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CASE REPORT

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Supportive care in a patient with Alstrom syndrome with hyperphenylalaninemia and sleep problems

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Abstract

Alstrom syndrome is a rare genetic disorder with an autosomal recessive mutation in the ALMS1 gene. The disease's manifestations include ophthalmic problems, hearing loss, obesity, and cardiovascular disorders. In addition, medical cases include other organ complications. However, the overlapping variety of such symptoms with other diseases may delay the diagnosis. In this article, we describe the case of a 7-year-old female patient with Alstrom syndrome, and cardiovascular and hyperphenylalaninemia diseases since birth. Other symptoms included diabetes and ophthalmologic problems with skeletal disability. Blindness and hearing impairment were diagnosed, along with recurrence of respiratory problems at the age of 7 years. The patient's obesity-induced snoring predisposed her to uncontrolled blood glucose. In fact, respiratory tract problems and sleep disorders had occurred as a degraded cycle and left her with a severe disability for years. The similarity of the symptoms with other diseases had misled the physician in diagnosis. However, a polysomnography test (because of complaints of short sleep duration) recognized the source of the patient's sleep disorders and breathing problems. Eventually, we delivered a portable ventilator to the child for continuous positive airway pressure (CPAP) therapy. The child's breathing and oxygenation conditions improved. Using the ventilator and the CPAP system, we discharged her from the hospital without requiring oxygenation, in a stable condition. The procedure could prevent the patient from hypoxia and retinal problem.

KEYWORDS

Alstrom syndrome, obesity, polysomenography, sleep apnea, sleep medicine

1 | INTRODUCTION

Alstrom syndrome is a rare autosomal recessive genetic disorder caused by ALMS1 gene mutation with a prevalence of 1 million worldwide.[1] Molecular genetic analysis is used to confirm the clinical diagnosis, especially in asymptomatic heterozygous people. Symptoms first appear in the infancy period with different clinical manifestations, even in families with the same mutations.[2]

Symptoms of Alstrom syndrome include hearing loss (progressive bilateral sensorineural hearing loss), chronic and acute otitis media, severe retinal dystrophy, and visual

impairment since birth. These may also accompany other symptoms such as retinal degeneration, severe nystagmus, photophobia, and photosensitivity was reported.[2]

Multiple organ complications for example hyperinsulinemia, type two diabetes (T2DM), hypertriglyceridemia, short stature in adulthood, dilated cardiomyopathy (DCM), high blood pressure (HTN), progressive renal disease, pulmonary disorders, and multiple endocrine disorders (including hypogonadism and hyperandrogenism, hirsutism, alopecia, pathological examination of cystic ovaries, abnormal breast growth, premature puberty, endometriosis and irregular menstruation or amenorrhea) are visible in patients.[3]

Affected children are usually taller than 50% of normal children of their age, with rapid growth. However, the initial growth rate slows as the child matures, and hence, most of the adolescents and adults will have a short final height. Systemic abnormalities of insulin-like growth factors (IGFs), growth hormone deficiency,[4] pituitary dysfunction,[5] and short stature are apparent in Alstrom syndrome. Evidence about pituitary–adrenal axis and prolactin changes are not clear. Childhood obesity is an early and consistent feature obvious in most children with Alstrom syndrome. However, birthweight and body mass index (BMI kg/m^2) are within the normal range in the first few months since birth. Significant and rapid weight gain begins during the first or second year of life. Severe insulin resistance, impaired glucose tolerance, and acanthosis nigricans are, however, often present in early childhood.

Patients complain about neurosensory disorders, cardiovascular disease, renal, and hepatic abnormalities.[5] Manifestations include varying degrees of glomerular disease with reduced glomerular filtration and albuminuria. Hypertension, renal tubular acidosis, polyuria, and polydipsia develop over time. Nephrocalcinosis and lower urinary tract dysfunction, recurrent infections, vesicular reflux, urethral stricture with histopathologic focal glomerulosclerosis, and interstitial renal fibrosis described. Slowly progressive hepatic impairment begins with elevated transaminases and steatosis.[6] The initial manifestations are usually steatosis and hepatosplenomegaly.

