal	38	64	Negative
3	Stage 1 _A	Normal	54	59	Negative

Table 3. Genetics findings in 3 sisters with perrault's syndrome

Case No	Cytogenetics*	Sex-chromatin		FISH** Xcen-Probe (2X-signals)	Parental Consanguinity	Genetic mode of inheritance
		Barr-body	F-body			
1	46, XX	+	-	46,XX (2X-signals)	First Cousin	A.R.***
2	46, XX	+	-	46,XX (2X-signals)	First Cousin	A.R.
3	46, XX	+	-	46,XX (2X-signals)	First Cousin	A.R.

* Presentative of major cell line; ** Fluorescence in situ hybridization (FISH) with application of X-centromere - probe (in 30 mitoses and 100 interphases for each)

*** Autosomal recessive (A.R.)

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Table 4. Audiologic, clinical and C.T. Scan findings in 3 sisters with Perrault's syndrome and progressive hearing loss.

Case No	Clinical* C.T.Scan	Average threshold for the descending type curve		Speech discrimination Score (SDS-test)
		at the first test(1988)	at latest(1997)	
1	Normal	250,500+1000 H2(PTA) in 80-95 dB	250,500+1000 H2(PTA)in 100-110 db	0%
2	Normal	250,500+1000 H2(PTA) in 80-95 dB	250,500+1000 H2(PTA)in 90-120 db	0%
3	Normal	500,1000+2000 H2(PTA) in 73.3 dB	500,1000 in 70 dB	52% (in best condition) 20% (in the most recent test 1997)

* Presentative of major cell line; ** Fluorescence in situ hybridization (FISH) with application of X-centromere - probe (in 30 mitoses and 100 interphases for each)
*** Autosomal recessive (A.R.)

Serial, audiologic investigation from 1988 to 1997 showed a descending curve. The onset of progressive hearing loss was from the age of two. Speech discrimination was 0% (Table 4, Fig 4).

Case 2

This case was clinically, paraclinically and genetically, similar to case 1 except that her IQ was 102 and no mental retardation was observed in her (Tables 1-4, Fig 5).

Case 3

Case 3 had a borderline IQ of 74. This case was also clinically, paraclinically and genetically similar to her sisters (Case 1 and 2). However speech discrimination was revealed to be 52% in the best condition and 20% in the most recent test (Table 4, Fig 6).

DISCUSSION

The abnormalities of sexual development could interfere with the patient's life style. Advances in human genetics are changing the physician's approach to such problems. The major aim is to rule out any chromosomal aberrations, which may interrupt sexual development.

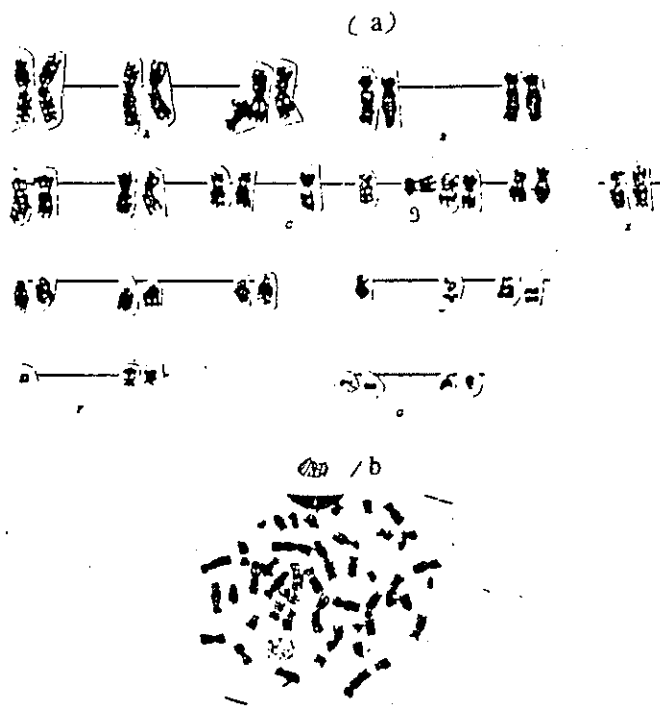


Fig. 1. A karyogram presenting a normal female karyotype (case 1)

