Case Report

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Alstrom syndrome with classical findings: a rare case report of monogenic ciliopathy co-occurrence in twins

Sagun Ghimire, MBBS[a,*], Suman Simkhada, MD[b], Samir Thapa[b], Kiran Ghising, MBBS[b]

Introduction and importance: Alstrom syndrome is one of the rarest monogenic ciliopathy belonging to autosomal recessive disorder. The pathophysiology of Alstrom syndrome is not well understood but based upon the available medical literature its mechanism can be linked with recessive mutation in Alstrom syndrome 1(ALSM1) gene resulting in various multiple organ involvement and poor prognosis. Moreover the co-occurrence of such syndrome simultaneously in twins in same period of time is considered rare.

Case presentation: Monochorionic diamniotic twins male born to healthy parents with significant antenatal and natal history along with decreased vision in both eyes in both twins since neonatal period. Throughout the childhood the disease progressed without any confirmatory diagnosis during which the twins underwent simultaneous multiple systemic involvement such as legal blindness in both twins at the age of 11 years, insulin resistance and features of diabetes mellitus, sensorineural hearing loss, subclinical hypothyroidism and various deranged metabolic panels. Certain diagnosis of Alstrom syndrome was made at the age of 16 years in both twins after whole-exome sequencing.

Clinical discussion: Based on genetic profile alstrom syndrome is a unique diagnosis. Along with its multi-organ involvement features, its progression and prognosis should also be looked upon while diagnosis and management in such syndromic patients. The diagnostic delay in such cases is also a matter of concern which can result in further delay in halting adverse effects of the disease itself. The multidisciplinary approach with involvement of endocrionologist, ophthalmologist and audiologist can bring upon improvement in quality of life of the patients.

Conclusion: With the prevalence of 1 in million cases Alstrom Hallgren syndrome is one of the rare genetic disorder with poor prognosis. In our case we present classical findings in twins who were diagnosed as Alstrom syndrome concurrently and further diseases progressed simultaneously.

Keywords: Alstrom Hallgren syndrome, monogenic ciliopathy, twins

Introduction

Alstrom syndrome is a rare autosomal recessive genetic disorder, thought to have a prevalence of less than one per million in the general population. It is characterized by the progressive development of multi-organ pathology[1]. It is caused by recessive mutations in Alstrom syndrome 1 (ALMS1) (Chr 2q13). Although its function is not completely understood, evidence to date suggests that ALMS1 plays a role in ciliary function, cell cycle regulation, endosomal trafficking, cell migration, and extracellular matrix production[2]. Diagnosis of Alstrom Syndrome can be difficult because some features begin at birth and others emerge as the child develops. There is considerable variation both within and among families. The major phenotypes usually observed in children with Alstrom Syndrome include cone-rod retinal dystrophy beginning in infancy and leading to eventual juvenile blindness, sensorineural hearing impairment,

HIGHLIGHTS

- Alstrom syndrome is one of the rarest monogenic ciliopathy belonging to autosomal recessive disorder with the prevalence of 1 in million cases alstrom syndrome is one of the rare genetic disorder with poor prognosis.
- The pathophysiology of Alstrom syndrome is not well understood but based upon the available medical literature its mechanism can be linked with recessive mutation in ALSM1 gene resulting in various multiple organ involvement.
- The co-occurrence of such syndrome simultaneously in twins in same period of time is considered rare.
- The multidisciplinary approach with involvement of endocrionologist, ophthalmologist and audiologist can bring upon improvement in quality of life of the patients.

Departments of [a]Surgery and [b]Internal Medicine, KIST Medical College and Teaching Hospital, Gwarko, Lalitpur, Nepal

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: Department of Surgery , KIST Medical College and Teaching Hospital, Gwarko, Lalitpur, Nepal. Tel.: +977 9846709636.*
E-mail: Sagunghimire01@gmail.com (S. Ghimire).

