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ALSTROM Syndrome (Cases Presentation and Review of Literature)

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Abstract:

Alström syndrome is a rare autosomal recessive disorder characterized by atypical retinal pigmentary degeneration, sensorineural hearing loss, obesity, on insulin dependent diabetes mellitus, and chronic nephropathy. The diagnosis is based on clinical, biological, and genetics criteria (autosomal recessive disorder on chromosome 2).

Aim is to present multiple members of the same family showing same systemic and ocular manifestations. All are variants of a rare Syndrome. We want to emphasize that the diagnosis of alstrom's syndrome is often difficult, because not all cardinal features appear initially. Methods include Three siblings, two sisters and one brother, are described. They had complete ophthalmic examination with electrophysiology and fundus photography. They also underwent general and metabolic examination and genetic study.

A diagnosis of AS should be considered in infantile cone and rod retinal dystrophy, particularly if the weight a above the 90th percentile or if there is infantile cardiomyopathy. Early diagnosis may lead to better survival of affected children in special institute and genetic counseling in the case of later pregnancies

Introduction:

The Cases:

The parents first degree cousins & are completely healthy. They had 8 children: 4 boys, and 4 girls. Three of them presented with same problems (figure 1), while the rest were healthy. According to the history, there are many family members (first degree cousins) who have almost the same features (figure 2).

Figure 1: Three family members involved in the study

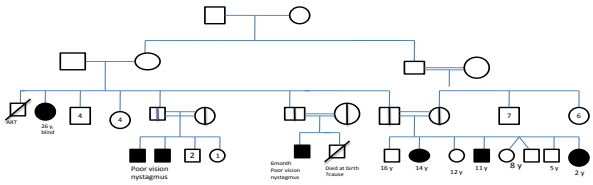

Figure 2: Family pedigree

Case No. 1

15 years old female second child of the siblings, was born term (normal pregnancy, delivery) and normal birth weight. First Presentation at age of 2 months, the child admitted to pediatrics PICU ward with H/O apnea and CHF diagnosed as dilated cardiomyopathy by echo. At age of 1 year, she started to walk and her parent observes that she is not seeing well, with photophobia.
Systemic Findings she is obese her weight above the 90 percentile while her height below 3 percentiles. Acanthosis nigricans, blackish Skin change over face, neck, axilla and groin regions noticed, recurrent chest problem. No polydactyly or syndactyly. She has bilateral sensorineural hearing loss, hepatosplenomegaly.
Blood workup and investigations reveals Chromosomal study 46, XX, Genetics molecule done was positive for ALMS 1. Endocrinology shows hyperinsulinemia, on metformin with high HbA1C. high TSH and low T4. FSH, LH, Progesterone, DHEAS, Progesterone and testosterone were normal. LFT: ALT, AST, total bilirubin high. PT, INR abnormal, Triglyceride and cholesterol were high.
Ophthalmologic Findings shows Poor vision CF 2m, Severe photophobia, Nystagmus, posterior sub capsular cataract and fundus examination showed white punctuate retinal changes with bulls macula and normal disc. Cone response study shows very poor cone response contaminated with pure noise, see figure 3 (A and B)

