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CASE SUTDY

ALL HYPOGONADOTROPHIC HYPOGONADISM PATIENTS WITH ANOSMIA ARE NOT KALLMANN'S

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ABSTRACT

Wereport a case of 26 year old Indian male patient of hypogonadotrophic hypogonadism. The patient presented ten years earlier to a centre where he was diagnosed to have hypogonadism which was central in origin along with anosmia. Eventually a diagnosis of kallman's was made. The patient was discharged with an advice of monthly injections of Testosterone which the patient was injected on three occasions & was lost to follow-up. Our case points out a possible misdiagnosis of Kallmann's if other differentials are not kept in mind. Cardiac conduction defects have been documented for the first time in CHARGE for the first time to the best of our knowledge. A corrected cleft palate may at times mask aatreticchoanalaperture, one of the major criteria for CHARGE. All the above points make our case unique. Finally, a diagnosis of CHARGE was made based on the appropriate investigations and managed accordingly.

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INTRODUCTION

CHARGE syndrome is often masked under the more common differentials of Hypogonadotropic Hypogonadism particularly Kallmans Syndrome. A short height, associated mental retardation, co-existent Cardiac or Cardio-Vascular abnormality, visual disturbance, auditory problems point towards a diagnosis other than Kallmanns.

Case Report

The patient now presents at 26 years of age for absence of secondary sexual characteristics & a small penis. Wereport a case of 26 year old male patient of hypogonadotrophic hypogonadism. Due consent regarding publication was taken from patient's guardian. The patient presented 10 years earlier to a centre where he was diagnosed to have hypogonadism which was central in origin along with anosmia. Eventually a diagnosis of kallman's was made. The patient was discharged with an advice of monthly injections of Testosterone which the patient was injected on three occasions & was lost to follow-up.

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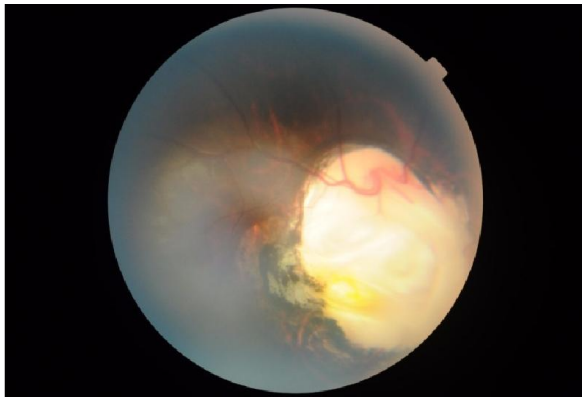
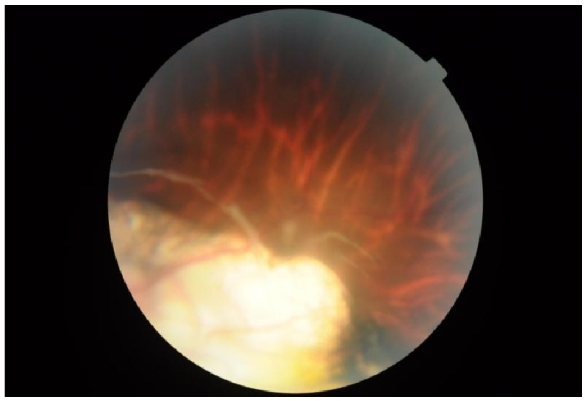
The patient now presents at 26 years of age for absence of secondary sexual characteristics& a small penis. The child was born of non-consanguineous marriage without any significant antenatal, intranatal or post- natal problems. The child had been operated for cleft lip & cleft palate at 4 years of age, the details of operative procedure are however missing. The parents noticed that the child had delayed development of social milestones in the form that he could follow commands only after 10 years of age & did not have formed speech till date. The parents observed that the child could not appreciate smell of foul & pungent smelling objects nor any sweet smells. The parents noticed that the child had difficulty in hearing since around 12 years of age. The child was admitted in school at 10 years of age where he could continue only for 3 years. On examination the child had short stature with a height of 150.6 cms & height SDS of –3.85& a target height SDS of -2.2. The ratio of Upper & lower segment was 0.87.Arm span of 151.6cms. The child had absence of secondary sexual characteristics including absence of beard, absence of axillary & pubic hair (P1) & a stretched penile length of 7centimetres. The testicular volume was bilaterally 3ml with absence of scrotal rugosity. The child had a low hairline. Examination of the vitals depicted that the child had asymmetry of pulse volume on the upper limbs with a pulse rate of only around 38 per minute.

