Hypokalemic Periodic Paralysis, Facial Dysmorphism and Ventricular Arrhythmia (Clinical Triad of Andersen-Tawil Syndrome)

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Abstract
Andersen-Tawil Syndrome (ATS) is a rare potassium channel disorder, characterized by episodic weakness, ventricular arrhythmias and dysmorphic features (short stature, scoliosis, clinodactyly, hypertelorism, small or prominent low set ears, micrognathia and broad forehead). We report a case of hypokalemic periodic paralysis with dysmorphic facial features and ventricular arrhythmia resembling Andersen-Tawil syndrome.

Introduction
Ellen Andersen and colleagues in 1963, described two cases of familial periodic paralysis associated with facial dysmorphism. Later in 1971 they described a case of an eight year old dysmorphic boy who used to experience episodes of muscle weakness with ventricular extra systoles. In 1994 Tawil further contributed to diagnosis and etiology of this rare entity and subsequently the syndrome was named as Andersen-Tawil syndrome. It is a heterogeneous autosomal dominant or sporadic disorder with variable clinical expression characterized by the clinical triad consisting of ventricular arrhythmias, periodic paralysis, and dysmorphic features.

In 2001, mutation in KCNJ2 gene, which encodes the α-subunit of the potassium channel Kir 2.1, was identified in approximately 60% of patients with ATS. Andersen Tawil Syndrome is unique channelopathy and represents the first link between cardiac and skeletal muscle excitability. The genetic defect in ATS is not like that in other forms of potassium sensitive periodic paralysis and is distinct from the long QT syndrome locus. A little above 100 cases of Andersen-Tawil syndrome have been reported worldwide.

Case Report
19 yr old male born of non-consanguineous marriage, was brought with complaints of sudden onset of weakness of all four limbs since two days. Weakness mainly started from lower limbs and gradually progressed to involve upper limbs as well. Patient denied any history of drugs intake or consumption of high carbohydrate meal and strenuous physical exertion before the episode. He had no history of recent vaccination. Past history revealed a similar episode of weakness suffered by him one and half years back, for which he was hospitalized and he recovered fully within five to seven days.

On examination he was fully conscious, co-operative and well oriented. Pulse was 102 per minute, regularly irregular and his blood pressure was 100/70 mm hg. He was of short stature with height of 150 cm and body weight of 40kg. He had also typical facial features like low set ears, micrognathia and retrognathia. Detailed CNS examination revealed normal higher function and no cranial nerve deficit. His motor system examination revealed generalized hypotonia with power of grade 0/5 (MRC scale) and areflexia without any muscle wasting in all four limbs.

There was no sensory deficit. There was no bowel or bladder involvement. Rest of systemic examination was unremarkable.

His electrocardiograph (ECG) on admission showed ventricular bigeminy with QT interval of 0.36 sec. (Figure 3). Laboratory investigation revealed that serum potassium was

Fig. 1 : Showing low set ears, micrognathia and retrognathia

Fig. 2 : Showing micrognathia

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2.4 mEq/L; rest of the investigations including complete blood count, urine routine examination, serum sodium and chloride, serum creatine phosphokinase (CPK), arterial blood gas analysis and thyroid profile were all normal.

He was treated with potassium supplementation (initially intravenous and subsequently oral) and on the 2nd day of hospitalization his quadriplegia completely resolved. Repeat serum potassium was 4.3mEq/L and repeat ECG showed sinus rhythm with no extra systole. Trans-thoracic echocardiography ruled out any structural heart disease. Nerve conduction study and Electromyography undertaken subsequently were normal. Among the siblings, his younger brother was also found having short stature and similar facial features and irregular pulse. His ECG showed sinus rhythm with occasional ventricular extrasystole. However he never reported any episode of muscular weakness.

Based on the clinical triad of periodic paralysis, ventricular arrhythmia and dysmorphic features shown by the patient and the findings of his younger brother also having similar dysmorphic features and ventricular extra-systole, the patient was labeled as a suspected case of “Andersen-Tawil syndrome.” However genetic study could not be done to confirm the diagnosis due to lack of facility. The patient was discharged from hospital on full recovery after five days with advice to continue oral potassium supplements and tablet Acetazolamide and to report for regular follow-up in out-patient department.

