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Case Report

Insulin Resistance: Alström Syndrome

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Abstract
Alström syndrome is a rare ciliopathy affecting about 1 in 1,000,000 individuals. It is characterized by cone-rod dystrophy, insulin resistance, diabetes mellitus, cardiomyopathy, renal & hepatic dysfunction, hearing loss, advanced bone age & hypogonadism. Here, we report a case of insulin resistance which eventually got diagnosed as Alström syndrome.
Keyword: *Alström, Ciliopathy, Insulin Resistance, Hearing Loss.*

Introduction

Alström syndrome, first described in 1959, is a rare progressive autosomal recessive genetic disorder, which affects multiple systems manifesting as rod-cone dystrophy, hearing loss, diabetes mellitus due to insulin resistance, cardiomyopathy & sensory neural hearing loss. It is due to mutations in ALMS1 gene (2p13)[1]. The prevalence is less than 1:1,00,000[2] & about 700 cases have been reported so far in world[3]. Rod-cone dystrophy is 100%[3] & is seen from infancy. Other features are obesity (birth-age 5), short stature (puberty-adult), insulin resistance/type 2 diabetes mellitus (4-30 years), hypogonadotropic hypogonadism (1-3 years), urologic disease (adolescent-adult), progressive sensoryneural hearing loss (2-25 years), hepatic & renal dysfunction (adolescent- adult), dilated cardiom-yopathy (2 week- 4 month), developmental delay (birth-adolescent)[3,4]. Supportive findings can be recurrent pulmonary infections, normal digits, hyperlipidemia, scoliosis, flat feet, hypothy-roidism, hypertension, urinary dysfunction, growth hormone deficiency, & alopecia [1].

Differential diagnosis includes Bardet-Biedel syndrome, Achromatopsia, Leber congenital amaurosis, inherited mitochondrial disorders, Usher & Cohen syndromes.

ALMS1 gene has 23 exons & 12,871 base pairs encoding a protein containing 4169 amino acids

which plays an important role in ciliary function. It is expressed in retinal rods & cones, liver, organ of corti, pancreatic islets, renal tubules & hypothalamus. Collin et al (2002) studied this gene with real time PCR to explain different clinical findings & phenotypes[6]. Marshall et al (2007) reported mutations in exons 16,10,8,12 & 18 in 79 patients[1]. Hearn et al detected 6 different mutations in 7 families to confirm that ALMS1 gene is responsible for Alstrom syndrome[7].

Case Report

Our case is an 11 year old Indian male, who has gradual darkening & thickening of skin at nape of neck, axilla & groin since last 7 years. His past history is told by her mother. His parents' marriage is non consanguineous. He was born as a normal vaginal delivery with immediate cry at birth. He has been unable to fixate on objects and his eyes are constantly moving to & fro since the age of 6 months. He has gradually decreasing visual acuity since that time which started first as day blindness. He is also suffering from deafness since early childhood. He started walking at an age of 3 years which signify a developmental delay & has suffered many episodes of pneumonia as told by her mother. He doesn't go to school because of his impaired vision & hearing. He has been taking some local medications for his skin darkening since 7 years on & off without any relief. His parents brought him to our hospital because one of his routine reports revealed a high random blood sugar of >400 mg/dL. His other 2 siblings are absolutely normal. No family history of diabetes mellitus, any chronic illness or similar illness.

General physical examination of patient revealed search nystagmus in bilateral eyes with patient not being able to fixate; inability to hear commands; normal dental examination; dark pigmentation at nape of neck, axilla & groin suggestive of Acanthosis Nigricans; gynaecomastia; normal knuckle &hand crease pigmentation without any syn- or clyno- or poly- dactly; no abnormality in feet; no pallor, icterus, clubbing, cyanosis, lymphadenopathy, peripheral edema. Height of patient is 142cm & weight is 38 kg, BMI being 18.84 (normal). Vitals were normal.

On systemic examination; cardiovascular, gastrointestinal & respiratory systems were within normal limits. Nervous system examination revealed search nystagmus, decreased visual acuity with only finger counting & decreased hearing. Cranial nerves, motor & sensory system, bowel & bladder, cranium & spine, peripheral nervous system were normal & cerebellar functions couldn't be tested other than nystagmus.