Blood pressure in the right upper limb was 114/70 & that on the left upper limb had systolic of 50. The patient was admitted for detailed evaluation.

The patient had anosmia which was confirmed by bed side assessment with various perfumes &odours. The patient had significant visualdeficits. Fundus examination revealed Coloboma of Bilateral Optic Disc.



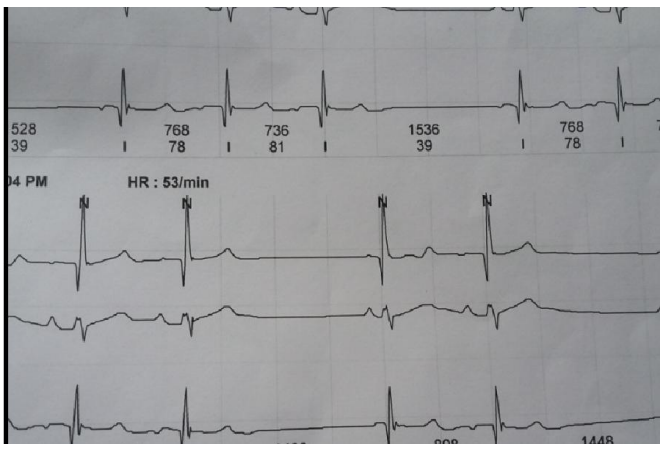
Right Eye



Left Eye

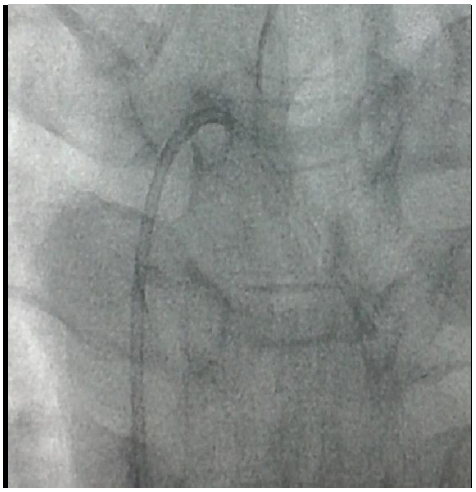
Coloboma of Optic Disc

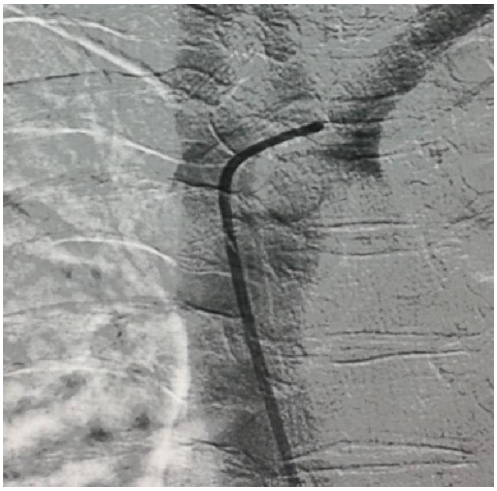
The child had detailed mental assessment which revealed moderate mental retardation with IQ of 45. Cardiology workup followed. ECG revealed Bradyarrhythmia with a rate of 46 per minute. Holter monitoring revealed Sick sinus syndrome.

