FAMILIAL PERIODIC PARALYSIS

SEVEN CASES IN A DURBAN FAMILY

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We have recently had the opportunity of observing classical periodic paralysis in a White family living in Durban, and can find no report of this familial condition in the South African medical literature.

Familial periodic paralysis is an uncommon inherited disorder characterized by episodes of weakness or paralysis of skeletal muscle without any concomitant disturbance in the endocrine, renal or nervous system. The following are criteria in the diagnosis:[1]

1. Intermittent episodes of flaccid paralysis of the muscles of the extremities, with loss of deep tendon reflexes.
2. Loss of excitability to electrical stimulation of nerve and muscle.
3. No objective sensory changes during the paralytic episodes.
4. No impairment of mental faculties during the episodes.

Although the exact cause of the disease has yet to be determined, it has been shown that the episodes are associated with an alteration in skeletal muscle physiology. This is reflected by abnormal changes in serum chemistry during the episodes.

At least three distinct genetically-determined types of the disease have been described:[2]

1. *Classical periodic paralysis*[3]—in which there is hypokalaemia during the paralytic episodes; response to administered potassium salts; and precipitation of paralysis by manoeuvres which lower serum K^+, e.g. rest after exercise, excessive carbohydrate feeding, and injection of insulin or adrenaline—(i.e. a hypokalaemic type).

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2. *'Sodium-responsive normokalaemic periodic paralysis'* (i.e. a normokalaemic type).

3. *'Adynamia episodica hereditaria'*, in which the serum K^+ increases during the episodes (i.e. a hyperkalaemic type).

Of these three, the hypokalaemic type is the commonest; the family cases reported belong to this group. In this communication we have presented the clinical features of 7 members of the family. We hope later to present the results of a trial of spironolactone therapy that is at present in progress.

THE FAMILY

The original affected member came to South Africa at the turn of the century. The genealogical tree of her

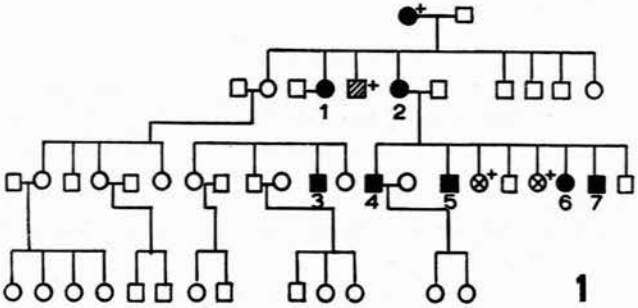

Fig. 1. Genealogical table. The cases reported are numbered and are shown as black squares (males) and circles (females). Unaffected males and females are shown as white squares and circles. The two crossed circles (+) indicate 'female, died in infancy', and the hatched square (+) 'male, died at 22 years following appendectomy; had 3 episodes of paralysis between age 16 years and death'.

descendants is shown in Fig. 1. This shows the inheritance pattern to be autosomal dominant. No evidence of any other hereditary disease was found in the family.

All seven of the living affected members were seen. One (case 1) had only one episode of paralysis in her life. Two (cases 2 and 3) had a mild form of the disease and had had spontaneous regressions. Another member (case 6) had mild episodes every week, while the remaining 3 cases had a particularly pernicious form of the disease—each had at least one episode of paralysis every day, and each required 30 - 40 G. of potassium chloride daily in order to remain active. It was to their credit that all were living full and normal lives.

CLINICAL FEATURES

A full description of the clinical features of periodic paralysis in over 400 cases has been presented by Talbott.[1] We have adopted his general scheme of presentation; this was done to facilitate comparison in order to obtain clinical perspective of the disease. A table of the features in each individual case is given for easy reference (Table I).

Age at Onset and Remission

In case 1 the one single episode occurred at the age of 19 years. In case 4 the first episode was at 18 months. In the others, the age of onset coincided approximately with the onset of puberty.

In cases 2 and 3 a spontaneous remission occurred at 41 and 22 years respectively.

Inciting and Precipitating Factors

An inciting factor was found in four of the seven cases. In case 2 the first episode occurred after prolonged exposure to cold and damp, in case 3 it followed involvement in a train accident, and in cases 5 and 6, it occurred during the night following participation in strenuous physical exercise.

Once the disease was manifest, a number of factors could either precipitate an attack or increase the severity if already present. Muscular inactivity (e.g. sitting still while watching football), particularly if preceded by strenuous exercise, was a precipitating factor in all cases, except of course case 1. Cold or damp weather adversely affected the disease in five cases. In case 4 the consumption of alcohol either started or worsened an attack; this was not reported by any of the others. In two cases the paralysis was more severe under emotional stress or tension.

In the cases in which daily potassium chloride supplements were taken, paralysis could be precipitated by withdrawal of KCl. It has also been noted by all the affected members that an excess of KCl puts them 'flat'.

Excessive intake of sodium chloride precipitated an episode in cases 3 and 5—both members had been advised to take salt tablets to prevent heat exhaustion when they moved to a more tropical area, and both have abandoned the practice.

In none of the cases did the size or type of meals make any difference to the paralysis. (We did induce paralysis in case 5 by administering 50 G. of glucose by mouth and 10 units of insulin by intramuscular injection.)