- a) Karyogram and the metaphase spread
b) The metaphase spread



Fig. 2. Fluorescence in situ hybridization (FISH) with application of X-Cen probe. The arrows demonstrate 2 signals of two X-Chromosomes

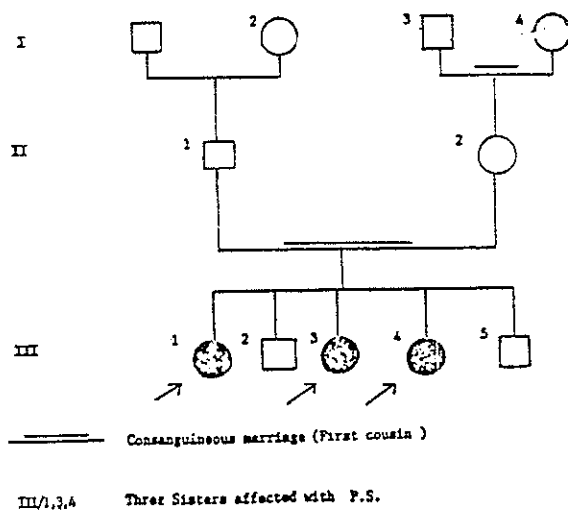


Fig. 3. Partial pedigree of the 3 sisters with perrault's syndrome

As the cytogenetic data show (Table 3), the normal female karyotype (46,XX) is confirmed by the results obtained from sex chromatin and FISH studies, positive Barr body, negative F-body and the presence of two signals on X-chromosomes. The pedigree of the patients' family with parental consanguinity was indicative of an autosomal mode of inheritance. However, genetic findings supported the involvement of a single gene as a fundamental disorder with an autosomal recessive (AR) control in the parental genetic make up which could be inherited with a probability of 25% to the offsprings at each gestation.

The pedigree of this family shows that all 3 sisters (Cases 1,2,3) are the offsprings of a consanguineous marriage (first cousin) (Fig 3). The AR-mode of inheritance is in keeping with previous reports (3,4,5,7). The normal situation in

all 3 sisters with regard to thyroid- function, levels of serum prolactin and the high level of serum gonadotropins was at the same level as that of the menopausal period.

The ovaries of none of the 3 cases responded to gonadotropins, and the ultrasonography was indicative of a hypoplastic uterus and ovarian dysgenesis. This would suggest the existence of a primary failure in all 3 sisters. With administration of progesterone, no success was gained, but the use of combined tablet therapy, composed of estrogen and progesterone, led to menstruation and after a few months the breasts of all 3 sisters developed normally. The audiometric examination, with the follow up study of the impedance was indicative of a normal tympanometry and the absence of acoustic reflex. Speech discrimination was 0.0% in cases 1 and 2.

Although the bilateral sensorineural hearing loss with a descending type curve was found in all 3 sisters (Table 4), a different range of threshold was seen in case 3 with 73.3 dB in the right ear and 70 dB in the left ear at the first hearing test (1988). This was followed by 110 dB in the right ear and 90 dB in the left ear at the last hearing test (1997), with 52% speech discrimination score (SDS) in the best condition and 20% SDS in the last test and the recruitment by stapedial reflex in the left ear.

The patients' parents and one of their brothers did not complain of hearing dysfunction; clinical evaluation and audiometric examination revealed normal patterns in them.

