CASE REPORT

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Andersen-Tawil syndrome (ATS) – Case report and literature review

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Abstract

Andersen-Tawil Syndrome (ATS) is a rare genetic disorder inherited in an autosomal dominant pattern caused by mutations in the *KCNJ2* gene encoding Kir2.1 protein forming potassium ion channel, leading to disruption of cardiac and skeletal muscle repolarisation. Clinical symptoms include periodic paralysis, ventricular arrhythmia associated with QT prolongation and typical skeletal and facial dysmorphic features. The aim of the study was to present characteristic features of the rare Andersen-Tawil syndrome (ATS) within the face and oral cavity of a 9-year-old boy. The patient was diagnosed with Andersen-Tawil syndrome (OMIM#170390) at the age of 8 due to the positive family history, typical dysmorphic features, and the presence of mutation in the *KCNJ2* gene confirmed by genetic testing. Typical manifestations of ATS were diagnosed: cardiac arrhythmia, short stature, scoliosis and clinodactyly. Clinical examination revealed typical facial dysmorphic features of ATS: broad forehead, triangular shape of the face, hypertelorism, microstomia, low-set ears, and mandibular retrognathism. Intraoral examination revealed: high-arched palate, crowding in the dental arches, hypomineralisation of enamel and high incidence of dental caries. Dental age assessment by Demirijan pointed to delayed development of permanent dentition. Cephalometric analysis revealed skeletal class II with high angle vertical jaws relation. Diagnosis of ATS requires high index of suspicion because of a great variability in the clinical manifestation of the syndrome. The subtle nature of the dysmorphic features often delays the diagnosis of this syndrome, and its potentially lethal cardiac arrhythmia remaining undetected.

Key words

Andersen-Tawil syndrome, dysmorphic features, craniofacial complex

INTRODUCTION

Andersen-Tawil syndrome (ATS) is a rare genetic disorder characterized by the classic triad of symptoms: ventricular arrhythmia associated with QT prolongation in electrograms (ECGs), periodic paralysis and dysmorphic skeletal and facial features. It is inherited in an autosomal dominant pattern, but ATS occurs sporadically resulting from a heterozygous mutation of *KCNJ2* gene. The gene encodes the inward rectifier potassium channel Kir2.1 protein, highly expressed in the myocardium, skeletal muscle and brain. Kir2.1 also plays a major role in developmental signaling, accounting for the characteristic facial dysmorphic features [1, 2, 3].

Probably the first mention of the syndrome was made in 1963 by Klein et al., who reported a particular form of periodic paralysis combined with premature ventricular contractions [1]. The first complete description of the syndrome with the characteristic triad of symptoms was made in 1971 by Ellen Damgaard Andersen et al. [2]. The syndrome was not correctly characterized until a number of patients were reported by Tawil et al. in 1994 [3]. In 2003, it was suggested naming the syndrome "Andersen-Tawil syndrome" in recognition for Tawil's contribution to the syndrome.

The exact prevalence of ATS is unknown, but estimates of 1/1,000,000 have been made. By 2004, at least 104 ATS patients had been reported in the literature worldwide. To date, this number has probably doubled [4].

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For the diagnosis of ATS it is important to note that not all ATS patients present with the same symptoms, even within a single family. There are mutation carriers who are completely non-penetrant for the mutation and patients who show, in all possible combinations, one, two or three of the classic triad of ATS symptoms. The diagnosis of ATS can be established in the presence of two of the following three symptoms: 1) periodic paralysis, 2) *KCNJ2* mutation with electrocardiographic abnormalities (enlarged U-waves, ventricular ectopy, nonsustained ventricular tachycardia or a prolonged QTc interval), and 3) characteristic facial and skeletal dysmorphic features (at least two). A patient with only one of the features mentioned above can be diagnosed with ATS on condition that there is one family member with an established diagnosis [3, 5, 6].