Investigations were-CBC & DLC were normal; fasting blood sugar-379 mg/dL; fasting Insulin-162.8 µIU/mL; thus a HOMA-IR of 151.6 (raised); HbA1c-14.8%; c-peptide- 9.2ng/ml; S.urea- 25 mg/dL; S.Creat.-1.1 mg/dL; $S.Ca^{2+}$, PO^{4-},Na^{+}, K^{+} were normal; T.bilirubin- 1.4 mg/dL; SGOT/PT- 135/159 IU/L; ALP-554 IU/L; GGT- 180 mol/L; Normal albumin & A/G ratio; T.lipid-1199 mg/dL; Triglyceride- 482 mg/dL; thyroid function tests, prolactin, growth hormone, LH, FSH, Testosterone, Cortisol, PTH were all normal; Normal ECG & chest X-ray. Urine examination revealed glucosuria without proteinuria or ketonuria.LDH & CPK were also normal.

USG abdomen revealed fatty liver; pure tone audiometry revealed moderate sensorineural hearing loss; fundus revealed a pale disc; fluorescein angiography of retina revealed pale disc with arteriolar attenuation & multiple window defects suggestive of retinitis pigmentosa like condition. 2D echo & MRI Brain with sella were normal.

So possibility of some syndrome was suspected. Applying criteria for Alström syndrome from Table 1 for this age group of patient, 1 major i.e. nystagmus & vision disorder, & 3 minor i.e. deranged liver function, insulin resistance & hearing loss, criteria lead us to the diagnosis of Alström syndrome in this case. ALMS1 gene study couldn't be done due to financial constraints of the patient.

Close differential diagnosis were- Bardet-Beidel syndrome, but there was no syn or polydactyly, no obesity, & hearing loss was present; & mitochondrial disorders, but there was no myopathy.

The boy has been advised dietary counseling, increase physical activity, vocational training. He has been put on Tab.Metformin 1000mg BD, Tab. Pioglitazone 7.5mg BD, Inj. Insulin (regular plus isophane) subcutaneous. Adjunctive treatment in form of multivitamins & calcium + vitamin D has also been given.