According to the pedigree, the inheritance of hearing disorder could be autosomal recessive as a result of parental consanguinity. Cochlear implantation was suggested for all 3 sisters; speech therapy and specific courses were organized for improving their hearing and intelligence. It is important for such patients and their family members who might be at high risk to consider the following recommendations:

1. To rule out any chromosomal abnormalities, in order to apply a proper therapeutic

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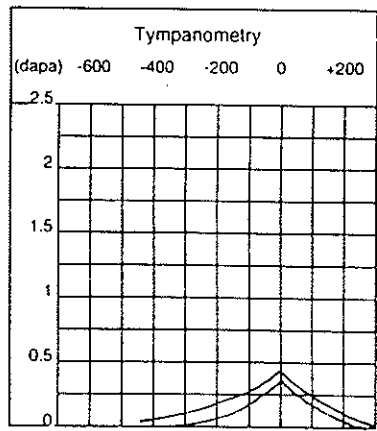
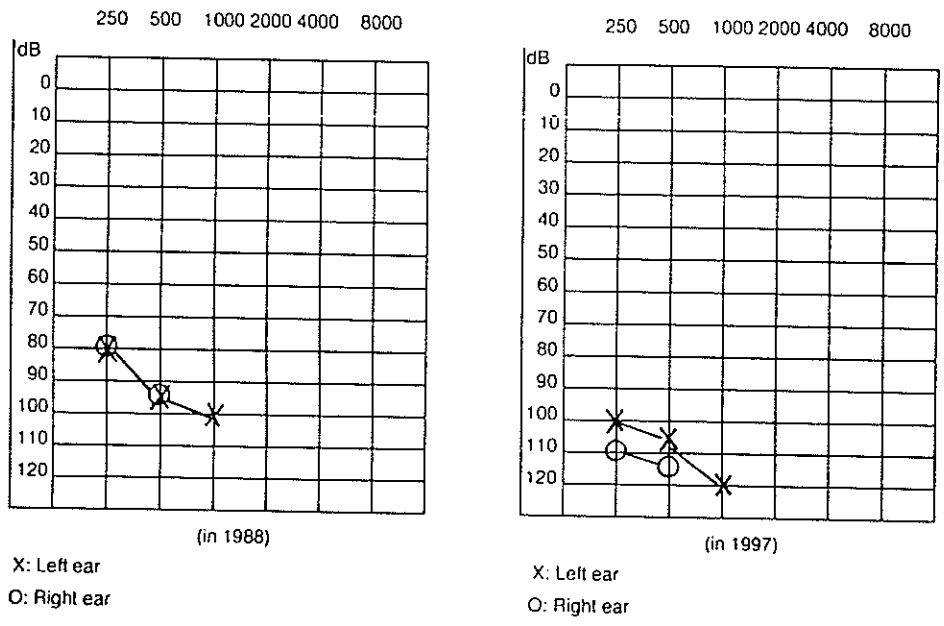


Fig. 4. Tonal audiometry showing sensorineural hearing loss (case 1)