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insulin resistance, and obesity. In some cases, infants present with congestive heart failure (CHF) due to dilated cardiomyopathy (DCM). As patients reach adolescence, more of the major phenotypes develop, including type 2 diabetes mellitus (T2DM), hypertriglyceridemia, and adolescent-onset DCM. Short stature, scoliosis, alopecia, and male hypogonadism and hyperandrogenism in female patients may be present when patients reach adulthood. Pulmonary, hepatic, and renal phenotypes are progressive. Fibrosis in multiple organs has been described[3]. Currently there are no specific treatments for Alstrom syndrome that can cure the disease, prevent the complications, or reverse the complications. A multidisciplinary approach is currently preferred to detect, predict, and treat the complications of Alstrom syndrome[4]. The article is presented in accordance with CARE guidelines for case reports[5]. Here, we present a case of twin siblings with signs and symptoms consistent with AS and associated with two AMLS1 variants. This case report has been written as per Surgical Case Reports (SCARE) guideline[6].

Case summary

Patients demography

In this report we describe monochorionic, diamniotic twin boys who were born pre term at 36 weeks to a healthy 28-year-old mother and healthy 32-year-old father, with natal history of low birth weight of 1500 g in one twin and 1200 g in another twin with APGAR score of 6\10 and 7\10 and post-natal history of raised total serum bilirubin for which both twins were kept under phototherapy. There is no history of delay in attainment of age related milestones . Parents are of Asian heritage who deny consanguinity, both alive and well as well as two twins siblings currently aged 16 years . The family structure is outlined in (Fig. 1). Family history was not significant for any genetic disease on the paternal and maternal side.

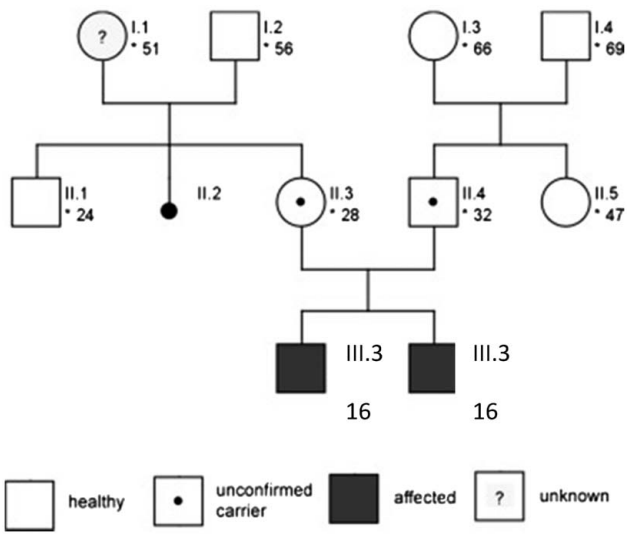

Figure 1. Pedigree chart of the twins family.

Clinical evaluation

On physical examination, there was evidence of central obesity in both twins with the BMI (BMI in both) being 34.9 kg/m^2. Their blood pressure was within normal percentile with a regular pulse of 80 beats per min. Behaviourally, they do not demonstrate several features concerning for autism spectrum disorder, including poor eye contact, lack of a social smile, and disinterest in social interaction. Their weight since birth has been increasing , and height within mid parental range. There was no evidence of poly- or syndactyly or any other features suggestive of Bardet-Biedl syndrome. Features of hirsutism were also absent on the face, abdomen, and arms. There was significant history of decreased vision in both eyes since neonatal period .Both the twins presented at 4 years of age with visual symptoms suggestive of photosensitivity. There were features suggestive of rotatory nystagmus. Amsler grid and colour vision tests were normal. Visual field revealed concentric contraction in both eyes. The fundoscopy showed pale optic discs, atrophic maculopathy, golden appearance of peripheral and midperipheral fundus, coarser pigmentary changes with a "bone-spicule" configuration and arteriolar narrowing. The red free pictures demonstrated the atrophy of internal retinal layers and the infrared pictures revealed the atrophy of the external layers of the retina in posterior pole of the fundus. The flash ERG showed a reduced amplitude of photopic and scotopic b-wave. The multifocal ERG demonstrated the normal function of the central retina. EOG revealed decreased Arden ratio in both eyes. The pattern VEP revealed the P100 amplitude reduction by 80% and elongation of latency by 120% in the right eye and normal in the left eye. Subsequent ophthalmologic exam showed visual acuity of counting finger from 2 and half metre binocularly only due to high hyperopia with amblyopia. The findings were consistent with cone-rod dystrophy through electroretinography (ERG). Subsequently there was progressive visual loss and legal blindness was declared to both of the twins at the age of 11 years. The cardiovascular examination was unremarkable with no any significant echocardiography and electrocardiography findings . There were not any features suggestive of congestive heart failure, myocarditis, dilated cardiomyopathy. Cardiac catheterization and endomyocardial biopsy were not performed. A comprehensive systemic panel did not identify any disease causing mutations and screening for evidence of metabolic and mitochondrial diseases was negative. The patients also showed features such as weight loss, polyuria, polydipsia, predilection to sweet foods.