Chronic respiratory infections that begin in the early childhood and lead to chronic bronchitis, asthma, and chronic rhinosinusitis are common among affected children. The severity of lung problems varies from recurrent bronchial infections to chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS). Pulmonary hypertension is common, indicating an inflammatory process in small airways. In interstitial fibrosis, in which patients cannot maintain adequate oxygen saturation may require persistent positive airway pressure (CPAP). Blood oxygen saturation can decrease rapidly.

Most people with Alstrom syndrome have usual intelligence, mild-to-moderate development delay, fine abilities, and intellectual development. Patients suffer from autistic spectrum troubles and seizures disorders. Hence, affected children may fail to clearly explain their vision and hearing disorders, and therefore, periodic examinations are required. However, patients (especially adults) may appear to be free of psychological problems, major depression, obsessive–compulsive and psychotic behavior.

Distinctive features of face such as deep eyes with round faces, hyperostosis frontalis, large corners, premature baldness on forehead, and thin hair have been reported in Alstrom syndromes. Most children have bulky feet and short toes with brachydactyly, but no polydactyly and syndactyly. Scoliosis and hypnosis are recurrent with varied severity levels. Also, they may have compound cardiovascular problems with limited lung function. People may experience chronic abdominal pain, distention, or constipation.

The phenotypic features of Alstrom syndrome are similar to Bardet–Biddle syndrome (BBS) and Wolfram, Cohen, Bimond II, and Usher syndromes. Alstrom syndrome is an autosomal recessive disorder caused only by a mutation in ALMS1. In contrast, Bardet–Biedl syndrome is caused by mutations in at least 14 genes involved in primary eyelash function.[1]

Diagnoses and treatments of the above symptoms are usually based on clinical observations and delayed (because of gradual development and variable expression).

The previous case reports lack the sleep problems of the patients with Alstrom. In the present case, we report the sleep problems of a child with Alstrom who was referred to the pediatric sleep clinic and treated. Reporting these types of cases can help to make readers familiar with sleep complications, prevent delays in diagnosis, and better management.

2 | CASE PRESENTATION

We hospitalized a 7-year-old girl with a known case of Alstrom syndrome in the pediatric clinic, with complaints of severe pneumonia, pulmonary hypertension, blindness, hearing loss, snoring, obesity, night sweating, and short sleep duration for several months. Although her disease was under control for 1 month since admission, we examined her for sleep disorders, short sleep durations, and anxiety.

3 | THE PATIENT'S PAST MEDICAL HISTORY

The patient was a term baby with a weight of 2.65 kg, height of 50 cm, and head circumference of 35 cm. She has

had a good growth in height, weight and head circumference in the first 2 months from birth with normal examination results. However, the physicians prescribed special milk for her due to the hyper phenylalanine diagnosed during screening tests (Table 1).

In addition, physicians noticed a heart murmur and patent ductus arteriosus (PDA) since birth. Therefore, she was a heart surgery candidate because of her condition. The child was resuscitated in the operating room before the survey, and hence, the surgeons postponed the operation. The slope of the weight graph increased rapidly after 2 months up to more than 95th percentile, and she became obese gradually.

At the age of 3, she had a history of uncontrolled blood glucose. At the age of 5, the child was diagnosed with fatty liver disease from her sonography results. At that age, she experienced a seizure attack. Other symptoms were impaired speech, delayed development of skills such as standing and walking, behavioral problems such as emotional immaturity and inappropriate outbursts, and clumsiness or poor coordination. According to the early symptoms, the doctors suspected that the disease was Bardet–Biedl, and for up to 3 years, the treatment was based on the diagnosis. For her lung disease, antibiotics were prescribed along with different respiratory sprays (like salbutamol and corticosteroids). She has also been under treatment with metformin and a diabetic diet due to her serum glucose.

With the onset of symptoms of hearing loss at the age of 4 years old, the physicians referred the child to a genetic center. Genetic tests confirmed that the ALSM1 gene was autosomal recessive in both parents (Table 2).

The patient had complaints of poor sleep during the night, although the arterial blood gas (ABG) was in the normal range (Table 3). After the first polysomnography (PSG), the physicians ordered the NIV therapy (bi-level ST, IPAP 10, and EPAP 4) with the setup shown in Table 4. However, the patient and her parents' compliance were too low to tolerate the mask and the ventilator.