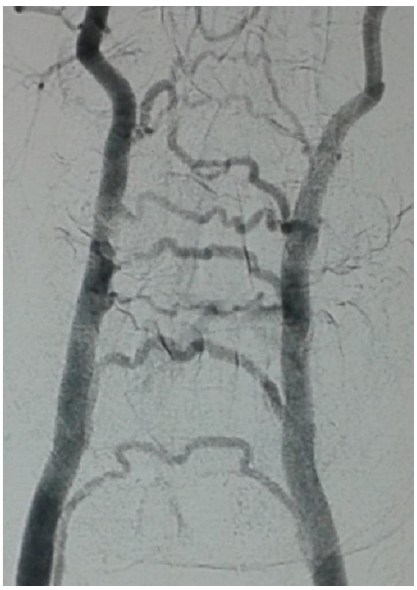


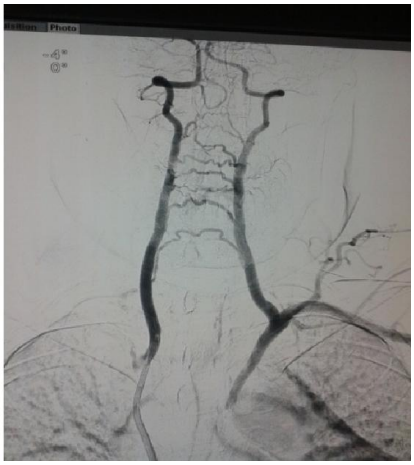
Holter showing Sick Sinus Syndrome

Next we started to evaluate for the discrepancy of Blood pressure on both upper limbs. A Digital Substraction Angiography was planned. DSA revealed Right Sided Aortic Arch, Total occlusion of origin of left Subclavian Artery with collaterals developing between left & right Vertebral Artery with retrograde flow through the left vertebral supplying the Left Subclavian distal to the block.

