

## Andersen's Syndrome: a Single or Multiple Gene Channelopathy?

Valeria Sansone and Giovanni Meola

*Division of Neurology I, University of Milan, San Donato Hospital San Donato Mil., Milan, Italy*

### Abstract

We studied and performed genetic linkage studies and mutational analysis on 11 patients from 5 unrelated kindreds with Andersen's syndrome (AS). Our data suggest AS is a distinct periodic paralysis occurring in the setting of either hyper- or hypokalemia, with severe cardiac involvement (LQT) and distinct skeletal abnormalities whose gene defect is still unknown.

**Key words:** Andersen's syndrome, periodic paralysis, channelopathy, myopathy, LQTS.

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The periodic paralysis and the non-dystrophic myotonias are a group of hereditary myopathies that share the common phenotype of episodic muscle weakness or paralysis in the absence of abnormalities of the motor nerve, neuromuscular junction or contractile proteins [14]. A hallmark of these disorders is the acute depolarization of the sarcolemma that accompanies the paralytic episodes, usually sparing the cardiac and respiratory muscles.

Genetic linkage studies and mutational analysis have identified 3 chromosomes responsible for 3 different groups of periodic paralysis, each involving a different channel protein. The sodium-channelopathies are linked to chromosome 17q and include hyperkalemic periodic paralysis (in which attacks of weakness occur in the setting of increased serum levels of potassium), paramyotonia congenita (in which attacks are precipitated by cold), and potassium-aggravated myotonias, including the acetazolamide-sensitive periodic paralysis [5, 20, 21], PAM (in which myotonia is precipitated by a spontaneous rise in serum potassium levels). This condition has also been called myotonia fluctuans because of the fluctuating nature of symptoms. The calcium-channelopathies are linked to chromosome 1q and refer to hypokalemic periodic paralysis, in which attacks of weakness occur in the setting of decrease serum levels of potassium, usually precipitated by a carbohydrate-rich meal [22]. The chloride-channelopathies are linked to chromosome 7q and refer to both autosomal and recessive forms of myotonia congenita [9, 10]. Although a potassium channel has been identified in a group of hereditary ataxias [4], therefore disorders of the central nervous system, none of the periodic paralysis or the non-dystrophic myotonias has yet been linked to the adult skeletal muscle potassium channel.

In periodic paralysis, onset of weakness is often diagnosed by the patient, after the first attack and some measures can be used to abort the attack. When weakness

develops, all 4 limbs may be affected to the extent that the patient is unable to move or lift one arm or leg from the bed. The attack may last from several hours to days. Different events, foods, drugs or other factors have been identified so far in triggering the attacks of weakness. Individuals with periodic paralysis often appear normal between attacks, and do not complain of persistent muscle weakness and pain between attacks. However, in some variants a fixed weakness with a persistent myopathy can eventually develop [14]. In patients with hypokalemic periodic paralysis, repeated attacks of paralysis often give rise to persistent proximal weakness involving the lower limbs especially, generally not associated with significant muscle atrophy. The frequency of attacks might be worsened by the treatment of the disorder with oral potassium. On CT scans, weakness in the limbs correlates to abnormally high amounts of fat and connective tissue within the affected muscle groups [15].

Although the acute depolarization of the sarcolemma that occurs in periodic paralysis generally spares the cardiac and respiratory muscle membranes, in some forms of periodic paralysis, cardiac dysrhythmias are a primary manifestation of the disease, independent of serum potassium levels. Table 1 summarizes most of the reported cases so far. In most cases the familial nature of the disorder was clear and the cardiac involvement was severe, sometimes fatal, always involving ventricular dysrhythmias and independent of the serum potassium levels [6, 7, 8, 11, 16, 17, 18, 24]. Of the reported cases of periodic paralysis with cardiac involvement, Andersen described in 1971 a boy with attacks of muscle weakness, severe cardiac involvement and dysmorphic features and, although unable to identify the disorder amongst others described to that date, recognized the possibility of a new syndrome [1]. In 1994, Tawil et al described 4 patients with hyperkalemic periodic paralysis, ventricular arrhythmias and similar dysmorphic

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Table 1. Periodic paralysis with cardiac involvement.

	PERIODIC PARALYSIS	VENTRICULAR TACHYCARDIA
Klein et al. 1963	HypoKPP	+
Andersen et al. 1971	normoKPP	+
Levitt et al. 1972	HypoKPP	+
Lisak et al. 1972	normoKPP	+
Stubbs et al. 1976	hypoKPP	+
Kramer et al. 1979	hypoKPP	sinus arrhythmia
Yoshimura et al. 1983	normoKPP	+
Gould et al. 1985	hyperKPP?	+
Fukuda et al. 1988	?	+
Baquero et al. 1995	hyperKPP?	+

features to the boy described by Andersen and coined the term Andersen's syndrome (AS) [22]. Genetic linkage studies excluded chromosome 17 in these patients and the syndrome appeared distinct from a clinical and genetic point of view to previously reported periodic paralyses.

