Case Report

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Perrault Syndrome: A Rare Cause of Primary Amenorrhoea

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Abstract

Perrault syndrome is an autosomal recessive disorder with sensorineural hearing loss in both female and male, and gonadal dysgenesis in female only. We present here a case which presented to our gynae department with complain of primary amenorrhoea. She was congenitally deaf and mute, born out of non consanguinous marriage. She had delayed developmental milestones. On examination she had delayed pubertal development with normal external genitalia. Pelvic sonogram showed hypoplastic uterus with streak gonad. Hormonal tests revealed hypergonadotrophichypogonadism (raised FSH with low estradiol). Karyotype was normal (46 XX). Audiology showed profound bilateral sensorineural hearing loss. MRI brain showed demyelination in deep white matter and periventricular region of parietal and occipital lobes.

Keywords: Hypogonadism; Sensorineural Hearing Loss; Amenorrhoea.

Introduction

Primary amenorrhoea is usually a result of a genetic or anatomical defect. In a young woman, Gonadal dysgenesis is the most common cause (30-40%), followed by Mullerian Agenesis and Androgen Insensitivity Syndrome. Features of primary ovarian failure (no development of secondary sexual characters with high FSH and low estradiol) with streak gonads points towards Gonadal dysgenesis. Karyotype is a must to rule out Turner's syndrome which is the most common cause of gonadal dysgenesis. Pure 46,XX Gonadal Dysgenesis is rare, providing evidence that autosomal genes are also involved in germline differentiation and migration. XX-GD when combined with nerusensory deafness is known as Perrault Syndrome. We present here a case of sporadic Perrault Syndrome due to its rarity and to add to the spectrum of presentations.

Case Report

A 18 year old girl presented to our gynae OPD with complain of Primary amenorrhoea. She had prelingual deafness with mutism. She had no neurological or visual complain. She was born out of a non consanguinous marriage. She had 3 brothers with normal hearing and intellect and had a sister who also had normal hearing who died at age of 2 due to drowning.She had history of delayed motor milestones with sitting at 1.5, crawling at 2 and walking without support at 3 yrs. She had no history of medical disease or similar illness in her family.

On examination she was of 34.5 kg with height 158 cm and arm span of 173 cm more than her height (Ratio – 1.095). She had sparse axillary and pubic hairs (Tanner 1) with underdeveloped rudimentary breasts (tanner 2). She had noTurner's phenotype like webbing of neck, widely spaced nipples or cubitus valgus. She had normal external genitalia.

On systemic examination no cardiovascular or neurological finding was elicited.

On audiometry, she was found to have Bilateral profound sensorineural hearing loss and was advised a trial of hearing aid for only awareness.

On investigations she had normal haemogram,

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LFT, RFT, Serum Ferritin and serum electrolytes. Her ultrasonography showed small hypoplastic uterus(2.68x1.51x1.15 cm) with a streak gonad(1.28 x1.5 cm) on right side with left ovary not visualised (Figure 1).

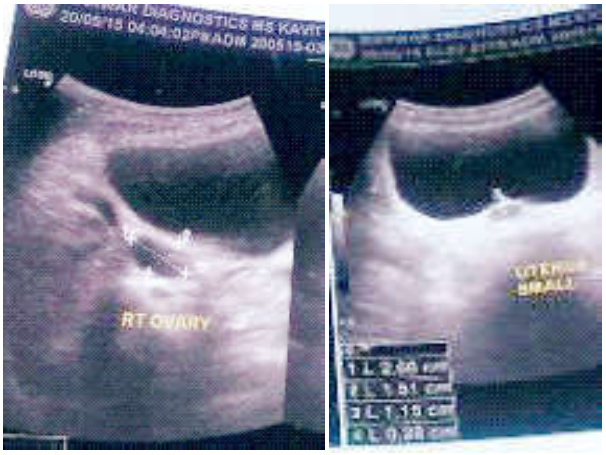

Fig. 1: USG showing hypoplastic uterus with streak gonad.

Her hormonal studies showed normal thyroid profile(TSH- 1.66 mIU/ml) and prolactin levels (29.22 ng/ml), with a high FSH(148.74 mIU/ml) and low estradiol (14.25pg/ml) suggesting hypergonadotrophic hypogonadism. Karyotype was normal 46 XX(XX gonadal dysgenesis). Skeletal X-Ray of hands revealed arachnodactyly, with bone age consistent with person between 12 to 15 years (Figure 2).

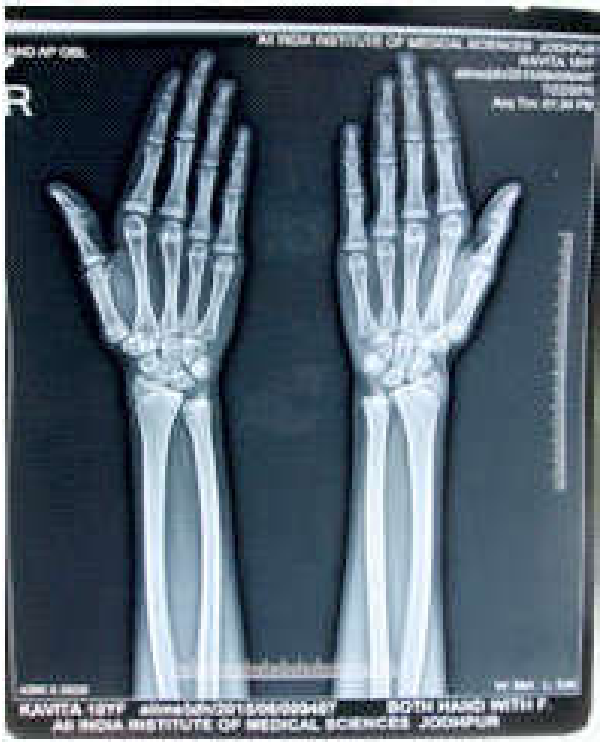

Fig. 2: Arachnodactyly with bone age between >12 and <15 yrs.