### Discussion

Anderson-Tawil Syndrome is an uncommon heterogeneous autosomal dominant disorder characterized by periodic paralysis, dysmorphic features and cardiac arrhythmias.

In 1971, Anderson et al, described a boy with low-set ears, hypertelorism, broad nasal root, mandibular hypoplasia, soft and hard palate defects, scaphocephaly, clinodactyly, short stature, ventricular extra-systoles and attacks of muscular weakness. Tawil et al in 1994 first named this entity Andersen-Tawil syndrome and proposed a clinical triad including some minor anomalies, cardiac arrhythmia and potassium sensitive periodic paralysis as the criteria for establishing the diagnosis of this disorder.

Inheritance is autosomal dominant with incomplete penetrance and variable expressivity.

Two types of Andersen-Tawil Syndrome are distinguished by their genetic study.

- Type 1, which accounts for about 60 percent of all cases of the disorder, is caused by mutations in the KCNJ2 gene.
- The remaining 40 percent of cases are designated as type 2 (KCNJ2 gene mutation negative); the cause of the condition in these cases is unknown.

The protein made by the KCNJ2 gene forms a channel that transports potassium ions into muscle cells. The movement of potassium ions through these channels is critical for maintaining the normal function of skeletal muscles used for movement and cardiac muscle. Mutation in KCNJ2 gene alters the usual structure and functions of potassium channels or prevents the channels from being inserted correctly into the cell membrane. Many mutations prevent a molecule called PIP2 from binding to the channels and effectively regulating their activity. These changes disrupt the flow of potassium ions in skeletal and cardiac muscle, leading to the periodic paralysis and irregular heart rhythm, characteristic of Andersen-Tawil syndrome.

Researchers have not yet determined the role of the KCNJ2 gene in bone development and it is not known how mutation in the gene lead to the developmental abnormalities often found in Andersen-Tawil syndrome. Clinically confirmed diagnosis of ATS is defined by at least two of the following three criteria:

1. Presence of clear-cut episodes of transient muscle weakness with or without a fixed deficit, typically following exertion or prolonged rest or atypical history with otherwise typical examination findings (absent reflexes with normal sensation during an episode) OR unexplained hypokalemia between episodes OR abnormal long-exercise nerve conduction study.

2. Heart conduction defects: prolonged QTc interval on 12-lead electrocardiogram OR ventricular ectopy, including uniform or multiform premature ventricular complexes, polymorphic ventricular tachycardia (VT), or bidirectional VT.

3. Presence of two or more of the following physical features: low set ears, hypertelorism, small mandible, clinodactyly, syndactyly, micromelia of hands or feet —OR—
   - Meets one of the above three criteria and has at least one family member with two of the criteria —OR—
   - Does not meet the above three criteria, but possesses a mutation in the KCNJ2 gene.

Management of attacks of episodic weakness depends on the associated serum potassium concentration. Ventricular arrhythmias hold the greatest potential for morbidity and mortality. The cardiac arrhythmias are well controlled when the plasma potassium, levels is in the high normal range (4.2-4.5meq/L). Tocainide and flecainide have been tried with potassium supplements. Implantation of cardiac pacemaker/defibrillator is sometimes required. The episode of weakness may differ between patients because of potassium variability. Acetazolamide decreases the attack frequency and severity. Some patients need potassium sparing diuretics and potassium supplements. Prognosis mainly depends on management of cardiac arrhythmia. Though muscle weakness is disabling, patients usually remain ambulatory throughout life.

### Conclusion

Diagnosis of ATS requires high index of suspicion due to great variability in clinical presentation. Moreover the full syndrome is not always present. The subtle nature of the cardiac and dysmorphic features often delays the recognition of this
syndrome and its potentially lethal cardiac dysrhythmias, as the present case remained undetected during his previous episode of periodic paralysis. Clinical genetic testing of ATS type 1 is often not possible due to lack of facility and diagnosis of type 2 is essentially clinical.

References

