Brief Communication

Unusual presentation of Kallmannn syndrome with contiguous gene deletion in three siblings of a family

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ABSTRACT

We report the case of 3 brothers aged 34, 24, and 22 years, unmarried, who presented to our endocrinology clinic with absence of secondary sexual characters. There was no such history in other siblings, but their maternal uncle had similar complaints. On examination, all 3 had pre-pubertal appearance, voice, and genitalia along with anosmia and bimanual synkinesia. Cryptorchidism was noticed in 2 while third person had small hypoplastic testes. It was also noted that all 3 patients had icthyosis mainly involving trunk, back, and limbs. The hormonal assays were consistent with isolated hypogonadotrophic hypogonadism. IQ testing revealed mental retardation in the 2 patients. Ultrasound showed ectopic right kidney in one patient, atrophic right kidney in the second patient while the third patient had normal kidneys. MRI brain of all the patients showed poorly visualized olfactory tract and bulb. Kallmann syndrome (KS) was diagnosed based on hormonal evaluation and MRI results. Of the four types of KS: Synkinesia, renal anomaly, and X-linked pedigree pattern in our patients pointed towards X-linked type 1 KS as the possible cause. But, icthyosis and mental retardation are not usual presentation of type 1 KS. They are usually seen as a result of contiguous gene deletion of KAL1, steroid sulfatase (STS), and mental retardation (MRX) gene on X chromosome. Hence, the possible gene defect in our cases is inherited defect in contiguous gene deletion. The contiguous gene deletion as the cause of KS in 3 patients of same family is very rare and worth reporting. Also, the significance of phenotype-genotypic association in Kallmann syndrome is discussed

Key words: Contiguous gene deletion, kallaman's syndrome, familial

Introduction

Kallmann syndrome is the most common cause of isolated hypogonadotrophic hypogonadism. The diagnosis is made on clinical grounds and by hormonal assay confirming hypogonadotrophic hypogonadism. The finding of hypoplasia or aplasia of olfactory bulbs demonstrated by MRI also aid in diagnosing Kallmann syndrome. We here report 3 cases of Kallmann syndrome within the same family.

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Case Report

A 34-year-old male unmarried male A presented to our endocrinology clinic with complaints of absence of secondary sexual characters. On probing, he also gave history of similar symptoms in 2 of his brothers having similar complaints. All 3 were called to our clinic for further workup. Two of them (B and C) gave history of absent testes in scrotum while the third had small testes. They had 5 more brothers and 6 sisters, neither of whom had any such complaints. In B, C there was history of poor performance in school and delayed developmental milestones. There was history of similar complaints in maternal uncle who had died due to some unknown cause.

On examination, all 3 had pre-pubertal appearance, voice, and genitalia along with anosmia and synkinesia of upper limb. Testes were small and hypoplastic in A, while in B

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and C, they were not palpable in the scrotum or inguinal canal. It was also noted that all 3 patients had icthyosis mainly involving trunk, back, and limbs.

All 3 patients underwent routine biochemical investigations, hormonal assays, and radiological scans. Hormonal assays revealed isolated hypogonadotrophic hypogonadism with normal thyroid function tests and basal cortisol level. Growth hormone provocation test did not reveal any growth hormone deficiency. In B and C, USG showed that the testes were hypoplastic and inguinal in location. It also revealed atrophic right kidney in A, ectopic right kidney in C while C had normal kidneys. MRI brain of all the patients revealed poorly visualized olfactory tract and bulb. Patient B had a 4 × 2 cm cyst in cerebellopontine angle, arachnoid cyst. All 3 were diagnosed as a case of Kallmann syndrome and treated with testosterone injection to induce secondary sexual characters.