Laboratory evaluations

All clinical and demographic data of our two twins are presented in (Table 1) which shows severe hyperglycaemia with diabetic ketoacidosis in both twins simultaneously . Subsequently it lead to hospital admission and was managed with an insulin regimen. Further investigations (Table 2) showed severe triglyceridemia, increase in transaspartase levels, grade two fatty liver ,mild splenomegaly, central obesity and severe acanthosis nigricans. Based on our clinical and laboratory evaluation diagnosis of severe insulin resistance was made. Following this, patient was treated with insulin sesnsitisers, fibrates, statins. On further assessment bilateral moderate sensory hearing loss was also present. Additionally MRI of the brain was done which did not showed any significant findings suggestive of space occupying lesions.

Table 1

Summary of the clinical characteristics of twins with Alstrom syndrome.

Clinical presentation	Twin 1	Twin 2
Sex	M	M
Age	16 years old	16 years old
Birth weight (g)	1500	1200
Vision		
Diminished visual acuity	+ (Infancy)	+ (Infancy)
Rotatory nystagmus	+ (Infancy)	+ (Infancy)
Photophobia	+ (4 years)	+ (4 years)
Hyperopic astigmatism	+ (4 years)	+ (4 years)
Reduced ERG	+ (Infancy)	+ (Infancy)
Cardiac	—	—
Respiratory		
Upper respiratory tract	Recurrent infections: pharyngitis, tonsilitis, purulent rhinitis, otitis media (4 years)	—
Lower respiratory tract	Obturative symptoms (4 years) Bronchial asthma (7 years)	Non-infectious episodes of obturation (2 years) Bronchial asthma (3 years)
Sensorineural hearing loss	+(13 years)	+(13 years)
Obesity	+ (4 years)	+ (4 years)
Hypogonadism	—	—
Renal	—	—
Orthopaedic	—	—
Hepatic	Elevated transaminase levels (13 years)	Elevated transaminase levels (13 years)
Diabetes	+	+
Endocrine	Subclinical hypothyroidism (13 years)	Subclinical hypothyroidism (13 years)
Mental development	—	—
Other clinical symptoms	Allergies (4 years)	

M, male.

Genetic findings

Genetic analysis using whole-exome sequencing (Fig. 2) was done in both twins at 16 years of age which showed pathogenic compound heterozygous mutations at chr2:g.73449346T > A in variant 1 in Exon 8 and at chr2:g.73490738C > T in variant 2 in exon 10 in both twins molecularly confirming AS. In both the twins the first variant c.2819T > A(p.Leu940Ter) was predicted to result in premature protein termination, and the second variant c.8779C > T(p.Arg2927Ter) was predicted to result in translational frameshift and premature protein termination along with total genes analyzed (Fig. 3)which confirmed Alstrom syndrome.

Currently both the twins are legally blind , have bilateral sensory hearing loss and are under medications for diabetic mellitus, hypercholesterolaemia. Both the twins are in constant follow up with the endocrinologist.

Table 2

Laboratory investigations.