The dysmorphic features are highly variable and include short stature, scoliosis, clinodactyly, syndactyly, brachydactyly, tapering fingers, hypertelorism, mandibular hypoplasia, low-set ears, malar hypoplasia, broad nasal root, micrognathia, ptosis, cleft palate, high-arched palate, broad forehead, thin upper lip, triangular shape of the face, and dental abnormalities (delayed tooth eruption, persistant primary dentition, oligodontia, dental crowding, enamel hypoplasia and discolorations) [7]. Novel findings include small hands and feet (<10th centile for age) and joint laxity. The mechanism behind the skeletal and cranial dysmorphologies in ATS has not been elucidated. One theory mentions dysfunction of osteoclasts as a result of alterations in ion homeostasis. However, a loss-of-function mutation in *KCNJ2* might impair the adequate functioning of osteoclasts by disrupting their ion balance. A problem with this theory is that the bone hypoplasia seen in ATS patients suggests an enhanced rather than impaired functioning of the osteoclasts [8].

Cardiac manifestations vary from an asymptomatic long QT syndrome to life-threatening ventricular tachyarrhythmia requiring an implantable defibrillator, but most patients exhibit either a long QTc interval or a prolonged QU interval with characteristic U-wave morphology [7]. Episodes of muscle weakness may fluctuate in severity and usually begin before the age of 10 years or in adolescence. Mild permanent weakness may be seen in some patients [9]. Recently, Yoon et al. colleagues described a distinct neurocognitive phenotype associated with ATS, characterized by deficits in abstract reasoning and executive dysfunction, suggesting that the clinical phenotypes of ATS may involve the central nervous system (CNS). These observations support previous studies that Kir2.1 has an important role in neural development [10].

Genetic testing may confirm the clinical diagnosis of ATS by revealing the presence of a pathogenic mutation in *KCNJ2*. In particular, mutational analysis could assist in the diagnosis of patients exhibiting only one of the ATS symptoms. It should, however, be kept in mind that a mutation in *KCNJ2* cannot be identified in a minority of ATS patients. Type 1 of ATS, in which a mutation in *KCNJ2* gene can be identified, accounts for about 60–70% of all ATS patients. The remaining 30–40% of ATS cases is designated as type 2 (ATS2), for which the genetic cause is still unknown [11, 12, 13].

The aim of the study was to present characteristic features of the rare Andersen-Tawil syndrome (ATS) within the face and oral cavity of a 9-year-old boy.

CASE REPORT

A 9-year-old boy was admitted to the Chair and Department of Paediatric Dentistry, referred by a cardiologist, with the aim of performing complex dental treatment and prophylaxis. According to information from the genetics department, the patient was diagnosed with Andersen-Tawil syndrome (OMIM#170390) at the age of 8 due to a positive family history, typical dysmorphic features, and the presence of mutation in the *KCNJ2* gene confirmed by genetic testing. The family history of the patient revealed the prevalence of a prolongation of the QT interval, ventricular arrhythmia, short stature and typical dysmorphic features in his mother, maternal grandfather and his mothers' sisters. The boy was diagnosed with long QT syndrome, short stature, scoliosis, clinodactyly of the fifth finger and neurocognitive defects, and he remained under the specialist control of a neurologist concerning possible occurrence of periodic paralysis episodes and muscle weakness.

Clinical examination, extraoral and intraoral photographs (Fig. 1, 2, 3), orthopantomograph (Fig. 4) and a lateral cephalometric radiograph were performed (Fig. 5). The physical examination revealed typical facial dysmorphic features of ATS: broad forehead, triangular shape of the face, hypertelorism, microstomia, low-set ears, mandibular retrognathia and convex facial profile. Intraoral examination revealed: high-arched palate, crowding in the dental arches, hypomineralisation of the enamel of permanent teeth and high incidence of dental caries. Dental age assessment by Demirijan indicated delayed development of the permanent dentition. Cephalometric analysis by Segner and Hasund revealed skeletal class II with mandibular retrognathism and high angle vertical jaws relation.