Discussion

Kallmann syndrome is the most common cause of isolated hypogonadotrophic hypogonadism (IHH)[1] accounting for 60% cases of IHH.[2] IHH along with anosmia or hyposmia constitutes Kallmann syndrome. Those with normal smell sensation are grouped under Normosmic IHH. Kallmann syndrome has a prevalence of 1 in 7500 males and 1 in 50000 females.[1] Most cases are sporadic, but it can also be inherited as X-linked recessive, autosomal-dominant, or autosomal-recessive. Incomplete penetrance has been seen in the autosomal-dominant variety. The basic defect is in the hypothalamus due to defect in migration of GnRH secreting neurons from neuroepithelium of nasal placode. Since olfactory neurons also arise from nasal placode, these patients have associated anosmia/hyposmia. The migration is guided by various signaling molecules. Few of them are identified, and defect in them are found to cause Kallmann syndrome.

Five causal genes have been identified to date, namely, KAL1, FGFR1 (fibroblast growth factor receptor-1 gene), PROKR2 (prokineticin receptor-2 gene), PROK2 (prokineticin-2 gene), and FGF8 (fibroblast growth factor-8 gene).[1] Each genetic form shows clinical heterogenicity within families, indicating role of other factors than gene defect in expression. Among them, the most common gene defect is KAL1 gene present on X chromosome coding for anosmin-1 (Type 1 Kallmann), which plays role in cell surface signaling and migration. This is usually the most severe form with the least variability in the same family. Most of the inherited cases are X-linked. Synkinesia is a unique feature present in up to 80% of X-linked cases,[2] being almost exclusive to this type. Unilateral renal aplasia or dysplasia is another feature present in around 30% patients.[2] In our cases, all 3 had bimanual synkinesia, one patient (A) had renal aplasia while the other patient (B) had an ectopic right kidney.

FGFR1/FGF8 gene defect is responsible for mostly sporadic autosomal-dominant type 2 Kallmann syndrome, which has variable penetrance. PROKR2 gene defect cause type 3 Kallmann while PROK2 cause type 4. Both of these are usually autosomal-recessive but are known to present in homozygous, heterozygous, or heterohomozygous fashion. The CHD7 (chromodomain helicase DNA binding protein 7) and NELF (Nasal Embryonic LHRH Factor) genes are the other rare genes involved in Kallmann syndrome. But, only 30-40% cases (10-20% KAL1, 10% FGFR1, 5% PROKR2, 5% PROK2) of Kallmann syndrome can be explained by these known gene defects.

All of our patients were male with, synkinesia, family history in maternal uncle and unilateral renal abnormality in 2 of our patients points towards X-linked-recessive inheritance. These patients had height <3rd percentile in contrast to normal or tall stature seen in Kallmann syndrome. But, this can be explained, as their parents were also short stature. Two of the 3 patients were above MPH. Also, GH stimulation test did not reveal any GH deficiency. Apart from these, icthyosis was seen in all 3 patients and mental retardation in 2 patients (IQ 74 and 47). Combination of Kallmann syndrome, icthyosis, and mental retardation are reported due to contiguous gene deletion of KAL1 and steroid sulfatase (STS) gene and mental retardation (MRX) gene in X chromosome.[3] The KAL1, STS, and MRX genes are situated on X chromosome in that order. Hence, the presence of icthyosis and mental retardation in our cases points towards the contiguous gene deletions. Also, arachnoid cyst in cerebellopontine angle was reported in MRI in one patient. There are few case reports of arachnoid cysts in Kallmann syndrome, the importance of which is not yet clear.[4]

On treatment with testosterone depot preparation, all 3 of our patients developed significant secondary sexual characters over 6 months. We do not yet have any data on the fertility status, as all 3 are unmarried.

Conclusion

The report highlights the genotype-phenotype association seen in Kallmann syndrome. Hence, family history, pedigree, and phenotypic associations should be analyzed. These may guide us in pinpointing the possible genotype and search for other associated anomalies. Also, contiguous gene deletion as the possible cause of Kallmann syndrome

in 3 members of a family is very rare and not reported in existing literature. Although the clinical suspicion is strong, the confirmation of the genotype and gene deletion is possible only after gene analysis, which was not available to us.

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