S.N	Investigations	Twin 1	Twin 2
1.	Glycosylated Haemoglobin (HbA1c)	15.1%	11.8%
2.	Total cholesterol	369 mg/dl	283 mg/dl
3.	HDL-cholesterol	31 mg/dl	24 mg/dl
4.	LDL-cholesterol	97 mg/dl	70 mg/dl
5.	Triglyceride	2557 mg/dl	1593 mg/dl
6.	Post-prandial serum insulin	61.3 mU/l	45.9 mU/l
7.	Serum C peptide	1.85 ng/ml	3.46 ng/ml
8.	Urinary sugar	++++	++++
9.	Urinary acetone	Positive	Positive

Discussion

Alstrom syndrome is a rare autosomal recessive genetic disorder which is caused by a mutation to the ALMS1 gene which affects many systems in the body[3,7]. Symptoms usually appear in infancy with great variability in age of onset and severity of clinical symptoms, even within families bearing identical mutations[8]. Alstrom syndrome comprises of wide spectrum of disorder such as cone-rod dystrophy in infancy, hearing loss, childhood truncal obesity, hyperinsulinemia and insulin resistance, type 2 diabetes mellitus (T2DM), hypertriglyceridemia, short stature in adulthood, dilated cardiomyopathy (DCM), and progressive pulmonary, hepatic, and renal dysfunction. Fibrosis of unknown aetiology develops in multiple organs[8]. The estimated incidence of the syndrome ranges from 1 in 500 000 to 1 in 1 000 000[9]. Approximately 1200 cases of alstrom syndrome have been identified worldwide[10]. The condition is equally common in both males and females[11]. Alstrom syndrome is caused by mutation in ALMS 1 gene which is located on short arm of chromosome number 2[12,13]. Pathophysiology of Alstrom syndrome is related with the ALMS 1 protein which comprised of 4169 amino acids[14]. The ALMS1 protein is a protein which is found in primary cilia within the centrosomes and the basal bodies. Absence of the AMLS1 protein impairs the formation of cilia[15] Hence Alstrom syndrome can be classified as a ciliopathy which is a disorder that results in abnormal formation or functioning of cilia[16,17]. AMLS1 protein was found to be related to energy metabolism homoeostasis, cell differentiation, ciliary signalling pathways, cell cycle control and intracellular trafficking[13]. Photoreceptor dystrophy is most common symptoms which affects 100% of patients with ALMS and it develops in between birth to and first 15 months of life which is usually

A

INTERPRETATION

Diagnostic findings related to phenotype:

Variant 1:

Gene (Phenotype Number/ OMIM number)	Disease and Inheritance	Chromosome and Position	Variant details
ALMS1 (OMIM number: 203800)	Alstrom syndrome (AR- Autosomal Recessive)	chr2: g.73449346T>A	Exon/ Intron No: Exon 8 Nucleotide change: c.2819T>A Amino Acid Change: (p.Leu940Ter) Transcript Id: NM_015120.4

Molecular consequence	Allele Frequency	Zygosity	Clinical Significance
Nonsense	1000 Genome: Novel gnomAD : 0.0065%	Heterozygous	Pathogenic

B

Variant 2:

Gene (Phenotype Number/ OMIM number)	Disease and Inheritance	Chromosome and Position	Variant details
ALMS1 (OMIM number: 203800)	Alstrom syndrome (AR- Autosomal Recessive)	chr2: g.73490738C>T	Exon/ Intron No: Exon 10 Nucleotide change: c.8779C>T Amino Acid Change: (p.Arg2927Ter) Transcript Id: NM_015120.4

Figure 2. (A and B) Whole-exome sequencing suggestive of Alstrom syndrome.

accompanied by nystagmus and photophobia[18]. Initially there is loss in function of cons tissue followed by loss in function of rods which ultimately leads to early loss of vision[19].

In context to our case, both the twins patient developed ophthalmological symptoms suggestive of photosensitivity at 4 years of age. On evaluation visual acuity was found to be 20/540 and electroretinography showed features suggestive of con-rods dystrophy. History of progressive vision loss was present. Most of the ALMS patient develops truncal obesity, hyperlipidaemia, hyperinsulinemia and insulin resistance within first 5 years of life[20]. Hypertriglycemia is also common feature of this condition which will eventually lead to acute pancreatitis[21,22]. Clinical features of our patients include severe acanthosis nigricans, polyuria, polydipsia and central obesity. Laboratory investigations showed severe hyperglycaemia, severe triglyceridemia, grade 2 fatty liver, raised in trans aspartate level.

