Clinical Case Report

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Alström syndrome

A novel mutation in Saudi girl with insulin-resistant diabetes

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Abstract

Rationale: Alström syndrome is an autosomal recessive disorder characterized by hearing loss, blindness, obesity, non-insulin dependent diabetes, and others.

Patient concern: A 10 years old Saudi girl, who presented with diabetic ketoacidosis and found to have hearing loss and blindness.

Diagnosis: Alström syndrome.

Interventions: Multidisciplinary team approach, with echocardiography, hearing test, eye exam and genetic test for Alström syndrome.

Outcomes: The patient has retinitis pigmentosa, bilateral hearing loss, double diabetes with weakly positive anti-insulin antibodies and DNA analysis showed novel mutation for Alström syndrome.

Lessons: the combination of obesity, diabetes, hearing loss and blindness should alert the physician to test for Alström syndrome.

Abbreviations: DKA = diabetic ketoacidosis, MAF = minor allele frequency, MRI = magnetic resonance imaging, NGS = next-generation sequencing, TDD = total daily dose.

Keywords: ALMS1, Alström syndrome, double diabetes, insulin-resistant diabetes, Saudi

1. Introduction

Alström syndrome is a rare autosomal recessive disorder (OMIM; 203800) caused by mutations in ALMS1 gene in chromosome 2p13. It affects about 1:100,000 individuals[1] and only 800 patients with this disorder have been identified.[2] Alström patients typically show obesity, retinal dystrophy, sensorineural hearing loss, and endocrinological features including insulin- resistant diabetes, hypertriglyceridemia, hypothyroidism, and hypogonadism. Other features that lead to the correct diagnosis are dilated cardiomyopathy and progressive pulmonary, hepatic, and renal failure.[3,4]

Insulin- resistant diabetes is diagnosed in 80% of the affected individuals older than 16 years of age.[1] In general, monogenic diabetes is uncommon, accounting for 1% to 4% of pediatric diabetes.[5] The key features of insulin resistance syndromes are the presence of acanthosis nigricans with increased insulin concentrations or increased insulin requirement.

In this report we describe a patient with retinitis pigmentosa, sensorineural hearing loss, and diabetes mellitus. Diagnosis was made by molecular genetic analysis of ALMS1 gene. To date, a total of 239 disease causing ALMS1 mutations have been reported,[4,6] but to the best of our knowledge, the mutation found in the reported case has not been described before in literature.

2. Subjects and methods

2.1. Case presentation

A 10 years old Saudi girl came to the emergency department complaining of persistent vomiting, with hyperglycemia. Her blood gases showed metabolic acidosis and she was admitted in the intensive care unit for severe diabetic ketoacidosis and a newly diagnosed diabetes mellitus. Clinical examination revealed her weight on the 80th centile and her height on the 50th centile. Horizontal nystagmus with evidence of Insulin resistance in the form of acanthosis nigricans were observed (Fig. 1). Her biochemical profile was as follows: HbA1c was 14% and C-peptide level of 0.40 ng/mL (reference 1.1–4.4 ng/mL). Fasting lipid profile: cholesterol level is 4.57 mmol/L (3.10–5.10 mmol/L) and triglycerides level is 5.07 mmol/L (0.00–1.70). Liver enzymes and renal function test are normal. Thyroid stimulating hormone 2.75 mIU/L (0.35–4.94 mIU/L), free T4 is 12.57 pmol/L (9.01–19.05 pmol/L). ACTH level is normal.

Further evaluation with auditory test (Figs. 2 and 3) revealed bilateral moderate sensorineural hearing loss, right ear threshold 55 dBHL, left ear threshold 50 dBHL, and tympanogram type A.

Ophthalmological examination showed poor vision, poor color vision, retinitis pigmentosa with attenuated vessels, and mild pale disc.

MRI brain showed empty sella turcica (Fig. 4) and she has been evaluated by psychologist and found to have mental retardation. Echocardiography and abdominal ultrasound were normal.

Family history revealed a brother who has died at age of 12 years, after multiple admissions to the hospital due to his

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Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

The authors have no conflicts of interest to disclose.

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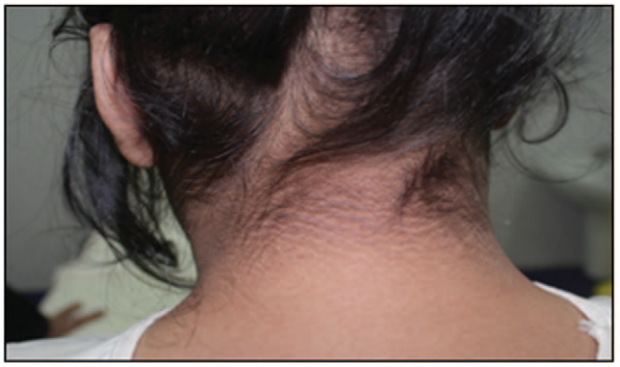

Figure 1. Acanthosis nigricans on the back of the neck of the patient.