The patient started for the first time to complain of the loss of eyesight at the age of 7. Blindness and hearing loss made the child restless, depressed, less active, and anxious. Parents complained about the child's short sleep duration at night, agitation, severe obesity (resistant to diet), and anxiety (resistant to depressants or anxiety drugs). The patient gradually became dependent on oxygen as she had shortness of breath without an oxygen supply.

For recurrent admission to a children's hospital, we performed a sleep PSG test. The PSG test results demonstrated that the patient spent 5:52 h in bed and had a total sleep time of 4:05 h. Sleep efficiency was as low as 69.7%. Analysis of sleep stage distribution revealed a decreased deep sleep (N3 phase) and increased REM phase (Figure 1).

The total respiratory events were 173, and the calculated respiratory disturbance index (RDI) was 42.3 per hour. Obstructive Apnea score was 28, Central apnea 1 mixed apnea was 0, and hypopnea was 142 (Figure 2).

The baseline oxygenation was 94% during sleep. PSG illustrated several dips associated with respiratory events. The lowest oxygen saturation was shown to be 84%, and the oxygen desaturation index ODI was 16.8. There were 63 total arousal times with an arousal index (Al) of 15.5 per hour. The diagnosis was obesity hypoventilation syndrome (OHS), and the patient underwent NIV treatment.

With hospitalization and ventilator training by skilled doctors, the shortness of breath, restlessness, anxiety during the day, and prolonged night awakenings gradually improved. Eventually, we delivered a portable ventilator to the child for continuous positive airway pressure (CPAP) therapy. We discharged the patient after a long period of hospitalization without requiring any oxygen supply. In inpatient follow-up visits, the patient showed that she completely tolerated a 4-h NIV therapy at nighttime. She did not require oxygen during the day with O_2 saturation of 95%. The ophthalmic check-up did not also show any blindness progression.

4 | DISCUSSION

Alstrom syndrome is a rare genetic disease that affects the cardiovascular, respiratory, endocrine, hepatic, gastrointestinal, auditory, ocular, and musculoskeletal systems. Partial nocturnal hypoxia gradually increases as silent symptom in obese children. Therefore, paying attention to sleep efficiency and sleep duration is a good step in discovering this silent problem. In present study, we explained the sleep problems and the treatment of a case with Alstrom syndrome.

The disease is characterized by sensorineural hearing loss and trunk obesity at an early age. Insulin resistance, hyperinsulinemia, type 2 diabetes, hyperlipidemia, hepatic steatosis, and progressive pulmonary fibrosis are the other

TABLE 1 The patient's phenylalanine test results.

Parameter	Result	Unit	Method	Reference range
Phenylalanine	952	Mmol/L	HPLC	0_124

TABLE 2 The parental genetic test results.

Gene	Inheritance	Disease	Varient	Classification	Zygosity
ALMS1	Autosomal recessive	Alstrom syndrome	NM_015120,4:C.10723C>T Chr2_73799730(hg19) (p.Gln3575Ter)	Stop gained/likely pathogenic	Homo

TABLE 3 Arterial blood gas test.

Test	PH	HCO_3	CO_2	BE	PaO_2
Result	7.42	20	31.3	−4	34.3

TABLE 4 Ventilator setup.

Rx settings: operating mode: bi-level ST
Mask type: nasal mask
IPAP: 10 cmH_2O
EPAP: 4 cmH_2O

complications. Typically, patients have short stature, cardiovascular problems, liver, and kidney malfunctioning combined with the disease.[7] The gradual development of fibrosis in several organs leads to a decreased life expectancy.

There is a considerable variation in the age of onset and severity of clinical symptoms, even within the family, possibly because of environmental and genetic variation.[8] Bardet–Biddle syndrome and Alstrom syndrome have similarities in manifestations.[9] The clinical similarities can easily mislead the physicians in the diagnosis of the Alstrom syndrome, as was the case in this case report.