ALMS patients may also show infertility caused by hypogonadism especially in men) and women may have polycystic ovarian syndrome, hirsutism, and insulin-resistant hyperandrogenism[23]. Features of hirsutism were absent in our patients. Other endocrinological conditions includes hypothyroidism, changes in the age of onset of puberty, and short stature as a result of alterations in the growth hormone/insulin-like growth factor 1 axis[24–27]. The Patient did not exhibit any features of short stature as the height of both individual lies in between 15th and 50th centiles. Cardiological conditions such as Dilated Cardiomyopathy and Congestive Cardiac Failure occurs in ~70% of patients during childhood or adolescent period which are common cause of death[28–30] But there were absence of features suggestive of congestive cardiac failure, dilated cardiomyopathy and myocarditis in our patients. Another important feature of ALMS is progressive sensorineural hearing loss, which occurs in the first decade of life in 70% of patients that may progress to a moderately severe hearing loss or deafness, between the first and second decades of life[24]. During auditory assessment of our patients were found to have bilateral moderate sensory hearing loss.

Renal failure, pulmonary failure and hepatic dysfunction are other common conditions present in AMLS patients[24]. Diagnosis

A

RPE65	100.00%	RPGR	100.00%	RPGRIP1	100.00%
RPGRIP1L	96.50%	RS1	100.00%	SAG	100.00%
SCAPER	100.00%	SDCCAG8	100.00%	SLC24A1	97.88%
SLC38A8	100.00%	SNRNP200	100.00%	SPATA7	100.00%
SRD5A3	100.00%	TIMM8A	100.00%	TIMP3	100.00%
TMEM237	100.00%	TOPORS	100.00%	TPP1	100.00%
TRIM32	100.00%	TRPM1	100.00%	TSPAN12	100.00%
TTC8	100.00%	TTLL5	100.00%	TUB	100.00%
TULP1	100.00%	USH1C	100.00%	USH1G	100.00%
USH2A	100.00%	VCAN	100.00%	VPS13B	100.00%
WDPCP	100.00%	WDR19	100.00%	WHRN	100.00%
ZNF408	100.00%	ZNF423	100.00%	ABCC6	100.00%
ACBD5	100.00%	ADIPOR1	100.00%	AFG3L2	100.00%
AHR	100.00%	ALPK1	100.00%	AMACR	100.00%
ARL13B	100.00%	ARL3	100.00%	ARSG	100.00%
ASRGL1	100.00%	ATXN7	100.00%	CA4	100.00%
CCT2	100.00%	CEP19	100.00%	CEP250	100.00%
CLCC1	100.00%	CLUAP1	100.00%	CTC1	100.00%
CTNNA1	100.00%	CYP2R1	100.00%	DHX38	100.00%
DMD	100.00%	DRAM2	100.00%	ELOVL1	100.00%
ESPN	100.00%	EXOSC2	100.00%	GDF6	100.00%
GNB3	100.00%	GRN	100.00%	HK1	100.00%
IFT172	100.00%	IFT27	100.00%	IFT74	100.00%
IFT81	100.00%	JAG1	100.00%	KIF3B	100.00%
LAMA1	100.00%	LIG3	100.00%	MAPKAPK3	100.00%
MIR204	100.00%	MMACHC	100.00%	MSTO1	100.00%
MT-TH	100.00%	MTTP	100.00%	MT-TP	100.00%
MT-TS2	100.00%	MVK	100.00%	NBAS	100.00%
NEUROD1	100.00%	OPN1SW	100.00%	P3H2	100.00%