### Materials and Methods

We report on 11 patients from 5 unrelated AS kindreds. All patients underwent detailed clinical and neurologic examination. Careful study of the type of paralysis that occurred, the triggering factors, precipitating events, duration of the attack was undertaken. The patients were given a special form to fill in on the characteristics of the attack when this occurred. When the type of attack that occurred was unclear and not confirmed by the decrease or increase of serum potassium levels, hypokalemic and hyperkalemic challenges were done according to standard protocols. In some cases, muscle biopsy was done to assess the degree of muscle involvement. All patients had EMG studies, to look for myotonia according to standard protocols, including the exercise test [19].

For genetic studies [22], in two three-generation kindreds we used markers tightly linked to the hyperkalemic periodic paralysis gene [20] and four long QT syndrome loci (LQT 1-4) [23]. Linkage to the LQT loci was looked for because 10 of 11 patients had a prolonged QT interval and also because this was the only manifestation of the syndrome in family members of typical AS kindreds. Kindreds were not large enough to perform linkage analysis to the calcium channel gene but mutational analysis was carried out for possible mutations as previously described [21].

### Clinical overview

A clear autosomal dominant pattern of inheritance was present in 10 of 11 patients. The patients' age ranged from 8 to 87 years and cardiac symptoms, when present, usually preceded the onset of muscle symptoms. Cardiac symptoms at onset usually included syncope with cardiac arrest or bouts of symptomatic ventricular tachycardias. Onset of

muscle symptoms was with an episode of periodic paralysis, without pain and not always triggered by a known event or precipitating factor. In some patients the attacks of weakness had been undiagnosed until the onset of the more severe cardiac symptoms. In most cases of severe paralysis, serum potassium was determined during the attacks and in two patients spontaneous attacks occurred in the setting of clear hypokalemia, in two others in hyperkalemia and in the remaining patients in normokalemia. Challenges were not performed in all patients because of the severity of the cardiac symptoms present. All probands had a definite interattack proximal weakness suggesting a limb-girdle type myopathy, in the absence of significant atrophic changes and with only mildly decreased tendon reflexes. The clinical diagnosis of persistent myopathy was confirmed by the presence of tubular aggregates in the muscle biopsies. Clinical, percussion, lingual or EMG myotonia was absent in all patients, including the ones with the hyperkalemic form of periodic paralysis. In most patients there were no signs of central nervous system involvement except for mild psychomotor delay in one patient in whom tendon reflexes and a Babinski sign were present. Brain and spinal cord MRI were normal in this patient.

Cardiac involvement varied from the presence of a prolonged QT interval in the absence of clinical symptoms in grandparents to the severe bidirectional ventricular tachycardia and cardiac arrest in the probands. The prolonged QT interval was often an isolated finding in otherwise typical AS kindreds. Three patients required a pace-maker and the remaining were on other class 1 anti-arrhythmic drugs with careful control of their ECG and serum potassium levels because of a potential worsening of their arrhythmia during the treatment itself or worsening of the periodic paralysis.

None of the patients had the severe dysmorphic features described by Andersen in the original article, but all had recurrent distinct skeletal and facial features. Often it was the distinctive facial appearance that suggested the diagnosis of AS compared to other forms of periodic paralysis or to other causes of sudden weakness. Most patients were short and small for age, usually with small or protruded chin (micrognathia), low-set ears, broad nose, short neck, and excessively set apart eyes (hypertelorism). All had clinodactyly or syndactyly of the fingers of the hands or feet, and this was a feature in the parents and grandparents of the probands as an isolated feature together with the prolonged QT.

From a genetic point of view, three families were large enough to test the hypothesis that AS might be allelic with long QT syndrome. However, linkage to the four long QT loci was excluded. Linkage analysis had previously excluded linkage of AS to the hyperkalemic periodic paralysis locus on chromosome 17. Linkage studies in the present kindreds confirm these observations. In addition, mutational analysis excluded common hypokalemic periodic paralysis mutations in the dihydropyridine receptor gene.

## Conclusion

AS is a distinct periodic paralysis occurring in the setting of hypo-, hyper- or normokalemia [12] in the presence of severe cardiac involvement, independent of serum potassium levels. In addition to the cardiac and muscle symptoms, there are constant and distinct facial and skeletal features, often the clue to the diagnosis of this periodic paralysis. The finding of the triad of periodic paralysis, long QT interval and the distinct skeletal and facial features suggests a syndrome, although the genetic defect is still unknown. The recent description of a case of periodic paralysis with cardiac arrhythmia associated with a sodium channel mutation, with no evidence of skeletal or facial distinctive features, suggests that there exist syndromes of periodic paralysis with cardiac involvement distinct from AS [2].