For Alstrom syndrome, physicians have reported several problems such as cardiopathy and ocular complications from the birth, which require a variety of care and various health needs.[10] The challenges posed by obesity need to be examined in terms of controlling the obese diet and from the perspective of diabetes.[4] Particularly, the patients' obesity makes the treatment challenging. For example, in one study, anesthesia and airway care in these patients were studied. In addition, there is an increased risk of comorbidities for individuals whose BMI is over 25.[11,12]

A range of obesity-related respiratory disorders, obstructive sleep apnea (OSA), OSA with obesity-related sleep hypoventilation (ORSH), or OHS can be seen in overweight patients, which may cause small sleep-induced hypoventilation. This can cause a disrupted cycle that affects various organs.[13]

Obesity in childhood and adolescence can harm almost any organ system. Medical consequences of obesity include hypertension, diabetes, insulin resistance, dyslipidemia, respiratory dysfunction including sleep apnea and

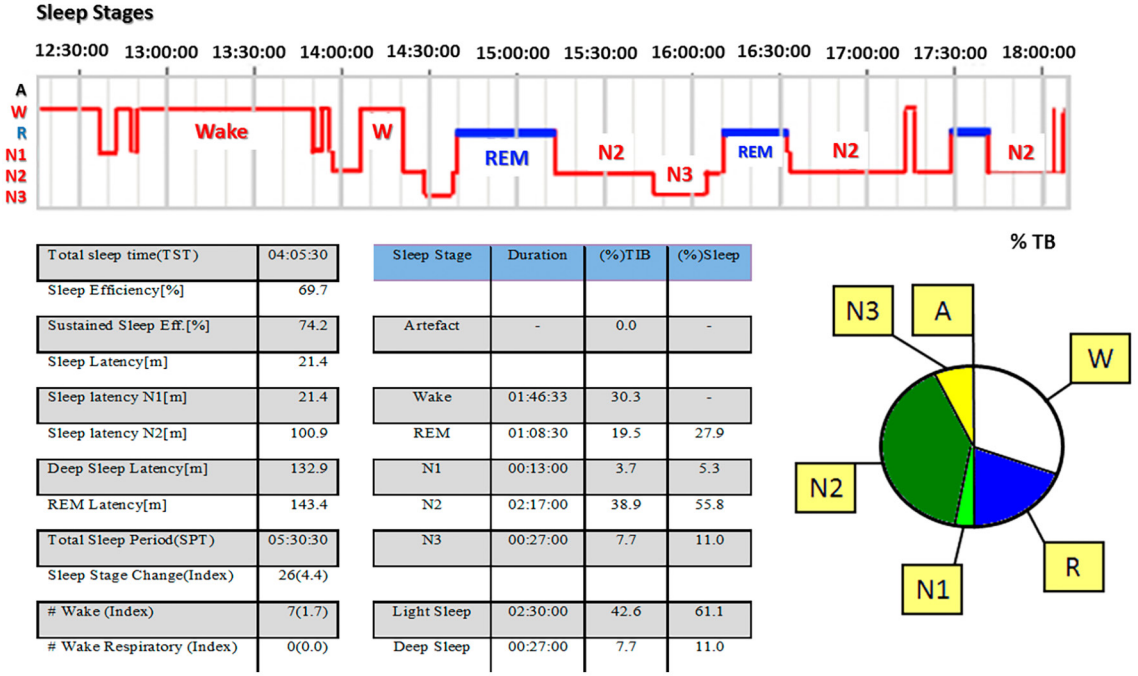

FIGURE 1 The patient's polysomnography test results.