B

GENES ANALYZED

Gene	Coverage	Gene	Coverage	Gene	Coverage
ABCA4	100.00%	ABHD12	100.00%	ACO2	100.00%
ADAM9	100.00%	ADAMTS18	100.00%	ADGRV1	100.00%
AGBL5	100.00%	AH11	100.00%	AIPL1	100.00%
AIRE	100.00%	ALMS1	100.00%	ARHGEF18	100.00%
ARL2BP	100.00%	ARL6	100.00%	ATF6	100.00%
ATOH7	100.00%	BBS1	100.00%	BBS10	100.00%
BBS12	100.00%	BBS2	100.00%	BBS4	100.00%
BBS5	100.00%	BBS7	100.00%	BBS9	100.00%
BEST1	100.00%	C1QTNF5	100.00%	CABP4	100.00%
CACNA1F	100.00%	CACNA2D4	100.00%	CAPN5	100.00%
CC2D2A	100.00%	CDH23	100.00%	CDH3	100.00%
CDHR1	100.00%	CEP164	100.00%	CEP290	100.00%
CEP78	100.00%	CERKL	100.00%	CFH	100.00%
CHM	100.00%	CIB2	100.00%	CLN3	100.00%
CLN5	100.00%	CLN6	100.00%	CLN8	100.00%
CLRN1	100.00%	CNGA1	100.00%	CNGA3	100.00%
CNGB1	100.00%	CNGB3	100.00%	CNNM4	100.00%
COL18A1	100.00%	COL4A1	100.00%	CRB1	100.00%
CRX	100.00%	CSPP1	100.00%	CTNNB1	100.00%
CTSD	100.00%	CWC27	100.00%	CYP4V2	100.00%
DHDDS	100.00%	EFEMP1	100.00%	ELOVL4	100.00%
ERCC6	100.00%	ERCC8	100.00%	EYS	100.00%
FAM161A	100.00%	FLVCR1	100.00%	FZD4	100.00%
GNAT1	100.00%	GNAT2	100.00%	GNPTG	100.00%
GPR143	100.00%	GPR179	100.00%	GRK1	100.00%
GRM6	100.00%	GUCA1A	100.00%	GUCA1B	100.00%
GUCY2D	100.00%	HCCS	100.00%	HGSNAT	100.00%

C

HMX1	100.00%	IDH3A	100.00%	IDH3B	100.00%
IFT140	100.00%	IKBKG	100.00%	IMPDH1	100.00%
IMPG1	100.00%	IMPG2	100.00%	INPP5E	100.00%
IQCB1	100.00%	KCNJ13	100.00%	KCNV2	100.00%
KIAA1549	100.00%	KIF11	100.00%	KIZ	100.00%
KLHL7	100.00%	LCA5	100.00%	LRAT	100.00%
LRIT3	100.00%	LRP2	100.00%	LRP5	100.00%
LZTFL1	100.00%	MAK	100.00%	MERTK	100.00%
MFRP	100.00%	MFSD8	100.00%	MKKS	100.00%
MKS1	100.00%	MYO7A	100.00%	NDP	100.00%
NMNAT1	100.00%	NPHP1	100.00%	NPHP3	100.00%
NPHP4	100.00%	NR2E3	100.00%	NRL	100.00%
NYX	100.00%	OAT	100.00%	OFD1	100.00%
OPN1LW	100.00%	OPN1MW	100.00%	OTX2	100.00%
PANK2	100.00%	PCDH15	100.00%	PCYT1A	100.00%
PDE6A	100.00%	PDE6B	100.00%	PDE6C	100.00%
PDE6G	100.00%	PEX1	100.00%	PEX2	100.00%
PEX7	100.00%	PHYH	100.00%	PLA2G5	100.00%
POC1B	100.00%	PPT1	100.00%	PRCD	100.00%
PROM1	100.00%	PRPF3	100.00%	PRPF31	100.00%
PRPF4	100.00%	PRPF6	100.00%	PRPF8	100.00%
PRPH2	100.00%	PRPS1	100.00%	RAB28	100.00%
RAX2	100.00%	RBP3	100.00%	RBP4	100.00%
RCBTB1	100.00%	RD3	100.00%	RDH12	100.00%
RDH5	100.00%	REEP6	100.00%	RGS9	100.00%
RHO	100.00%	RLBP1	100.00%	RP1	100.00%
RP1L1	100.00%	RP2	100.00%	RP9	100.00%