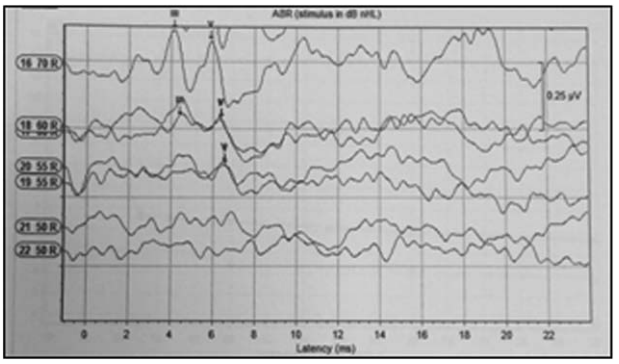

Figure 2. Audiometry of the patient (part 1).

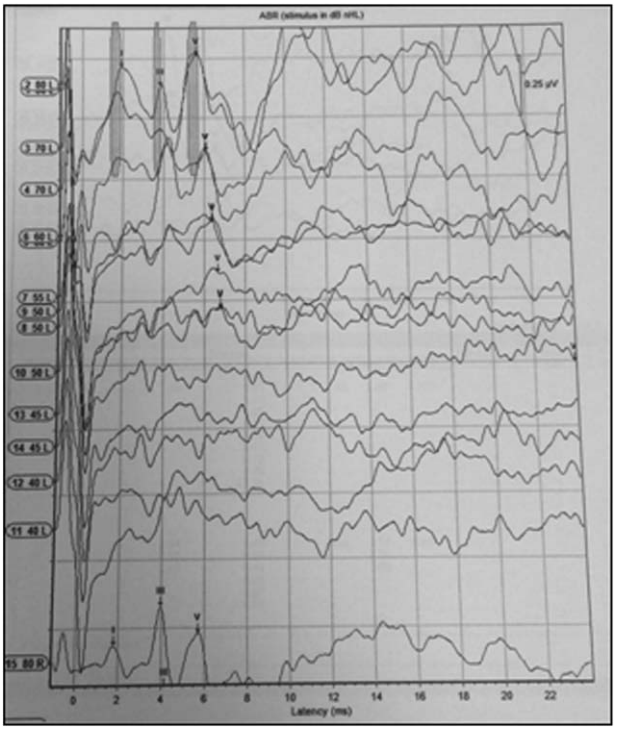

Figure 3. Audiometry of the patient (part 2).

cardiomyopathy. She has other 2 siblings, 12 and 20 years old, who were diagnosed with diabetes and currently on insulin and metformin. They also have poor vision and hearing loss. The family pedigree is illustrated in (Fig. 5).

The patient was labeled as having double diabetes based on presence of obesity, signs of insulin resistance, insulin deficiency and weakly positive anti-insulin antibodies So, started on intensive insulin regimen with insulin Glargine and premeals Aspart, TDD 0.85 U/kg/d, and metformin 500 mg twice daily. Upon follow-up in clinic after 6 months, her HbA1C dropped to 5.8%. Therefore TDD decreased to 0.4 U/kg/d. But there was no improvement in her vision or hearing.

3. Methods

Genomic DNA was fragmented, and the coding exons of the analyzed genes as well as the corresponding exon-intron boundaries were enriched using the Roche/NlmbleGen sequence capture approach, amplified and sequenced simultaneously by Illumina technology (next-generation sequencing, NGS) using an Illumina HiSeq 1500 system. The target regions were sequenced with an average coverage of 574-fold. For 99.4% of the regions