Andersen's syndrome does not respect the conventional classification of the periodic paralysis on the basis of variations in serum potassium levels because the attacks of paralysis may occur with decrease or increase according to the type of periodic paralysis associated in the AS syndrome in that particular kindred. It is not unexpected therefore that linkage to the known sodium, calcium or chloride channel genes was excluded. In the prototypical heart-hand syndrome (Holt-Oram syndrome), the complex phenotype is the result of a single-gene mutation so that this hypothesis cannot be ruled out in AS also [3]. Alternatively, the genetic lesion could involve more than one gene explaining the coexistence of abnormalities of cardiac and skeletal muscle membrane excitability and at the same time accounting for the characteristic physical findings. Patch-clamp studies in the Schwartz-Jampel syndrome, a disorder similar to AS in combining abnormal skeletal muscle membrane excitability with distinctive skeletal features, demonstrated abnormalities in multiple channels suggesting a multiple-gene disorder [13].

In conclusion the diagnosis of AS is made on the finding of autosomal dominant inheritance of periodic paralysis, ventricular arrhythmia, especially LQT and distinctive facial and skeletal features. This implies that a cardiac screening should be done in all patients with periodic paralysis, regardless of cardiac symptoms. Although the full clinical syndrome includes the triad described above, partial manifestations of the syndrome are common in family members of patients with the full AS triad, often with a prolonged QR as the minimal manifestation. AS should be considered in the differential diagnosis of LQT syndromes especially in the presence of distinctive physical features.

## Address correspondence to:

Prof. Giovanni Meola, Division of Neurology 1, San Donato Hospital, via Morandi 30, 20097 San Donato Milanese, Italy, tel. +392 52774480, fax +392 5274717.

## References

- [1] Andersen ED, Krasilnikoff PA, Overvad H: *Ada Pediatr Scand* 1971; 60: 559-564.
- [2] Baquero JL, Ayala RA, Wang J, et al: *Ann Neurol* 1995; 37: 408-411.
- [3] Basson CT, Solomon SD, Weissman B et al: *Circulation* 1995; 91: 1326-1329.
- [4] Browne DL, Gancher ST, Nutt JG et al: *Nature Genetics* 1994; 8: 136-140.
- [5] Fontaine B, Khurana TS, Hoffman EP et al: *Science* 1990; 250: 1000-1002.
- [6] Fukuda K, Ogawa S, Yokozuka H, et al: *JElectrocardiology* 1988; 21: 71-76.
- [7] Gould RJ, Steeg CN, Eastwood AB, et al: *Neurology* 1985; 35: 1208-1212.
- [8] Klein R, Ganelin R, Marks JF, et al: *JPediatr* 1963; 62: 371-385.
- [9] Koch MC, Steinmeyer K, Lorenz C et al: *Science* 1992; 257: 797-800.
- [10] Koty PP, Pegoraro E, Hobson G et al: *Neurology* 1996; 47: 963-968.
- [11] Kramer LD, Cole JP, Messenger JC, Ellestad MH: *Chest* 1979; 75: 189-192.
- [12] Layzer RB, Lovelace RE, Rowland LP: *Arch Neurol* 1967; 16: 455-472.
- [13] Lehmann-Hom F, Iaizzo PA, Franke C et al: *Muscle & Nerve* 1990; 13: 528-535.
- [14] Lehmann-Hom F, Engel A, Ricker K, Rudel R: in Engel AG, Franzini-Armstrong C (eds): *Myology*. 2nd ed, New York, McGraw-Hill, Inc 1994, pp 1303-1334.
- [15] Links TP, Zwartz MJ, Wilkink JT et al: *Brain* 1990; 113: 1873-1889.
- [16] Lisak RP, LeBeau J, Tucker SH, Rowland LP: *Neurology* 1970; 20: 386.
- [17] Levitt LP, Rose LI, Dawson D: *N Engl J Med* 1972; 286: 253-254.
- [18] Stubbs WA: *Proc Roy Soc Med* 1976; 69: 223-224.
- [19] McManis PG, Lambert EH, Daube JR: *Muscle and Nerve* 1986; 9: 704-710.
- [20] Ptacek LJ, Tyler F, Trimmer JS, et al: *Am J Hum Genet* 1991; 49: 278-382.
- [21] Ptacek LJ, Tawil R, Griggs RC et al: *Cell* 1994; 77: 863-868.
- [22] Tawil R, Ptacek LJ, Pavlakis SG, et al: *Ann Neurol* 1994; 35: 326-330.
- [23] Wang O, Curran ME, Splawski I, et al: *Nature Genetics* 1996; 12: 17-23.
- [24] Yoshimura T, Kaneuji M, Okuno T, et al: *Eur J Pediatr* 1983; 140: 338-343.