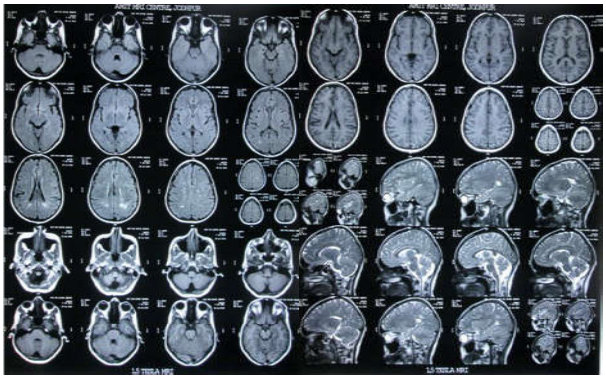

Fig. 3: MRI Brain showing demyelination in deep white matter and periventricular area in parietal and occipital lobes

She was planned for 2-D Echocardiography and to be put on Hormonal Replacement Therapy for development of her secondary sexual characters and prevent side effects due to estrogen deficiency; but she was lost to follow up.

Discussion

Perrault Syndrome is a "rare genetic disorder" with prevalence of less than 1/1,000,000 worldwide.Pure XX gonadal dysgenesis with sensorineural hearing loss is the hallmark. A spectrum of additional clinical features includes cerebellar ataxia, learning disability and peripheral neuropathy identified in some individuals.

The syndrome was first described in two sisters in 1951 by a French doctor called Perrault [1]. But understanding its cause had eluded scientists for over 50 years.Aittomaki et al (1994) hypothesized that there is a form of ovarian dysgenesis inherited as autosomal recessive disorder [2]. A number of projects have been undertaken to identify the candidate gene. Pierce et al(2010) did the exom sequencing of genomic DNA of one of the sisters with Perrault described by McCarthy and Opitz(1985) and Fiumara et al (2004) and identified compound heterozygous mutation in HSD17 B4 gene(601860) located on chr 5q23 encoding 17 beta-hydroxysteroid dehydrogenase type 4 [3]. In another family of mixed European descent described by Pallister and Opitz (1979), Pierce et al(2011) found mutation in HARS 2 gene (600783) that encodes histidyl-t RNA synthetasethat functions in mitochondria [4]. In 2013, a team lead by Dr. Bill Newman and Dr. Emma Jeckinson from biomedical Research Centre at University of Manchester found mutation in another CLPP gene located on chr 19p13 encoding mitochondrial ATP- dependent chambered protease [5]. They concluded that dysfunction in

mitochondrial protein homeostasis as the cause of PRLTS.

There is wide inter and intra family variability in phenotypic presentation. Ovarian dysfunction in Perrault Syndrome may range from primary amenorrhoea to Premature ovarian insufficiency to infertility. But there are few cases described who had initially menstruated and had born children. Onset of deafness is variable from 10 months to 31 years, and reported to be progressive and of varying severity. Absence of deafness in a patient with XX female gonadal dysgenesis does not rule out Perrault because she may develop deafness at a later age [6].

Clinical and genetic heterogeneity of the disease has prompted Pierece et al (2010) to classify it into type I, which is static without neurological disease, and type II, which is progressive neurological disease.Our patient falls into type I.

Gottschalk et al(1996) reviewed the neurological involvement in previous patients with Perrault Syndrome [7]. Neurological data are available on 14of 21 girls, 7 of the 14 had neurological abnormalities. He concluded that ataxia and mental retardation may not be incidental finding but pleotropic manifestation.Fiumara et al reported sensory and motor neuropathy in 2 pair of sisters [8]. This further supported neurological involvement. Nishi et al reviewed 21 patients from the literature and added ataxic gait, pesequinovarus, nystagmus, ophthalmoplegia to the spectrum [9]. The finding of abnormal body proportions noted in our patient has been earlier reported by Jacob et al (2007) [10].

Conclusion

Fewer than 100 cases have been reported in medical literature. Perrault Syndrome may be underdiagnosed if only one family member is affected, especiallyif only a male has sensorineural deafness without anaffected sister.

Any female with XX gonadal dysgenesis should be evaluated for hearing. If hearing is normal she should be followed as she might develop it later varying in severity. Some reported cases hadinitially menstruated and presented later with premature ovarian failure. So a female with deaf-mutism should have a multidisciplinary approach and should be followed up as she may develop premature ovarian failure later.

Genetic and phenotypic heterogenecity studies are putting new insight into the disease and newer modalities of diagnosis and therapy. Any patient with Perrault Syndrome should have multidisciplinary approach and proper follow up. It is also important to screen siblings of proband so that early diagnosis will help in timely intervention.

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