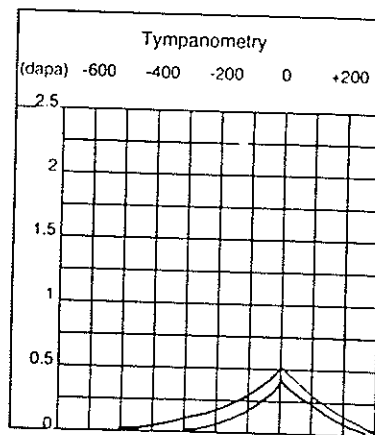
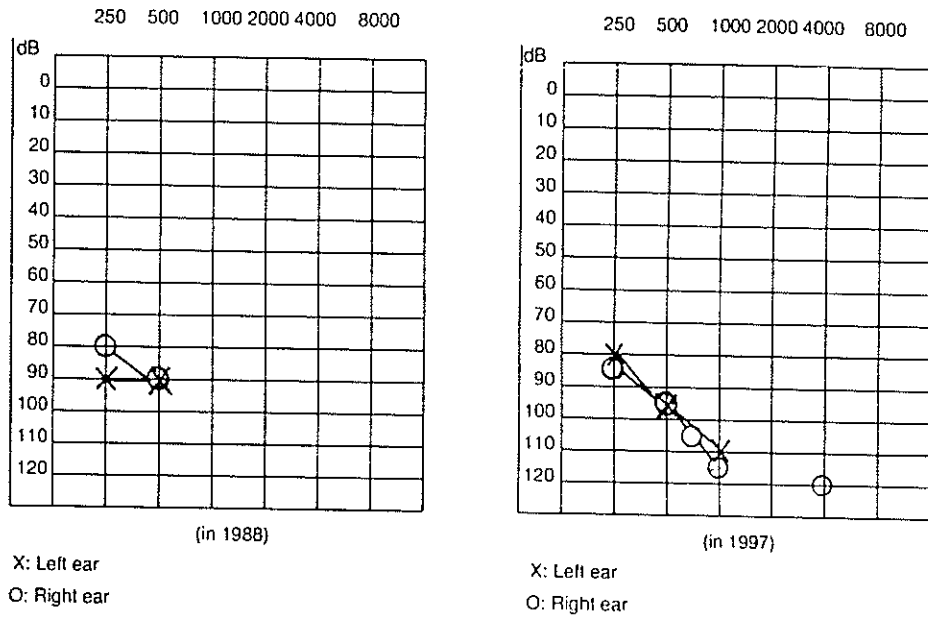
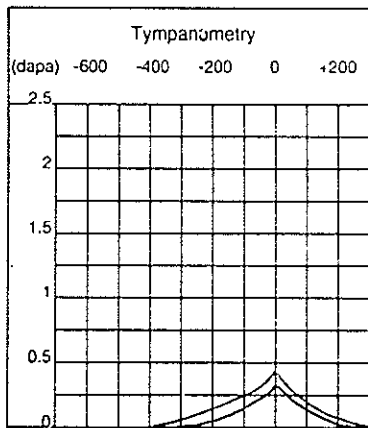
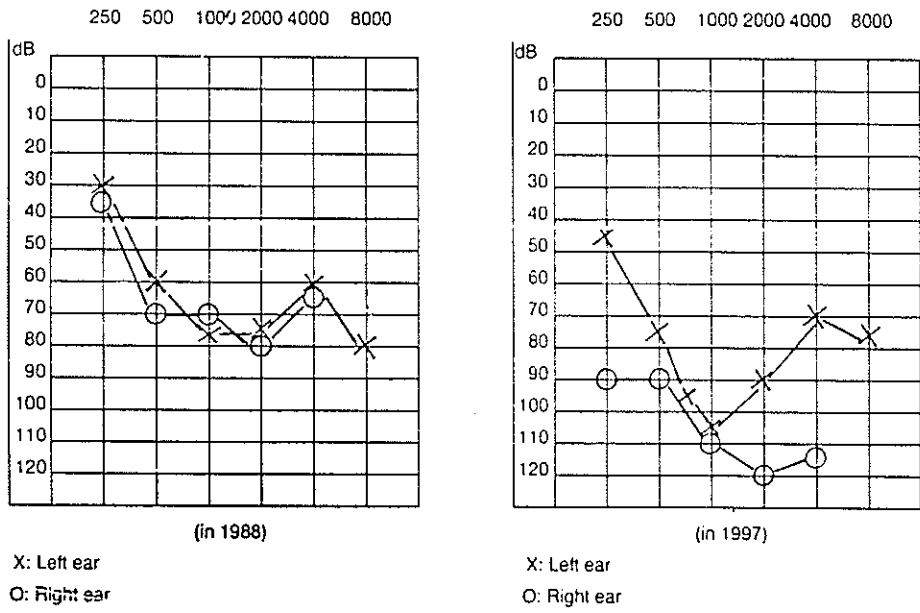


Fig. 5. Tonal audiometry showing sensorineural hearing loss (case 2)

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Acoustic Reflex				
Probe in R.		Freq. Hz	Probe in L.	
Ipsi	Contra		Contra	Ipsi
		500		No.R
		1000		110
		2000		N.R
		4000		N.R

Fig. 6. Tonal audiometry showing sensorineural hearing loss (case 3)

management and avoid the additive therapy (ies).

2. To achieve a normal life style for patients, both physically and psychologically, by menstruation and phenotypic development especially of the secondary sexual features.

3. Implantation for curing or improvement of hearing disorder.

4. To improve the intelligence and mental abilities by focussing on items 1-3 and also to plan proper, progressive courses, of speech therapy and any other essential courses, including, physical and mental training.

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