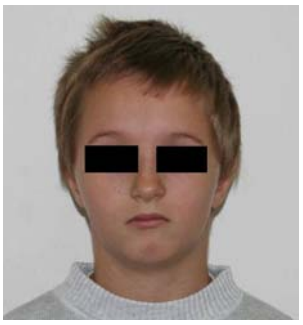

Figure 1. Extraoral photograph presenting characteristic facial features

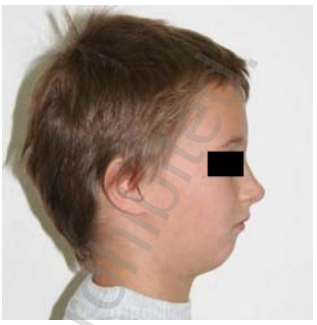

Figure 2. Extraoral photograph presenting convex facial profile pointing to the mandibular retrognathism

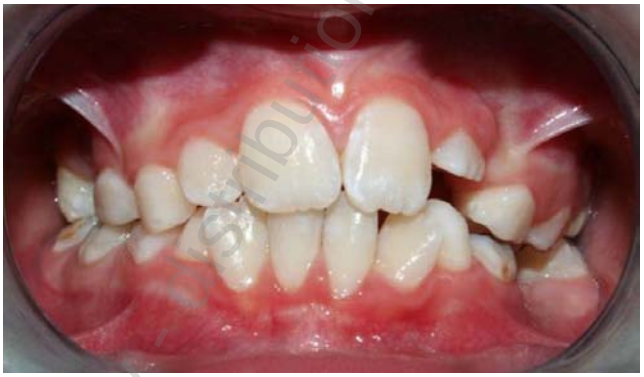

Figure 3. Intraoral photograph presenting dental arches in centric occlusion

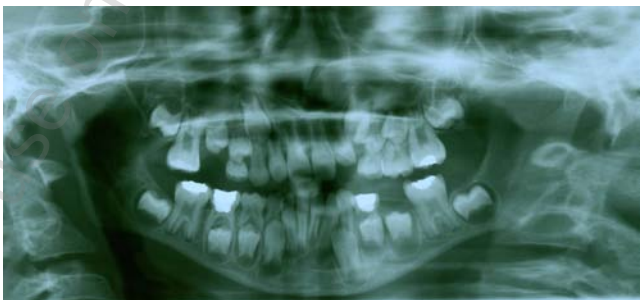

Figure 4. Orthopantomograph – assessment of dental age by Demirijan indicates delayed development of permanent dentition

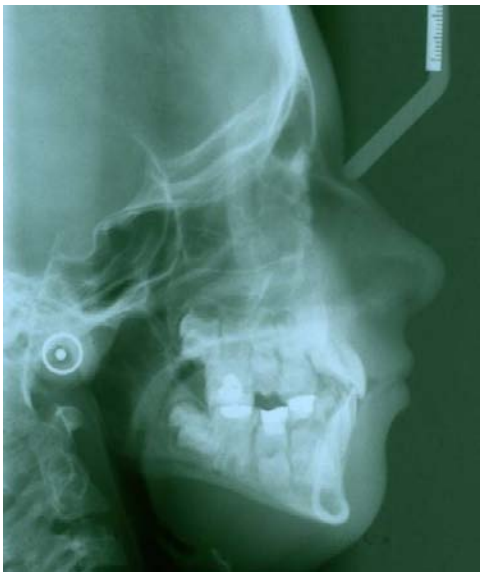

Figure 5. Lateral cephalometric radiograph – cephalometric analysis revealed skeletal class II with retrognathic mandible and high angle vertical jaws relation

DISCUSSION

A set of symptoms unique to ATS with regard to the other types of Long QT Syndromes (LQTS) are dysmorphologies that can be observed in the majority of ATS patients.

In 1971, Andersen et al. [2] described a boy with the following clinical symptoms: low-set ears, broad nasal root, mandibular hypoplasia, hypertelorism, soft and hard palate defects, scaphocephaly, clinodactyly, short stature, ventricular extra-systoles, and attacks of muscular weakness.