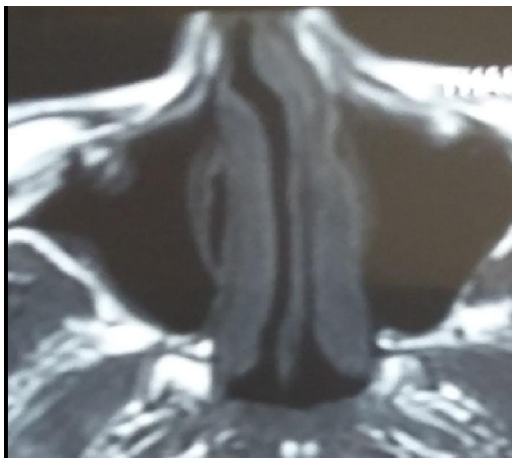






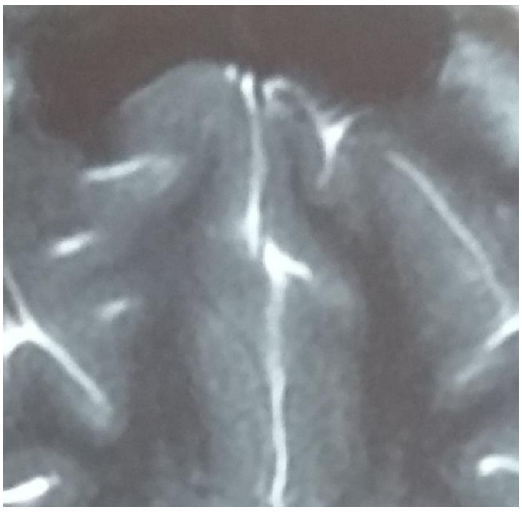


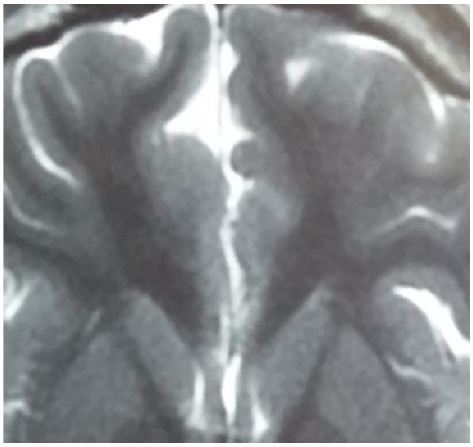
Digital Substraction angiography showing Right sided Aortic Arch, Occlusion of Left Subclavian Artery, formation of collaterals between right 7 left Vertebral Artery & retrograde flow through the left vertebral artery. Pure tone Audiometry revealed Bilateral Sensori-neural deafness. CT imaging of the upper respiratory tract revealed narrow choanal aperture which was probably corrected during the cleft palate surgery.



CT PNS showing U/L choanal atresia

Ct temporal bone however could not demonstrate any significant aplasia of semi-circular canals on either side. MRI imaging of the brain reveals hypoplasia of the olfactory bulbs & normal hypothalamo – pitutory apparatus.





MRI Brain showing Hypoplasia of Olfactory apparatus

The patient who initially was thought to be a classical Kallmann's, now is found to have the following components

- Coloboma of bilateral optic disc.
- Heart anomalies in the form of brady-arrythmia with anomalous outflow tracts
- choanal Atresia
- mental Retardation
- Genital Anomaly
- Ear anomaly

Relevant Blood parameters

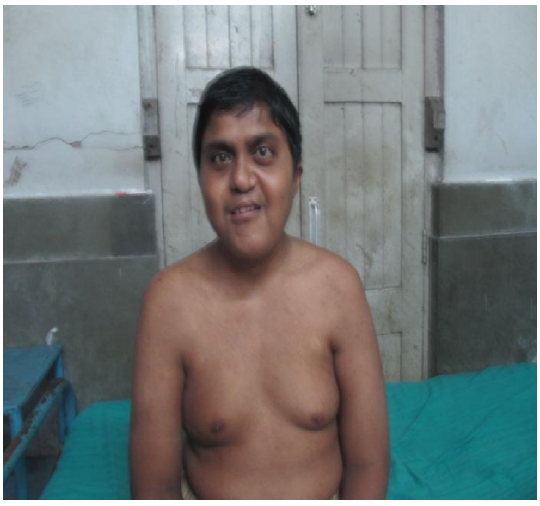
Sl.no	Blood Parametres	Value
1.	Hemoglobin	11.2 mg/dl
2.	Fasting Blood Sugar	79 mg/dl
3.	Post-Prandial Blood Sugar	101 mg/dl
4.	S. Creatinine	0.8 mg/dl
5.	S.Sodium	139meq/l
6.	S.Potassium	3.6 meq/l
7.	Liver Function Tests	Within normal limits