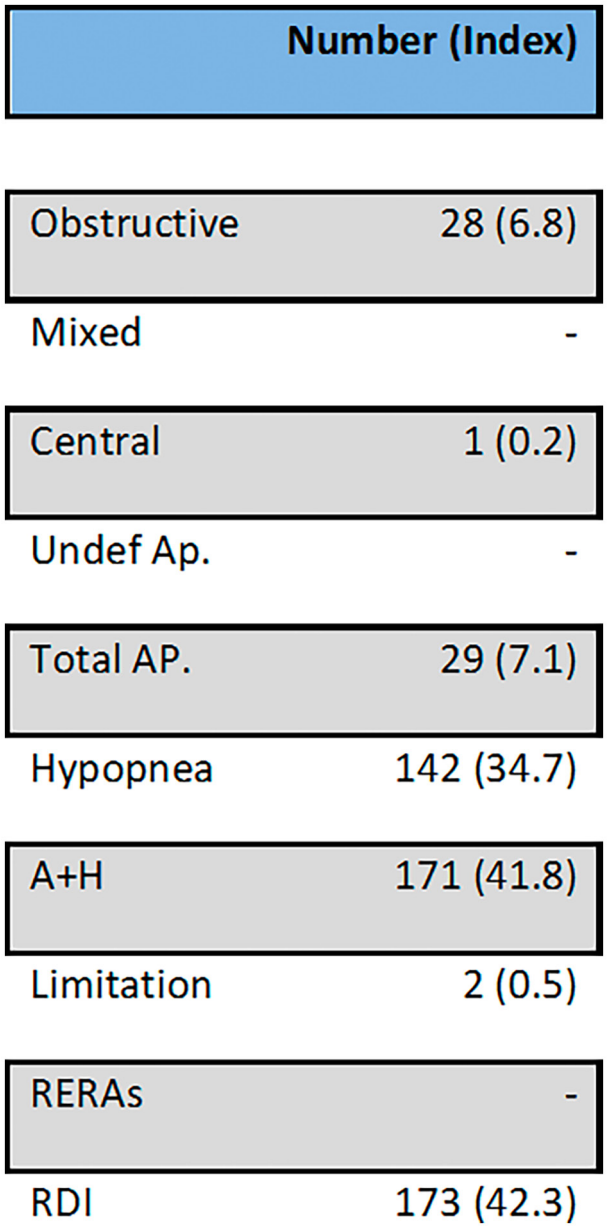

FIGURE 2 Results of the respiratory analysis.

OSA, polycystic vary syndrome, liver dysfunction, renal failure, tooth decay, and orthopedic problems.

Understanding the environment and reality of a child's life, along with physical and psychological assessment, help determine the level and nature of support needed to manage weight-related illnesses and achieve a healthy lifestyle change.[14] It is also important to note that the patients may suffer from sleep disorders because of obesity.

Due to the patient's intolerance to BiPAP, we again performed CPAP therapy with a PEEP pressure of 6 cmH_2O, and we gradually increased it to 8 cmH_2O. With the help of the nurse and gradually increasing the pressure, the patient completely tolerated it for 1 month. Night waking and anxiety disappeared. He did not have frequent lung infections. Eye sight vision did not improve during latter observation.

5 | CONCLUSIONS

Investigating sleep problems in syndromic patients is important to prevent the development of physical problems. These patients often suffer from silent nocturnal hypoxia due to the parent's lack of knowledge and the child's inability to express sleep problems. Sleep diseases in these children are hidden.

Reduced oxygen supply at night in these patients causes short sleep duration at night, which in the long-term may cause anxiety and irritability.

In Alstrom syndrome, the children often experience a lack of blood sugar control which may cause inability to lose weight. Obesity induces hypoventilation syndrome. The polysomnography test discovers sleep problems. NIV therapy (CPAP therapy, PEEP = 6 in our patient) reduces nighttime hypoxia, anxiety, and fragmented sleep. Patients will have better organ oxygenation in this treatment. It helps patients to control their weight. By improving and increasing the compliance of the lungs at night, children gradually reduce their dependency on oxygen during the day. By providing enough sleeping at night, anxiety, snoring, and respiratory obstructions related to obesity removed. This method of treatment reduces the child's need for hospitalization. In examining obese children when there is a doubt of syndromes or unclear diagnosis, investigating sleep problems may be a key step in preventing hypoxic silent problems. We emphasize the timely interventions for sleep problems by early initiation of oxygen therapy in cases of Alstrom syndrome with coexistent sleep problems.

AUTHOR CONTRIBUTIONS

Study conception and design: Shabnam Jalilolghadrm and Mersedeh Ghodsi. Data collection: Mersedeh Ghodsi and Marjan Ghodsi. Analysis and interpretation of results: Shabnam Jalilolghadrm, Fatemeh Saffari, Mehdi Alizadeh, AliReza Taremiha, and Mersedeh Ghodsi. Draft manuscript preparation and writing the article: Mersedeh Ghodsi.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Sleep Clinic of Qods hospital, Qazvin University of Medical Science. Restrictions, however, apply to the availability of these data, which were used under license for the current study and so are not publicly available.

ETHICS STATEMENT

We took the consent of the patient's parents to use her health information for research.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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