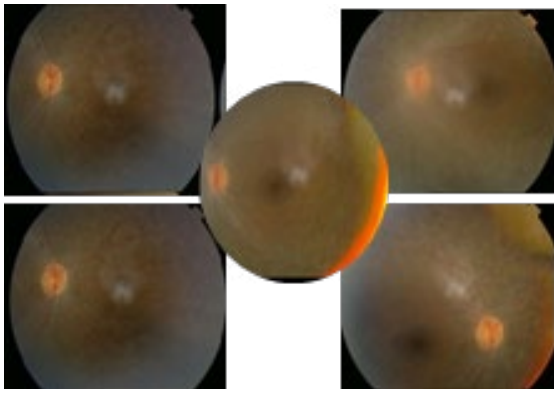

Figure 3 A: fundus imaging

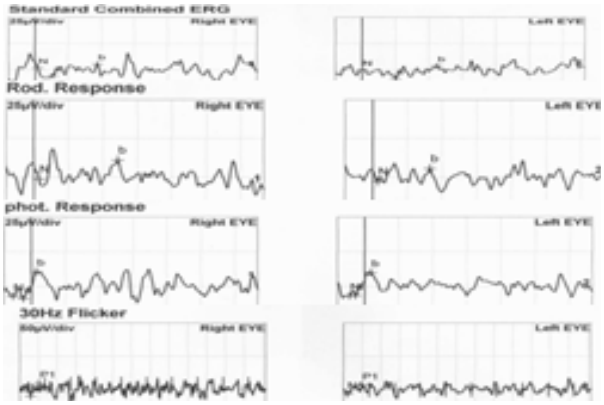

Figure 3 B: Electrophysiology Test

Case No. 2

12 years, male fourth child of the siblings was born at term. Normal birth weight, healthy child. He presented at age of five months with extreme light sensitivity (photophobia) and a wobbling of the eyes
Systemic findings show Diabetes mellitus type 2 at age of 11. he is obese, his weight above 95 percentiles and his height below 30 percentiles. Mild mentally retarded. Screening echo found to have large atrial septal defect and surgery done at age of 9years and ASD closed, finally he developed cardiomyopathy. Skin shows blackish change over face, neck, axilla and groin regions. Genital organs no pelvic hair, small penis. Flat foot with Scoliosis
Ophthalmic Findings shows Photophobia, Nystagmus, Poor vision CF 1m, Ptosis, Right exotropia 30 prism with hyperopia. Fundus examination showed disc normal with bull's maculopathy and whitish punctate retinopathy in the periphery with hyperpigmentation centrally. Cone response study shows very poor cone response contaminated with pure noise, there is mild identifiable response detects in rods see figure 4 (A and B)

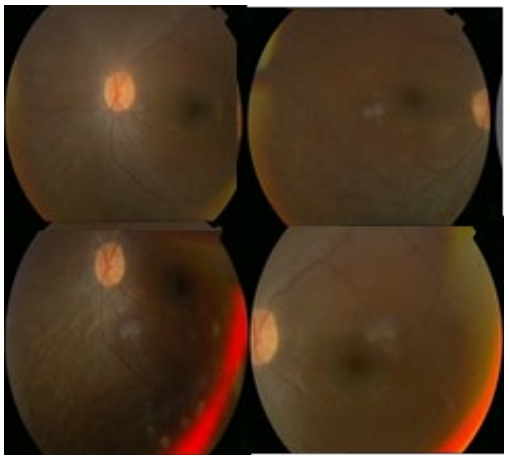

Figure 4 A: Fundus imaging

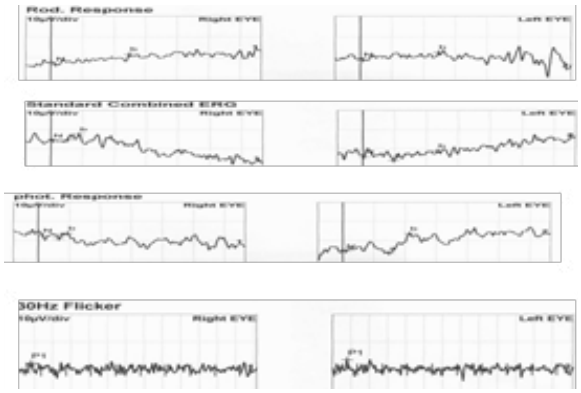

Figure 4 B: Electrophysiology Test

Case No. 3

2 years old female the last child of the siblings, was born at term (normal pregnancy and delivery). Normal birth weight, healthy child. Her first presentation was attack of apnea and cardiac arrested age of 2 months. At age of 6 months she started to have nystagmus

Eye examination findings: Poor vision, nystagmus, severe photophobia, hypermetropia with intermittent X(T), anterior segment normal, fundus examination showed some retinal pigmentary changes with normal disc and macula.

The full comparison between the 3 cases in ophthalmic and systemic features provided in Table 1 and 2.