D

PAX2	100.00%	PDE6H	100.00%	PEX6	100.00%
PGK1	99.84%	PLK4	100.00%	PNPLA6	100.00%
POC5	100.00%	POMGNT1	100.00%	PRDM13	100.00%
RDH11	100.00%	RGR	100.00%	RIMS2	100.00%
ROM1	100.00%	RTN4IP1	100.00%	SAMD11	100.00%
SEMA4A	100.00%	SLC25A46	100.00%	SLC37A3	100.00%
SLC6A6	100.00%	SPP2	100.00%	SSBP1	100.00%
TINF2	100.00%	TMEM216	100.00%	TMEM231	100.00%
TRAF3IP1	100.00%	TREX1	100.00%	TRNT1	100.00%
TTPA	100.00%	TUBB4B	99.40%	TUBGCP4	100.00%
TUBGCP6	100.00%	UNC119	100.00%	USP45	100.00%
ZFYVE26	100.00%	ADGRA3	98.81%	AMN	100.00%
AP3B2	100.00%	ARMS2	100.00%	ATP13A2	100.00%
B3GLCT	100.00%	BBIP1	100.00%	BCOR	100.00%
BMP4	100.00%	C2	100.00%	C3	100.00%
CCZ1B	86.75%	CEP41	100.00%	CFB	100.00%
COL11A1	100.00%	COL11A2	100.00%	COL2A1	100.00%
COL9A1	100.00%	COL9A2	100.00%	CROCC	69.06%
CTSF	100.00%	CUBN	100.00%	CYP1B1	100.00%
CYP27A1	100.00%	DTHD1	100.00%	DYNC2H1	100.00%
EMC1	100.00%	FBLN5	100.00%	FOXC1	100.00%
FOXE3	100.00%	FOXI2	100.00%	FRAS1	100.00%
FREM1	100.00%	FREM2	100.00%	FSCN2	100.00%
FUT5	100.00%	GNPTAB	100.00%	GP1BA	100.00%
GRIP1	100.00%	HMCN1	100.00%	HTRA1	100.00%
INVS	100.00%	IRX5	100.00%	IRX6	100.00%

E

ITIH2	100.00%	ITM2B	100.00%	KCTD7	100.00%
KIF7	100.00%	LRMDA	100.00%	MFN2	100.00%
MT-ATP6	100.00%	MT-ND1	100.00%	MT-ND4	100.00%
MT-ND6	100.00%	MT-TL1	100.00%	MYOC	100.00%
NAALADL1	100.00%	NEK2	99.63%	NR2F1	100.00%
NUMB	100.00%	OCA2	100.00%	OPA1	100.00%
OPA3	100.00%	OR2M7	42.81%	PAX6	100.00%
PDAP1	100.00%	PDZD7	100.00%	PITPNM3	100.00%
PITX2	100.00%	PITX3	100.00%	PLD4	100.00%
PODNL1	100.00%	POMZP3	100.00%	PRTFDC1	100.00%
RB1	100.00%	RGS9BP	100.00%	RIMS1	100.00%
SLC24A5	100.00%	SLC45A2	100.00%	SLC7A14	100.00%
SMOC1	100.00%	SOX2	100.00%	SPG7	100.00%
STRA6	100.00%	TCTN1	100.00%	TCTN2	100.00%
TCTN3	100.00%	TEAD1	100.00%	TEX28	100.00%
TMEM126A	100.00%	TMEM67	100.00%	TTC21B	100.00%
TYR	100.00%	TYRP1	100.00%	UBAP1L	100.00%
VAX1	100.00%	VSX2	100.00%	WASF3	100.00%
WFS1	100.00%	WT1	100.00%	ZNF513	100.00%
ZPR1	100.00%				

*Percentage of coding region covered

Figure 3. (A–E) Total genes analyzed during whole-genome sequencing.