Sansone et al. [5] described 11 patients from 5 kindreds with the classic triad of symptoms: potassium-sensitive periodic paralysis, ventricular arrhythmia and unusual facial features. Tristani-Firouzi et al. [6] presented a comprehensive clinical and *in vitro* study performed on a total of 17 kindreds with 10 different mutations. In the study, at least 2 dysmorphic features were diagnosed in 28 of 36 *KCNJ2* mutation carriers: 14 of the 36 had low-set ears, 13 were diagnosed with hypertelorism, in 16 of the 36 small mandibles were reported, 23 had clinodactyly, and 4 were diagnosed with syndactyly. Cleft palate was observed in 3 of 36 ATS individuals and scoliosis in 4 of them. Dysmorphic features were in the majority of cases mild and non-disfiguring and could easily have been overlooked in routine clinical examination. Andelfinger et al. [14] assessed a large kindred in which ventricular arrhythmia (in female members) and periodic paralysis (in male members) segregated as autosomal dominant traits. In some mutation carriers, dysmorphic features were reported, including hypertelorism, syndactyly, clinodactyly, mandibular hypoplasia, cleft palate and scoliosis, which combined with cardiodysrhythmic periodic paralysis, have been named the 'Andersen syndrome'. Yoon et al. [7] prospectively examined 10 individuals with genetically confirmed mutations in the *KCNJ2* gene, and observed a characteristic pattern of typical craniofacial features, as well as dental and skeletal anomalies. The characteristic craniofacial features included broad forehead, short palpebral fissures, malar, maxillary and mandibular hypoplasia, thin upper lip, high-arched or cleft palate, triangular shape of the face, relatively long nose with fullness along the bridge and a bulbous tip, and mild facial asymmetry. Dental anomalies were diagnosed in all patients and included delayed eruption of permanent dentition, oligodontia, and dental root anomalies. Skeletal anomalies included small hands and feet, brachydactyly, 2–3 toe syndactyly and toe clinodactyly. Tengan et al. [15] described a 33-year-old Brazilian male with episodic weakness and facial and skeletal dysmorphic features, such as clinodactyly of the fourth and fifth fingers, short stature, thoracic scoliosis, high arched palate, micrognathia and retrognathia. Detection of a mutation in the *KCNJ2* gene confirmed the diagnosis of ATS. The mutation was also found in a 6-year-old daughter, who was diagnosed with such dysmorphic anomalies as micrognathia, clinodactyly of the fourth and fifth fingers, and short stature. The other three relatives of the patient presented only a fifth finger clinodactyly.

Haruna et al. [16] observed at least two dysmorphic features in 17 of their 23 patients (74%), with mandibular micrognathia most frequently observed (11; 48%). Short stature was found in 8 (35%); clinodactyly in 6 (26%); hypertelorism in 6 (26%); low-set ears in 5 (22%); broad forehead in 4 (17%); and scoliosis in 1 (4%). Kotulska and Kucharz [17] described a patient with suspicion of Andersen-Tawil syndrome on the basis of such clinical symptoms as periodic muscular weakness, cardiac abnormalities and micrognathia. The presence of elevated creatine kinase activity in the father of the patient was an additional significant suggestion for the diagnosis. Kamate et al. [18] reported the case of a 14-year-old boy with periodic paralysis, prolonged QTc interval, short stature and facial dysmorphic features like micrognathia, retrognathia, clinodactyly of the fifth fingers, hypertelorism and high arched palate. Chan et al. [19] reported the case of a 35-year-old woman who presented with episodic paralysis, typical ATS facial and skeletal features, including short stature, broad forehead, ocular hypertelorism, small head size, low-set ears, mandibular hypoplasia and clinodactyly of the fifth fingers and toes, as well as transient ventricular bigeminy and prolonged QT interval, fulfilling the criteria for long-QT syndrome. Her case was later diagnosed as major depression at the age of 35 years, in addition to the clinical triad of ATS. Barajas-Martinez [20] reported a novel *de novo* *KCNJ2* mutation resulting in classical phenotypic features of ATS as well as polymorphic ventricular tachycardia mimicry in a 10-year-old female patient. The patient presented facial and skeletal dysmorphic features such as micrognathia and retrognathia, broad-based nose, hypertelorism, clinodactyly of the third digit, and syndactyly of the second, third and fourth toes; moreover, syncope, frequent ventricular extrasystoles, non-sustained polymorphic ventricular tachycardia (PVT), BiVT, and prolonged QTc, secondary to a novel *de novo* mutation in *KCNJ2*. Thakkar et al. [21] described a 19-year-old patient with a suspected Andersen-Tawil syndrome with the clinical triad of periodic paralysis, ventricular arrhythmia and dysmorphic features: short stature, low set ears, micrognathia and retrognathia. His younger brother also had similar dysmorphic features and ventricular extra-systole. Fernlund et al. [22] described a 5-generation family in which 10 of 21 individuals appeared to be *KCNJ2* mutation carriers. All *KCNJ2* affected family members showed dysmorphic features characteristic for ATS. All of them were of short stature, had small mandibles, dental engagement with enamel hypoplasia, and were prone to caries. Missing or ectopic teeth were noted in 7 of the 10 individuals. Cleft palate was found in three. Toe-syndactylia was seen in 3 of the affected individuals. Digit clinodactylia was seen in all mutation carriers. Muscular weakness was noted in only 2 members and only 1 family member had periodic paralysis. Life-threatening ventricular arrhythmias were observed during childhood in 5 of the 10 mutation carriers.

