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Case report

Atypical case of Naxos syndrome with anhidrosis from India

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ABSTRACT

Naxos syndrome, known as Naxos disease, is a rare genetic disorder characterized by arrhythmogenic right ventricular cardiomyopathy (ARVC), woolly hair, and palmoplantar keratoderma. First described on the Greek island of Naxos, it involves mutations in genes such as desmoplakin, plakoglobin, desmocollin-2, and SRC-interacting protein (SIP), crucial for cardiac and skin integrity. Management necessitates a multidisciplinary approach involving cardiology, dermatology, and genetic counseling. A 3-year-old girl from a third-degree consanguineous marriage exhibited sparse hair, absent sweating, delayed tooth eruption, and increased skin fragility. Clinical examination revealed erosions in periorificial areas, periorbital wrinkling, abnormal dentition, and generalized xerosis with mild hyperkeratosis of the palms and soles. Clinical differentials included Anhidrotic ectodermal dysplasia and McGrath syndrome. However, whole exome sequencing identified a homozygous JUP gene mutation (exon 5), indicating Naxos syndrome, albeit lacking classical palmoplantar keratoderma and wooly hair. Cardiac evaluation is deferred until the child reaches 10 years due to known cardiac abnormalities in Naxos typically manifesting in the 2nd decade. This case deviates from classical Naxos syndrome by lacking typical palmoplantar keratoderma or woolly hair, where hair sparsity can also occur. Notably, skin fragility, unreported in Naxos literature, and anhidrosis accentuate its uniqueness. Emphasizing genetic counseling, especially in consanguineous families, this case contributes to the limited literature on pediatric Naxos syndrome in India. It signifies the first reported child with atypical Naxos syndrome associated with anhidrosis and skin fragility, accentuating the need for broader awareness and research in such presentations.

1. Introduction

Naxos syndrome, also known as Naxos disease, is a rare genetic disorder characterized by woolly hair, which is present from birth, palmoplantar keratoderma, usually occurring after infancy and arrhythmogenic right ventricular cardiomyopathy (ARVC). It was first reported in families from the Greek island of Naxos in 1986 and involves mutations in genes such as desmoplakin (1), plakoglobin, desmocollin-2, and SRC-interacting protein (SIP). These are components of desmosomes which are the major cell adhesion junctions prominent in the epidermis and cardiac tissue which are crucial for cardiac and skin integrity. The main complication is heart failure and sudden cardiac death in childhood and adolescence (2).

2. Case report

A nine-year-old girl presented with very minimal hair over scalp, absence of hair over eyebrows and reduced sweating since 2 months of age. Her parents give h/o delayed tooth eruption, and increased tendency of peeling of skin to form raw areas. H/o atopy was present in the child and her father. No h/o chest pain, palpitations, and syncope. The developmental milestones of the child were normal. She is the first child born to third degree consanguineous parents who are expecting the second child. Other members of the family were not affected.

On general examination, the child was active and thriving well. Her pulse rate was 110/min, and she had a regular blood pressure of 100/70 mmHg. Systemic examination was found to be within normal limits.

Cutaneous examination revealed sparse brittle hair over scalp and absence of hair over bilateral eyebrows. Hair shaft microscopic examination showed elliptical cross section, axial rotation and kinking. Periorbital wrinkling was noted.

There were multiple erosions noted over periorificial areas. Intraoral examination revealed abnormal dentition. Marked xerosis was noted over skin on the rest of the body. Palms and soles showed thickening of skin along with hyper linearity with mild hyperkeratosis of the palms and soles.

Clinical differentials included Anhidrotic ectodermal dysplasia and McGrath syndrome.

Routine investigations were done which were found to be within normal limits. Whole exome sequencing was done which identified a homozygous JUP gene mutation (exon 5) variant c.794G>A (p.Arg265His), indicating Naxos syndrome.

ECG done showed sinus rhythm and did not reveal arrhythmias. Since the child was asymptomatic, further cardiac evaluation is deferred until she reaches 10 years due to known cardiac abnormalities in Naxos typically manifesting in the 2nd decade.

3. Discussion

Protonotarios et al. described a recessively inherited disease among four families in the Greek island of Naxos (1). Naxos disease is characterized clinically by palmoplantar keratoderma, woolly hair, and arrhythmogenic right ventricular cardiomyopathy (ARVC). They also mapped the genetic locus of Naxos disease to chromosome 17q21 and identified the plakoglobin gene mutation to be responsible.

Norgett et al. however identified desmoplakin gene mutation to be the culprit behind Naxos syndrome (3). The uniting element being that both plakoglobin and desmoplakin are involved in the desmosomal integrity and structure. Later, a 2-base pair (TG) deletion at the 3′ end JUP gene encoding for desmosomal proteins plakoglobin and desmoplakin was identified as the cause of Naxos disease.

Woolly hair is a structural abnormality of scalp hair where the rate of hair growth is usually normal but the anagen phase is truncated, resulting in shorter hair. In Naxos, woolly hair appears from birth. Palmoplantar keratoderma, however develops during the first year of life when the child starts to move around with their hands and feet.

The cardiac anomalies are characterized by tachycardia and ventricular arrhythmias. The histopathology of myocardium shows partial degeneration of the myo-

cardial wall with most of the muscle fibres replaced by fatty tissue with a few healthy fibres. These changes are mainly located over the right ventricle which justifies the right ventricular origin of most forms of VT observed in Naxos. Cardiomyopathy in Naxos disease usually presents in adolescence with 100% penetrance. Common manifestations include syncope, sustained ventricular tachycardia or sudden death. Patients with ARVC have an average annual risk of approximately 10% to develop sudden cardiac death (4).

This in turn makes the prevention of sudden cardiac death, the primary concern.

A multidisciplinary team approach including cardiology, pathology, genetics, and genetic counselling is recommended. Early screening and disease detection is thus of great importance. While there is no definitive cure for ARVC, treatment with beta blockers/antiarrhythmic medication is proven to be symptomatically beneficial. Since the disease transmission of Naxos syndrome is autosomal recessive, if both parents are carriers of the disease there is a 25% risk of having the affected child at each pregnancy. Since the mother of the child was pregnant during the time of presentation to us, adequate genetic counselling must be carried out along with cascade testing.

A close differential of Naxos is Carvajal syndrome. Here, left-sided ventricular cardiomyopathy occurs and becomes clinically apparent earlier during childhood with fifty percent of affected patients developing heart failure, leading to death during adolescence. Carvajal is caused by homozygous variants in desmoplakin, inherited as autosomal recessive and is characterized by woolly hair, striate palmoplantar keratoderma and left-sided ventricular cardiomyopathy.

4. Diagnosis

Considering the clinical presentation of sparse hair with woolly type of shaft abnormality and diffuse palmoplantar keratoderma a clinical diagnosis of Naxos syndrome was made. It was then confirmed by the presence of a JUP variant in homozygosity on whole exome sequencing.

5. Conclusion

What was interesting was that our case also shared similar clinical characteristics with previously reported cases of ectodermal dysplasia–skin fragility syndrome or the McGrath syndrome, these features being sparse hair, abnormal dentition, reduced/absent sweating, palmoplantar keratoderma and increased skin fragility seen as erosions around the mouth. To the best of our knowledge, atypical Naxos syndrome associated with skin fragility has not been reported earlier in literature in paediatric population accentuating the need for broader awareness and research in such presentations. Although we considered ectodermal dysplasia as a differential, based on the phenotypic and genotypic co relation, it can be considered a significant addition to the existing database.

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DISCLOSURE

All authors report no conflict of interest.

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