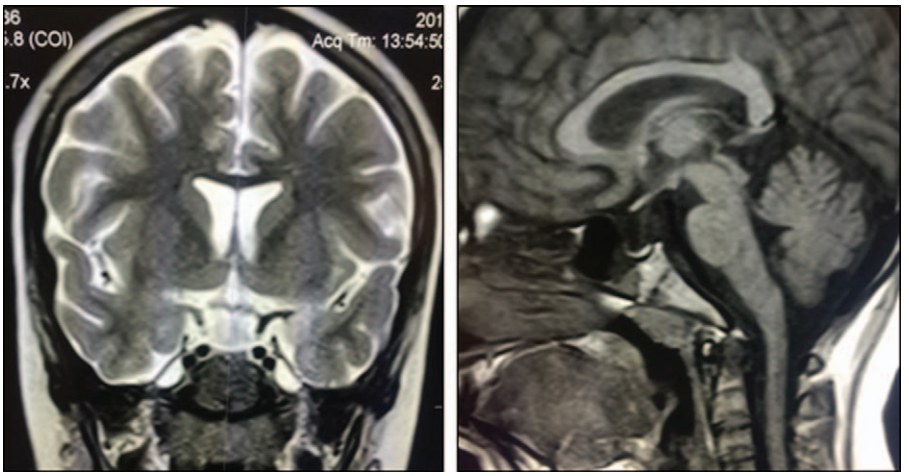

Figure 4. MRI brain demonstrates the sella filled with Cerebrospinal fluid and the infundibulum can be seen to traverse the space which is consistent with empty sella. CSF = cerebrospinal fluid, MRI = magnetic resonance imaging.

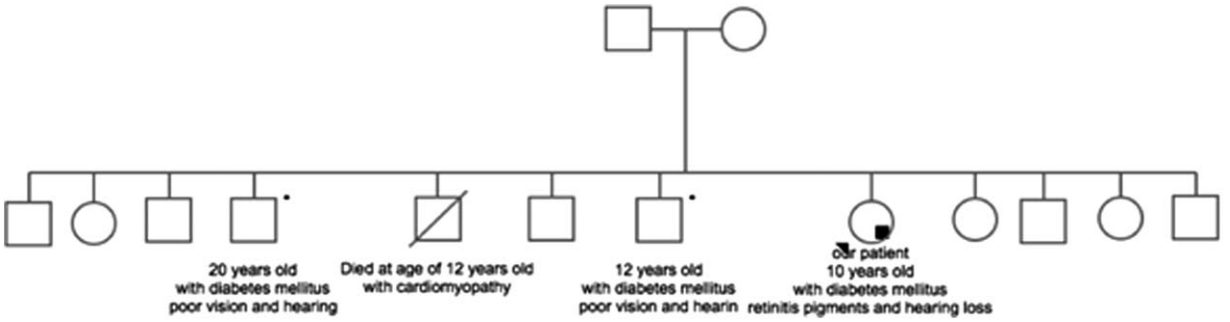

Figure 5. Family pedigree.

of interest a 20-fold coverage was obtained. NGS data analysis was performed using bioinformatics analysis tools as well as JSI Medical Systems software (version 4.1.2). Identified variants were filtered against external and internal databases and filtered depending on their allele frequency focusing on rare variants with a minor allele frequency (MAF) of 1% or less. Nonsense, frameshift and canonical splice site variants were primarily considered likely pathogenic. Assessment of pathogenicity of identified nonsynonymous variants was performed using bioinformatics prediction programs like Mutation Tester, Polyphen-2, Mutation Assessor, FATHMM, etc.

3.1. Molecular genetic analysis

Next-generation sequencing of known genes for Alström syndrome and Bardet-Biedl syndrome detected a homozygous deletion of 13 nucleotides in exon 20 of ALMS1 gene (c.12154_12166delCGCTCTGGGGAGC) (Fig. 6). The deletion results in nonsense mediated mRNA decay or in a frameshift leading to a premature termination codon (p. Arg4052Glyfs*2). Alström syndrome is an autosomal recessively inherited disease. Therefore, with the detection of ALMS1 mutation c.12154_12166del (p. Arg4052Glyfs*2) in homozygous state, the diagnosis of Alström was confirmed in our patient.

Additional analysis of known cilliopathy genes revealed one further putatively pathogenic heterozygous variant which is c. 12473T>C (p. Met4158Thr) in PKD1 gene. On the background of the identified ALMS1 mutation this aberration would not sufficiently explain the patient's phenotype. Nevertheless, a modifying effect of the detected variant cannot be ruled out.