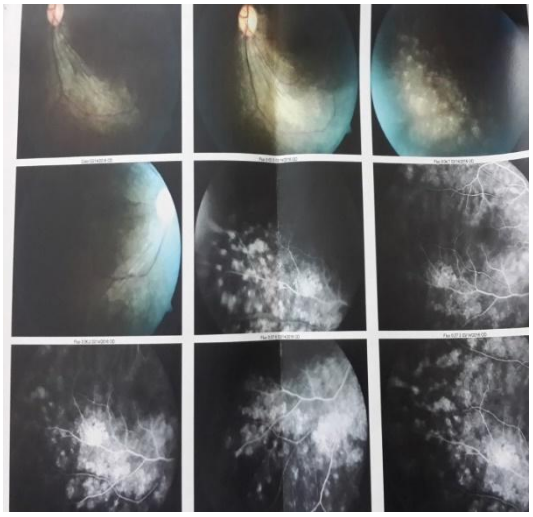

Figure 1 Fluorescein Angiography

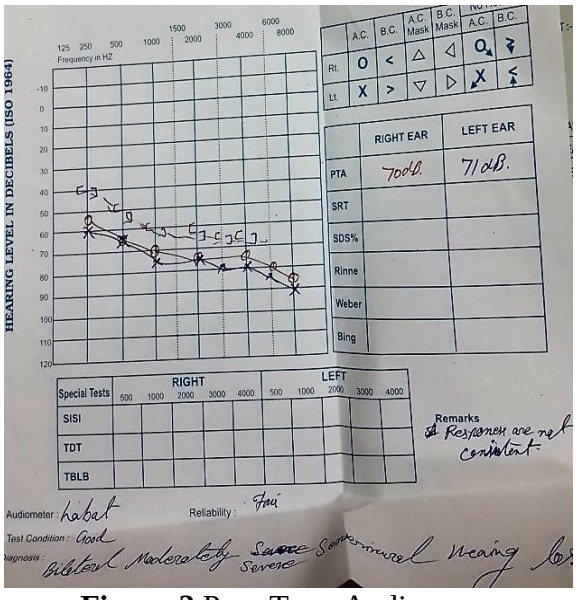

Figure 2 Pure Tone Audiogram

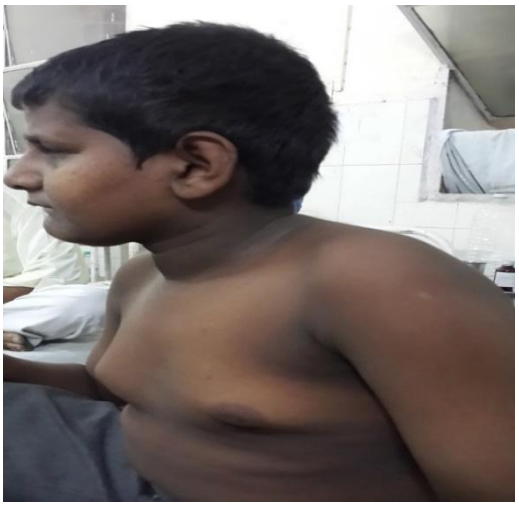

Figure 3 Gynaecomastia

Figure 4 Acanthosis Nigricans

Discussion

Alström syndrome is a rare inherited disorder with only a few hundred cases reported worldwide.

Onset of clinical features is variable. Ocular features in form of Nystagmus & photophobia develop in early infancy in majority of cases. Patients usually become completely blind by end of 2nd decade. Progressive bilateral sensoryneural hearing loss is seen in 88%, insulin resistance & diabetes mellitus type 2 in 68 %. Diagnosis of this syndrome is essentially clinical.

Table 1 Criteria for diagnosis of Alström Syndrome[5]

Age (years)	Criteria		Other supportive evidence	Diagnosis
	Major	Minor		
≤ 2*	• ALMS1 mutation in 1 allele and/or family history of AS • Vision (nystagmus, photophobia)	• Obesity • DCMP/CHF	• Recurrent pulmonary infections • Normal digits • Delayed developmental milestones	2 major criteria OR 1 major + 2 minor criteria
3–14	• ALMS1 mutation in 1 allele and/or family history of AS • Vision (nystagmus, photophobia, decreased acuity, cone dystrophy by ERG**)	• Obesity and/or insulin resistance • (History of) DCMP/CHF • Hearing loss • Advanced bone age • Hepatic dysfunction • Renal failure	• Recurrent pulmonary infections • Normal digits • Delayed developmental milestones • Hyperlipidemia • Scoliosis • Flat wide feet • Hypothyroidism • Hypertension • GH deficiency • Recurrent UTI	2 major criteria OR 1 major + 3 minor criteria
≥ 15	• ALMS1 mutation in 1 allele and/or family history of AS • Vision (legal blindness, history of nystagmus in infancy/childhood, cone and rod dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • (History of) DCMP/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Short stature • Males – hypogonadism • Females – irregular menses and/or hyperandrogenism	• Recurrent pulmonary infections • Normal digits • History of developmental delay • Hyperlipidemia • Scoliosis • Flat wide feet • Hypothyroidism • Hypertension • GH deficiency • Alopecia • Recurrent UTI or urinary dysfunction	2 major + 2 minor criteria OR 1 major + 4 minor criteria

*These diagnostic criteria should be re-evaluated when the patient becomes older; **ERG to be conducted only if the child is old enough for testing. AS-Alström syndrome; DCMP/CHF-dilated cardiomyopathy/congestive heart failure; ERG- electroretinogram; GH, growth hormone; UTI-urinary tract infections; T2DM-Type 2 diabetes mellitus.

It should be kept in differential diagnosis of Insulin resistance syndromes & should be differentiated from closely related Bardet-Beidel syndrome & some mitochondrial disorders.

Presence of dilated cardiomyopathy carries a poor prognosis[4].

Management is multidisciplinary with focus on management of diabetes mellitus, secondary complications, & vocational training. Also advise for prenatal testing.

Conclusion

Alström syndrome should always be considered in differential diagnosis of young child presenting with diabetes mellitus secondary to insulin resistance with a focus on other co-morbidities. This syndrome shares its features with a more common metabolic syndrome. In coming years, more such diagnosis will unfold the genetic basis of Diabetes & help in further management.

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