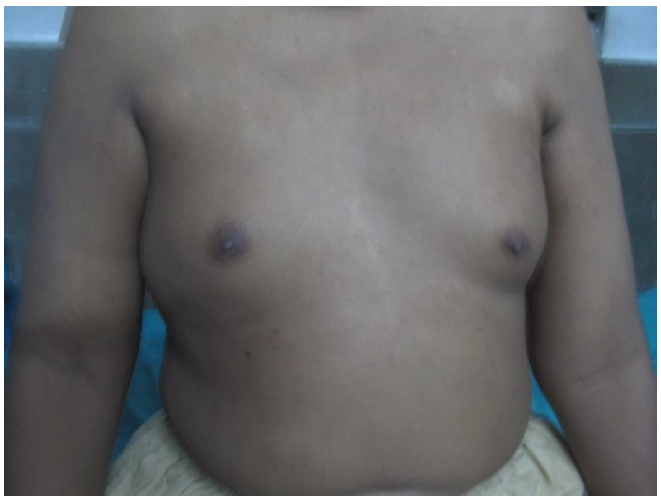
Relevant Hormonal Profile

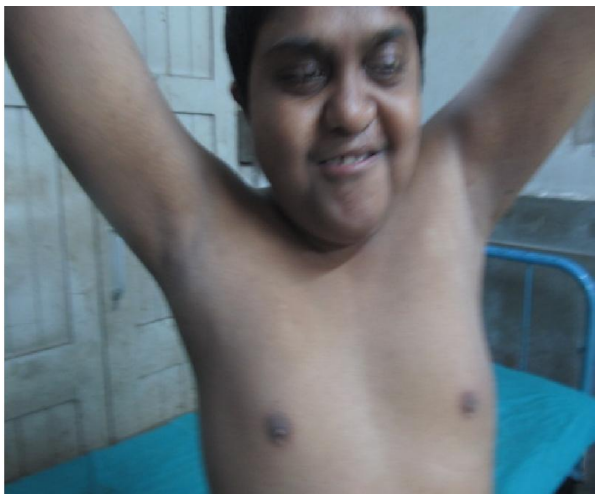
Sl.no	Hormone	Value
1.	Leutinizing Hormone (3 pooled)	0.39 mIU/ml
2.	Follicle Stimulating Hormone (3 pooled)	1.24 mIU/ml
3.	8 am S. Testosterone	< 0.25 ng/ml
4.	S. Thyroid stimulating Hormone	2.1 mIU/ml
5.	Free T_4	1.22 ng/dl
6.	8 am S. Cortisol	15.73 micro-gram/dl
7.	S. Prolactin	8.08 ng/ml
8.	S.IGF-1	120micro-gm/L(N-115-345 microgram/L)

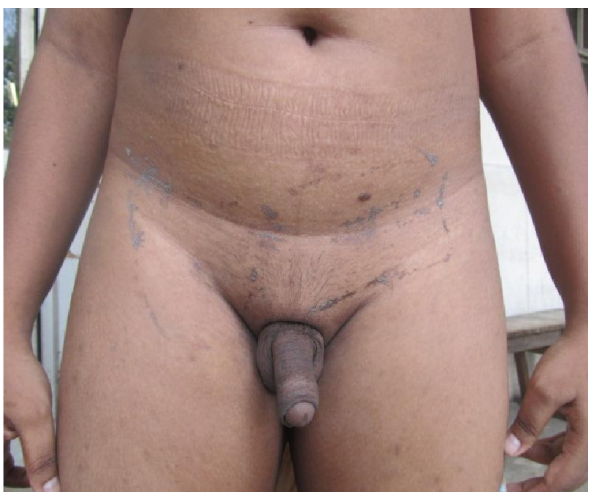
The hormonal profile confirms the presence of central hypogonadism. The remaining parameters are normal except for S.IGF-1 which was low normal for age. We however could not go for stimulation tests as the patient found it difficult to follow commands. From the aforementioned data our patient fits readily with the CHARGE syndrome. The diagnostic criteria for CHARGE has been depicted in the following table. According to Verloes criteria our patient fits with typical CHARGE as we have 2 major criteria with 3 minor criteria. Brady arrhythmias have not been mentioned as a component of CHARGE in the published literature to the best of our knowledge . We document Sick Sinus syndrome in the patient of CHARGE syndrome.