of Alstrom syndrome is quite challenging due to wide range of clinical presentation and also some symptoms presents later in life which decreases chance of diagnosing the condition early[31]. The molecular diagnosis of Alstrom syndrome is made when a patient is found to have two ALMS1 mutations, with one mutation coming from each parent. This screening is done by molecular genetic testing[31] Since two disease causing mutations are not always identified there are certain diagnostic criteria for various age groups. From infants to 2 years of age diagnosis is made if 2 major criteria are fulfilled (mutation in one allele of AMLS 1 and early cons-rod retinal degenerations) are present or 1 major criteria is present with obesity or dilated cardiomyopathy. From age

3–14 years diagnosis is made if 2 major criteria with at least one minor criteria (obesity/type 2 DM, hearing loss, renal failure, hepatic dysfunction, advance bone age) are fulfilled. Diagnostic criteria should be re-evaluated when patient grows elder. From age 15 through adulthood diagnosis is made if patient fulfills 2 major and 2 minor criteria[3]. In context of our case, Genetic analysis was done 4 year after the initial presentation to the hospital and based on a clinical phenotype suggestive of Alstrom syndrome, sequencing of ALMS1 was performed which showed pathogenic compound heterozygous mutations, molecularly confirming AS. The first variant (c.2816T > A; p. Leu939*) was predicted to result in premature protein termination, and the second variant (c.10837_10838delCA; p. Gln3613Alafs*2) was predicted to result in translational frameshift and premature protein termination which confirmed Alstrom syndrome. The phenotypic characteristics of alstrome syndrome can resemble Bardet-bidel syndrome which is a multi-system disorder. Primary ocular differential diagnosis due to visual impairment in first month of life include lebers congenital amaurosis and achromaptosia.

Presence of congestive heart failure and dilated cardiomyopathy receives a diagnosis of infectious myocarditis, mitochondrial dysfunction. Other differential diagnosis may include Usher syndrome and cohen syndrome[1]. Assessment of blood glucose level, Hba1c, gonadal function test (males), height and weight should be conducted for Endocrinal abnormalities. Electrocardiography and Echocardiographic examination should be carried out for underlying craniological abnormalities. Visual acuity, electroretinogram and audiometric assessment should be carried out to identify any sensory dysfunction. For the renal and Hepatic system renal function test and Hepatic function test should be performed[3]. ALMS is not curable but treatable condition. Assessment of various system should be done as disease affects multiple systems. A multidisciplinary approach is preferred for detecting, predicting and treating the complications of the syndrome but due to lack of any standard treatment protocol in management of such rare genetic disease have played an important role in acting as a potential hindrance in delaying the appropriate diagnosis and treatment of the patient. Similarly in our case as well due to absence of any standard modality guiding the diagnosis and treatment of the disease have resulted in late diagnosis when only the disease have progressed resulting poor prognosis. The disease condition affect many system and can eventually lead to various complications such as system failure. Thus the patient with Alstrom syndrome usually has shorter life span rarely exceeding 50 years of age[1].

Conclusion

With the estimated prevalence of 1 in 50 000 to 100 000 cases and around 1200 worldwide reported cases Alstrom syndrome is one of the rare genetic disorder. Alstrom syndrome is even rarer in twins. There is a significant diagnostic challenge in accurate diagnosis of Alstrom syndrome, as in this genetic disorder as patient advances in age various multi-system involvement arises. Moreover as the disease progresses the patients prognosis becomes even poorer. Genetic analysis is the mainstay modality for the diagnosis, and symptomatic management is the only effective means of diagnosis.

Ethical approval

Ethical approval is exempted in case of case reports in our Institution. Whereas written informed consent have been taken from patients mother itself.

Consent

Written informed consent has been taken with the parents (mother) of the twins and can be made available if asked upon by chief editor.

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Author contribution

S.G.: study concept, case presentation formulation, manuscript writing and review. S.S.: patient diagnosis and management , study concept, manuscript review. S.T.: manuscript review, discussion writing. K.G.: introduction writing, manuscript review.

Conflicts of interest disclosure

No any conflict of interest noted.

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The dissemination of the article data is freely accessed.

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This entitled paper was not invited.

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