Table 1: Ophthalmologic feature

	P1	P2	P3
Age	15	12	2
Sex	F	M	F
Nystagmus	+	+	+
Photophpia	+	+	+
Visual acuity First exam Last exam	2meter(1y) 11m(15y)	Not recoded 2m (13y)	Following the object
Pigmentary retinopathy	+	+	+
ERG Non detectable Cone-rod dystrophy	+	+	Not done

Table 2: systemic features

	P1	P2	P3
Sensoryneural hearing loss	+	+	+
Diabetes	+at age of 1Years	+ at age of 12 Years	+ at age of 2 Years
Acanthosis nigrican	+	+	+
Male hypogonadism	-	+	_
Renal impairment	_	_	_
Hepatic disease	+	+	+
Hypertriglecride	+	+	+
Cardiomyopathy	+	+	+

Discussion

Alstrom Syndrome (ALMS1, MIM #203800) is a rare monogenic condition caused by mutations in the gene ALMS1. Approximately 450 cases have been identified. (7,8). The distribution of AS is global without any gender predilection. With an estimated prevalence of < 1:100 000, only ~500 cases of AS have been reported in the literature thus far. (3, 11, 13, 17-20)

Since the condition was first described in 1959, (7-8). The diagnosis of Alström syndrome is based on cardinal clinical features that emerge throughout infancy, childhood, and young adulthood. Cardinal clinical features of this disorder are early-onset cardiomyopathy, progressive pigmentary retinal dystrophy, progressive sensorineural hearing loss, and childhood obesity. (2, 5, 8, 11, 19) most affected individuals develop severe insulin resistance, hyperinsulinemia, or type 2 diabetes mellitus in early adulthood, (5). Other metabolic disturbances, such as hypothyroidism, hyperuricemia, and hypertriglyceridemia, as well as dermatologic findings, such as acanthosis nigricans and alopecia, may also occur. (2,5,8,11,19).

In our cases all patients presented initially searching nystagmus and

photophobia. The earliest sign of Alstöm syndrome is often **visual impairment** as a result of a cone-rod dystrophy which occurs in 100% of affected patients within the first year of life (1,6,7,11). The retinal dystrophy progresses to include the rods, with visual acuity of 6/60 or less by age of ten years, increasing constriction of visual fields (8). An atrophic bull's eyes maculopathy rarely occurs in Alström syndrome (5). The electroretinogram is absent or attenuated with better preserved rod than cone function. Rod function is preserved initially but deteriorates as the individual ages. Fundus examination in the first decade may be normal or may show a pale optic disc and narrowing of the retinal vessels with bone-spicule pigmentary changes (11). Posterior subscapular cataract is common. Exudative retinopathy has also been reported in AS(3,11)

Sensorineural hearing loss is constant feature of Alström (2, 4, 12) and is presented in all three of our patient. 80 %-88% of affected individuals will develop bilateral sensorineural hearing loss (3, 6, 11). This usually occurs at a later age in childhood and is characterized by the initial loss of high frequency sounds. Progressive deterioration in hearing occurs. There is a high incidence of otitis media and fluid retention along with a high susceptibility to glue ear, which compounds the existing sensorineural impairment (3).

Cardiorespirotery feature include dilated cardiomyopathy occurs in approximately two thirds of patients with Alstrom Syndrome. The majority of those (60%) develop sudden onset CHF during their first months of life(3,6,7). A life-threatening episode of CHF can be one of the first symptoms noticed in affected infants, even before nystagmus is observed(7),in our patients the two female presented with infantile cardiomyopathy at age of two months before nystagmus while the third case was the boy he had cardiomyopathy at age of 10years and nystagmus started at age In addition to cardiac problems, AS-affected patients can have a variety of respiratory problems, including chronic asthma, sinusitis/ bronchitis, alveolar hypoventilation and recurrent pneumonia, one of the case getting recurrent chest infection.

Endocrinology features include Obesity in Alstrom Syndrome is an early and consistent feature observed in nearly all affected children 95 %(3). Excess weight gain does not usually begin until approximately 6 months to 1 year of age. Obesity our entire patient had truncal obesity and short stature and body mass index of more than 25 at early age. Hyperinsulinemia usually developed between ages 18 months and 4 years (92%). Insulin resistance and hyperinsulinemia, two of the earliest metabolic changes in Alstrom Syndrome, have been observed in patients as young as 1 year of age, before the child is obese. Most children will eventually develop Type 2 diabetes is diagnosed in over 80%, it may be present as early as the age of 4, with the median age of onset at 16 years. Acanthosis nigricans, skin condition sometimes associated with obesity and hyperinsulinemia (7,15). It presented in our three cases but we observe that it appear in the two female before one year while in the male it appears at age of 10 years.