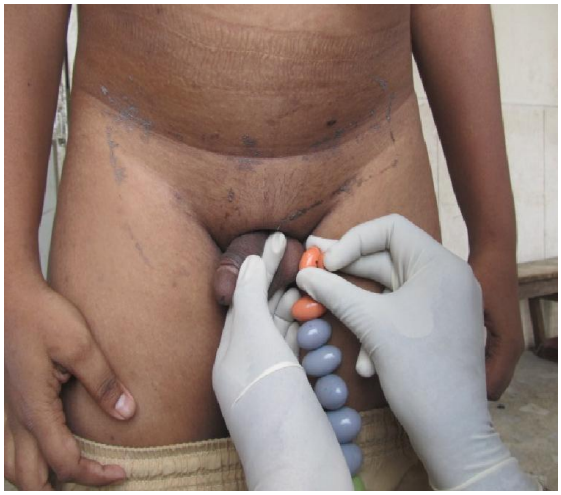
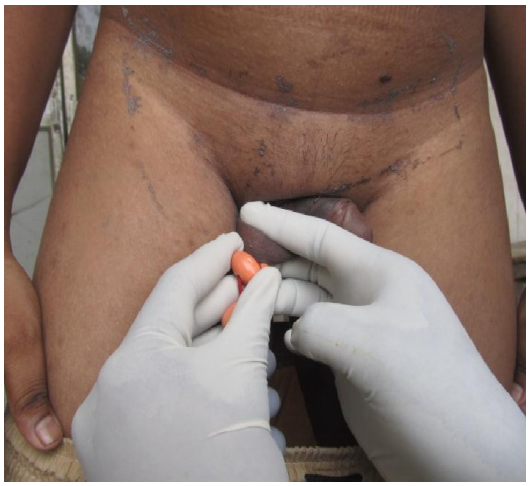
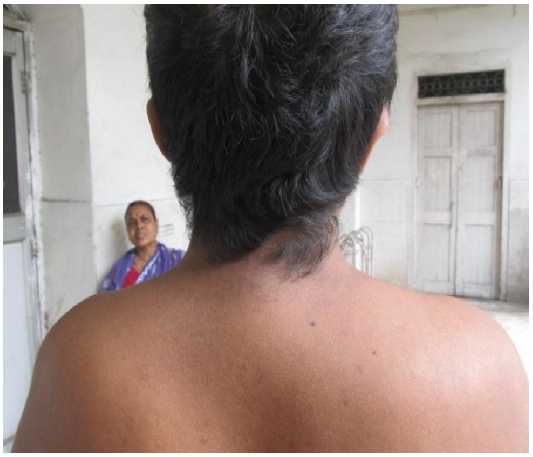
	Major criteria	*Minor criteria*	*Inclusion rule*
Pagon	1. Choanal atresia 2. Ocular coloboma	1. Heart defects of any type 2. Retardation (of growth and/or of development), 3. Genital anomalies 4. Ear anomalies (abnormal pinnae or hearing loss)	Four criteria out of six, and at least one major
Blake	1. Coloboma – of iris, retina, choroid, disc; microphthalmia 2. Choanal atresia – unilateral/bilateral, membranous/bony, stenosis/atresia 3. Characteristic ear abnormalities – external ear (lop or cup-shaped), middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects 4. Cranial nerve dysfunction – facial palsy (unilateral or bilateral), sensorineural deafness and/or swallowing problems	1. Genital hypoplasia – males: micropenis, cryptorchidism; females: hypoplastic labia; both males and females: delayed, incomplete pubertal development 2. Developmental delay – delayed motor milestones, language delay, mental retardation 3. Cardiovascular malformations – all types, especially conotruncal defects (eg, tetralogy of Fallot), AV canal defects, and aortic arch anomalies 4. Growth deficiencies – short stature, growth hormone deficiency 5. Orofacial cleft – cleft lip and/or palate 6. Tracheoesophageal-fistula – tracheoesophageal defects of all types 7. Characteristic face – sloping forehead, flattened tip of nose	Four majors OR three majors +three minors
Verloes	1. Ocular coloboma 2. Choanal atresia 3. Hypoplasia of semicircular canals	1. Rhombecephalic dysfunction (brainstem and cranial nerve III to XII anomalies, including sensorineural deafness) 2. Hypothalamo-hypophyseal dysfunction (including GH and gonadotrophin defects) 3. Malformation of the ear (internal or external) 4. Malformation of mediastinal organs (heart, esophagus,) 5. Mental retardation	Typical CHARGE: three majors OR two majors + two minors Partial CHARGE : two majors +one minor Atypical CHARGE: two majors but no minors OR one major + two minors