Table 1 presents an overview of the most prevalent facial dysmorphic features reported in the literature worldwide. It is the presence of these traits, however subtle, which is often the clue to the diagnosis. In accordance with classical descriptions of ATS phenotypes, dysmorphic features could be recognized from early childhood, but the cardiac symptoms do not occur until 7 years of age, or later. Data on the dental phenotype of ATS patients are limited. Yet, dental malformations can be expected, as the locus of *KCNJ2* appears to be linked with tooth development. The most frequently observed dental problems include delayed tooth eruption, persistent primary dentition, oligodontia, dental crowding, enamel hypoplasia and discolourations [7].

Table 1. Facial dysmorphism in Andersen-Tawil syndrome (ATS)

Author	Year	Facial dysmorphologies
Andersen et al.[2]	1971	low-set ears, hypertelorism, broad nasal root, mandibular hypoplasia, soft and hard palate defects, scaphocephaly
Sansone et al.[5]	1997	broad nose, broad forehead, high-arched or cleft palate, hypertelorism, low-set ears, mandibular hypoplasia
Tristani-Firouzi et al.[6]	2002	high-arched or cleft palate, hypertelorism, low-set ears, mandibular hypoplasia,
Andelfinger et al.[14]	2002	hypertelorism, small mandible, cleft palate
Yoon et al.[7]	2006	broad forehead, high-arched or cleft palate, hypertelorism, low-set ears, mandibular hypoplasia
Tengan et al.[15]	2006	micrognathia, retrognathia, arched palate
Haruna et al.[16]	2007	broad forehead, hypertelorism, low-set ears, mandibular hypoplasia
Kotulska and Kucharz[17]	2008	micrognathia
Kamate et al.[18]	2009	micrognathia, retrognathia, hypertelorism, high arched palate
Chan et al.[19]	2010	broad forehead, hypertelorism, small head size, low-set ears, mandibular hypoplasia
Barajas-Martinez [20]	2011	micrognathia and retrognathia, hypertelorism, broad-based nose
Thakkar et al.[21]	2012	low set ears, micrognathia and retrognathia.
Fernlund et al.[22]	2013	small mandible, dental engagement with enamel hypoplasia, missing or ectopic teeth, cleft palate

CONCLUSIONS

The diagnosis of ATS requires a high index of suspicion because of the great variability in the clinical manifestation of the syndrome. The subtle nature of the dysmorphic features often delays the diagnosis of this syndrome, and its potentially lethal cardiac arrhythmia remaining undetected. Dental professionals may be the first physicians to identify unrecognized facial dysmorphism suggesting a genetic disorder, and refer the patient for further examination and investigation. Thus, it is very important to have the knowledge and awareness of the clinical manifestation of the rare Andersen-Tawil syndrome within the craniofacial complex.

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