Hyperlipidemia, particularly hypertriglyceridemia, can be present from early childhood. In some patients, a sudden, rapid rise in triglycerides places them at risk for pancreatitis. A hypothyroid condition, mostly primary (low free thyroxine (FT4), high thyroid-stimulating hormone (TSH)), is observed in approximately 20% of patients. Other endocrinologic manifestations of AS include hypothyroidism, hypogonadism (particularly among men), alterations in the onset of puberty, ovarian cysts and hirsutism (among females), and short stature with abnormalities in the IGF-growth hormone system [3,13].

Dermatologic findings include Acanthosis nigricans, found in our three patients, consists of areas of hyperpigmentation and papillary hypertrophy, usually on the neck and the flexor creases (3, 15). These skin changes sometimes occur in association with obesity or diabetes.

Liver disease, pulmonary fibrosis and renal failure. Additional features in some cases include hypothyroidism, male hypogonadism, short stature and mild to moderate developmental delay (25-30%) however the majority of patients are of normal intelligence (5,7,16,17).

Molecular genetic testing

Alström syndrome is associated with ALMS1 gene. ALMS1 gene is estimated to detect mutations in 25%-40% of individuals (3,4).. The diagnosis of Alström syndrome is based on clinical findings but there is however considerable variation in the clinical picture (6,7,16,17).

Differential diagnosis

The similarity to other syndromes and delay in onset of some of the clinical features in Alstrom Syndrome often results in misdiagnosis. (10 – 15) A detailed comparison of features observed in Alstrom Syndrome and other disorders with phenotypic overlap

	Alstrom syndrome	Bardet beidal	Congenital achromatopsia	Leber amaurosis LCA	Wolfram (DIDMOAD)	cohen	Biemond II
vision	Cone dystrophy	Night blind with Cone -rod dystrophy	Cone dystrophy	Cone dystrophy (infancy)	Optic atrophy	Rod-cone dystrophy with bulls macula and peripheral vision loss	Coloboma Aniridia Cataract Microphthalmia
cardiac	+	Congenital heart disease					
respiratory	Respiratory failure						
Hearing loss	+	+			+		
renal	Glomeruloscler -osis	Structure anomaly			Diabetic nephropathy		
obesity	+	+				+	+
DM	+	+			DI, IDDM		
hypogonadism	+	+					+
mental		retarded			Behavioral problem	delay	retarded
hepatic	steatosis	steatosis			+		
ortho	Short finger Flat feet scoliosis	Poly-synechi- brachy dactyl				Narrow limbs	Scoliosis Poly-dactyl
Face and head features		High arched palate				features	Microcephaly

Management

No treatment of cure, there is a must need for Intensive medical and multidisciplinary decisions. There is no treatment for the vision loss, there is rapid and progressive loss of visual function to <20/200 by 10 years of age and no light perception by 20 years of age. Annual assessment of vision and hearing; weight, height, and body mass index; heart (including echocardiography); plasma insulin concentration; lipid profile; plasma ALT, AST, and GGT concentrations; pulmonary function; thyroid function. Every two to three months, fasting plasma glucose concentration; closer follow-up if fasting or postprandial blood glucose concentrations are elevated. Twice-yearly urinalysis and plasma concentrations of electrolytes, uric acid, BUN, and creatinine. Every one to two years, renal and bladder ultrasound examinations if symptomatic and/or if urinalysis is abnormal.

Conclusion

A diagnosis of Alstrom Syndrome should be considered in infantile cone and rod retinal dystrophy, particularly if the weight a above the 90th percentile or if there is infantile cardiomyopathy. Early diagnosis may lead to better survival of affected children in special institute and genetic counseling in the case of future pregnancies. Multidisciplinary team has the most effective rule in management.

Author Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) nal approval of the manuscript version to be published. Yes.

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