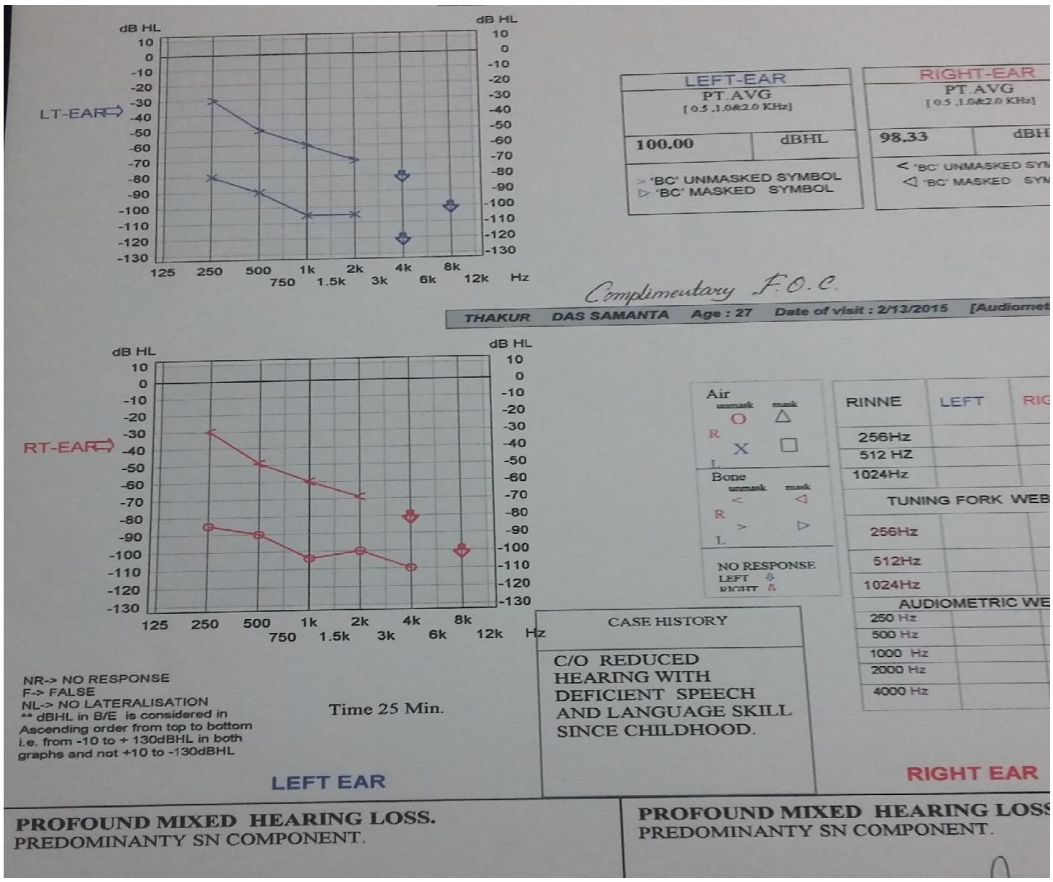


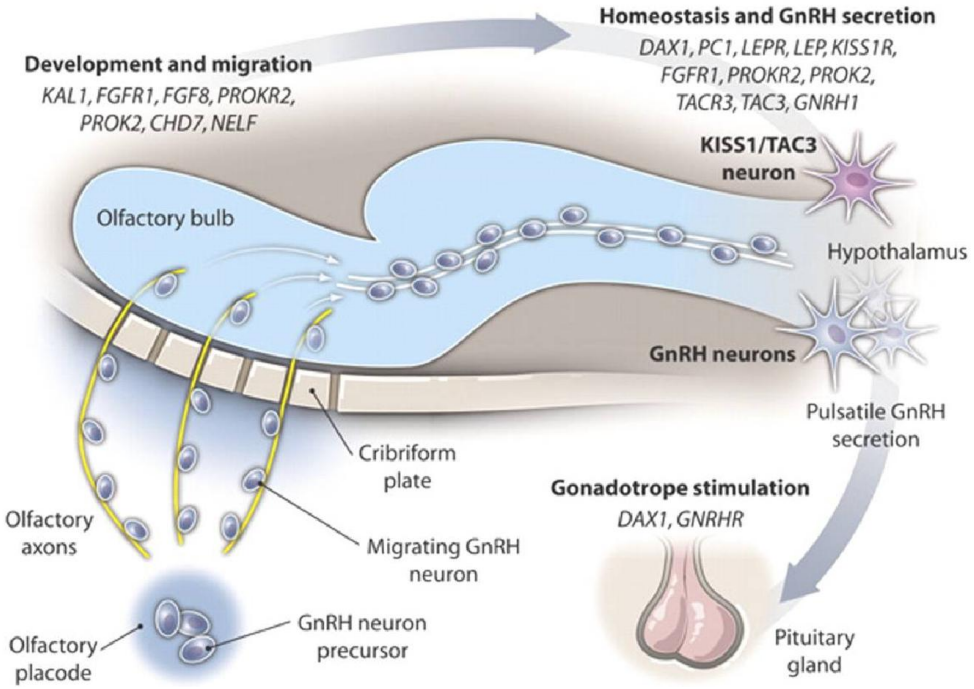




Low Hair line





DISCUSSION

CHARGE syndrome is often masked under the more common differentials of Hypogonadotropic Hypogonadism particularly Kallmans Syndrome. A short height, associated mental retardation, co-existent Cardiac or Cardio-Vascular abnormality, visual disturbance, auditory problems point towards a diagnosis other than Kallmanns. Hypogonadism occurs when GnRH neurons fail to migrate along with the olfactory axons from the nasal placode towards the hypothalamus. The protein products of KAL1, FGFR1, PROKR2 & PROK2 are thought to be involved in this migration process. (2,3). *CHD7* encodes a protein of the chromodomain (chromatinorganization modifier) family. This family shares a unique combination of functional domainsconsisting of two N-terminal chromodomains, followed by a SWI2/SNF2-like ATPase/-helicase domain and a DNA-binding domain. It is assumed that *CHD* protein complexes affect chromatin structure and gene expression and thereby play important roles in regulatingembryonic development. Also the expression of further downstream genes controlling Gonadal axis chiefly kisspeptinswill be similarly affected . It has been depicted that these kisspeptins also have facilitatory influence on somatotroph expression(6) which explains the short stature low IGF-1& probable co-existing Growth hormone deficiencies in these patients. Therefore, one might speculate that *CHD7* acts upstream to influence the expression or actions of *KAL1, FGFR1, PROK2* and/or *PROKR2 &*finally kisspeptins during development

Migration of the GnRH releasing neurones from the olfactory placode to the hypothalamus. Also listed are the genes which have an influence at each stage of the migration. Prof. N.Pitteloud 2011

Chalouhi *et al*.tested the olfactory function of 14 children with CHARGE syndrome and showed that allchildren had some degree of olfactory deficiency (1).

Pinto *et al*. showed that olfactorydeficiency and abnormal olfactory bulbs were present in all 18 CHARGE syndrome patients in their cohort (4). MCJ Jongmansa et.al from their analysis of 36 patients concluded all patients with hypognadotropic hypogonadism with anosmia should be investigated for CHARGE (5) as was true to our case.

Conclusion

Our case points out a possible misdiagnosis of Kallmann's if other differentials are not kept in mind . Cardiac conduction defects have been documented for the first time in CHARGE for the first time to the best of our knowledge. A corrected cleft palate may at times mask a atreticchoanalaperture, one of the major criteria for CHARGE. All the above points make our case unique.

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CHD7 mutations in patients initially diagnosed with Kallmann syndrome – the clinical overlap with CHARGE syndrome

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