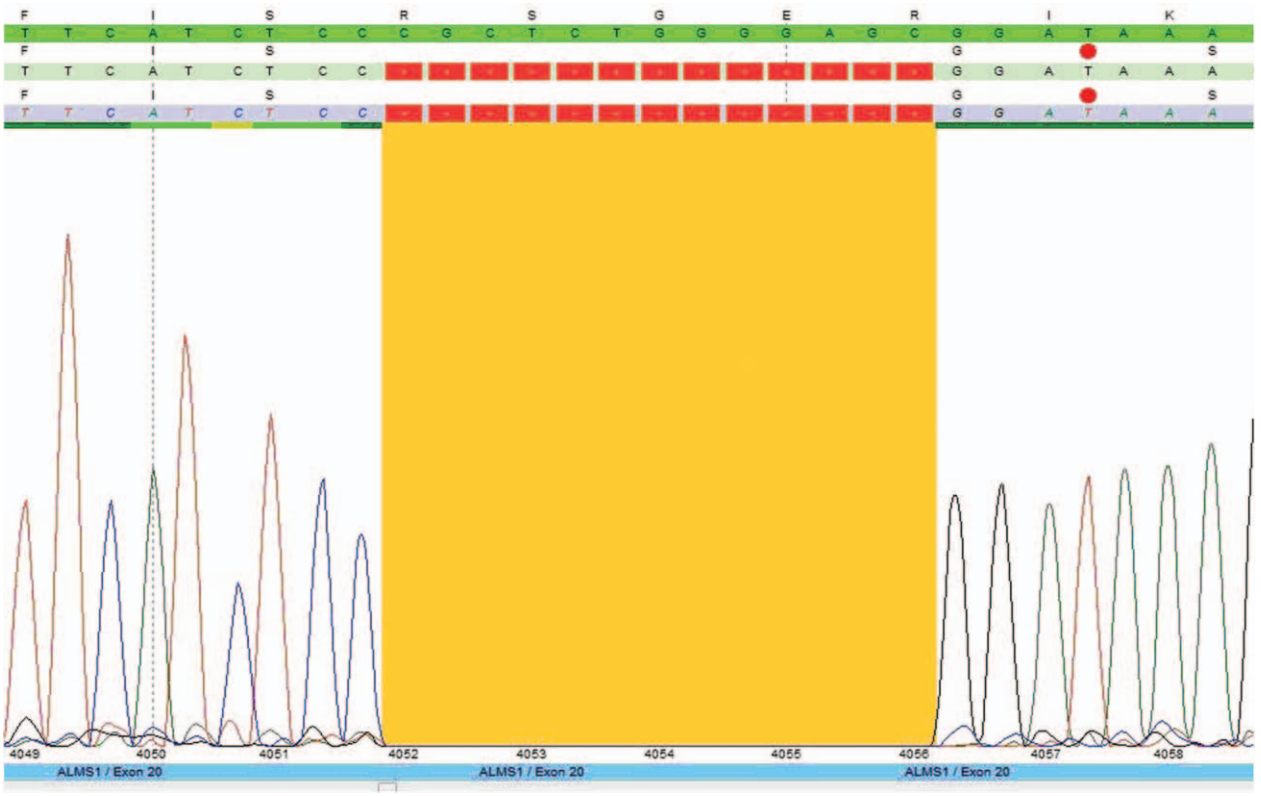

Figure 6. Molecular genetic testing of the patient showing a novel mutation.

4. Discussion

Alström syndrome (OMIM; 203800) is an autosomal recessive disorder characterized by obesity, hearing loss, retinitis pigmentosa, and dilated cardiomyopathy.[3,4] Approximately, 80% of patients with Alström syndrome develop noninsulin dependent diabetes. In our patient, we have been able to detect a homozygous deletion in exon 20 of ALMS1 gene (c.12154_12166del). This deletion results in nonsense or in frameshift leading to a premature termination codon (p. Arg4052Glyfs*2) and can be considered pathogenic.

In a cohort study of 204 families, worldwide, 109 novel mutations have been identified,[4,6] extending the number of known mutations in ALMS1 gene to 239. This mutations in exons 3, 5, 8, 9, 10, 12, 14, 15, 16, 17, 18, 19, and 21 as well as introns 2, 9, and 15. Mutations in exons 20, as in our case, have not been reported before. The high consanguinity rate in Saudi Arabia, ethnicity and geographical backgrounds all have significant impact on the distribution of mutations. We believe that there could be similar mutations but went undetected.

Regarding reports from Saudi Arabia, to date, 2 report cases by Aldahmesh et al and Abu-Safieh et al have reveled 4 and 2 novel mutations respectively.[7,8]

Most molecular genetic analysis studies target known ciliopathy genes for Alström syndrome mainly ALMS1 gene. Mutations in PKD1 gene have not been associated with Alström syndrome genotype or phenotype before. Renal failure occurs in 50% of affected individuals and typically does not emerge till after adolescence. Whether it is due to hypertension or other features of metabolic syndrome is unclear. Several hypotheses may explain the relation between the identified pathogenic variant in PKD1 gene and the future risk of developing kidney disease but it needs to be tested. So, we are aiming to follow-up our patient for further evaluation to determine the phenotype correlation with the disease.

By reporting this novel mutation, we are hoping to expand our knowledge regarding the genotypic spectrum of the disease, especially in the Saudi population. We set a strict follow-up plan for our patient and her family as genetic testing was done for each member of the family. It showed two brothers with the same novel mutation and the parents are heterozygous for the same mutation.

Acknowledgments

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