Prodromata

No specific prodromata were noticed by any of the cases.

Paralysis

In all seven cases the paralysis was bilateral (in case 7 there was a slight asymmetry of the weakness, but this was due to residual weakness in one leg from old poliomyelitis). In three of them (cases 1, 2 and 3) it involved mainly the legs and was only a partial paralysis. In the other four the paralysis involved the neck, legs, arms and back, in that order of sequence and severity; it progressed to complete paralysis unless KCl was taken. It was a flaccid type of paralysis and involved neither the muscles of the face or throat nor the sphincters. In only one case, on very rare occasions, did it affect the respiratory muscles (case 4).

TABLE I. CLINICAL FEATURES

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*	*Case 7*
Name	C.E.P.	L.P.	T.P.	R.P.	G.P.	M.P.	D.P.
Sex	female	female	male	male	male	female	male
Age	53 yrs.	50 yrs.	27 yrs.	30 yrs.	28 yrs.	19 yrs.	17 yrs.
Age:							
At first episode	19	15	15	18 mth.	14	11	14
At onset of cyclical episodes	—	—	—	14	18	—	14
Of spontaneous remission	19	41	22	—	—	—	—
Inciting factors:							
Muscular inactivity	0	+	+	+	+	+	+
Cold and damp	0	+	0	+	+	+	+
Alcohol	0	—	0	+	0		0
Emotional stress	0	0	+	0	+	0	0
Prodromata	0	0	0	0	0	0	0
Observations during paralyses:							
Muscles involved:							
Neck	0	0	+	+	+	+	+
Legs	+	+	+	+	+	+	+
Arms	0	0	+	+	+	+	+
Back	0	+	+	+	+	+	+
Respiration	0	0	0	+	0	0	0
Progress centrally	0	+	+	+	+	+	+
Partial (P) or complete (C)	P	P	P	C	C	P	C
Unilateral (U) or bilateral (B)	B	B	B	B	B	B	B
Recovery phase		not observed		starts in upper extremity and progresses to back, legs and neck			
Frequency	once only	1/week	1/week	more than 1/day	more than 1/day	1/week	more than 1/day
Duration:							
With spontaneous recovery	6 hrs.	24-48 hrs.	48 hrs.	24-72 hrs.	24-36 hrs.	?	?
After KCl	—	—	30 mins.	2 hrs.	1-2 hrs.	15-20 mins.	2 hrs.

0 = absent, + = present.

Mental faculties were unimpaired during paralysis in all cases, although in cases 2 and 5 there was increased mental 'irritability'.

During episodes of paralysis no objective sensory changes were observed (cases 4 - 7). Subjective changes were experienced in cases 2 (generalized itching), 3 (soreness of the affected muscles), 4 (generalized itching, particularly of face), and 7 (paraesthesiae of hands and feet).

During paralysis, no alteration was noted in the pulse rate, respiratory rate, or blood pressure. In no case was there any enlargement of the thyroid, and no case showed any clinical evidence of muscular atrophy.

Recovery

In the members still having episodes, recovery began in the upper extremity and progressed to the back, the legs, and lastly the neck. In all, recovery was facilitated by muscular activity, and paralysis was terminated within 15 - 90 minutes by the ingestion of 5 - 20 G. of KC1. The recovery time and the dose required were proportional to the severity of the attack.

Frequency and Duration of Paralysis

The frequency of attacks varied considerably. In case 1 the only attack lasted 6 hours. In cases 2 and 3 (episodes every week or two) each lasted 24 - 48 hours. Both these members have had spontaneous regressions of the disease. In case 6 the disease took a fairly mild form, with about one episode per week. This member did not know how long she would take to recover spontaneously, because she took KC1 as soon as she felt weak.

In cases 4, 5 and 7 there was at least one episode a day. All these patients were paralysed to some extent every morning on awakening, and had to take repeated doses of KC1 during the day. In all of them the episodes were infrequent at first (about once a month) and had increased in frequency over the years. In case 4 there was a marked increase in frequency at puberty. Recovery, if allowed to take place spontaneously, took about 24 - 48 hours; in case 4 it sometimes took as long as 72 hours.

Electrolyte Levels

These were investigated in three cases (4, 5 and 7). An episode of paralysis was easily precipitated in them by merely withdrawing KC1 supplements. During paralysis there was a decrease in the serum potassium and a slight increase in the serum sodium (Table II). The relation between serum potassium and serum inorganic phosphate was studied, and an inverse relationship was found to exist. The graph showing this in case 5 is shown in Fig. 2.

TABLE II. SERUM Na^+ AND K^+ CONCENTRATIONS BEFORE AND DURING AN EPISODE OF PERIODIC PARALYSIS IN CASES 4, 5 AND 7

		Case 4	*Case 5*	*Case 7*
Serum Na^+	Before	143	141	142
(mEq./l.)	During	146	141	144
Serum K^+	Before	5·7	5·2	4·6
(mEq./l.)	During	3·2	2·9	2·7

DISCUSSION

The first case of familial periodic paralysis was reported by Shaknowitsch in 1882, although a clear-cut description of a patient with sporadic periodic paralysis was given by Musgrave in 1727. By 1941 over 400 typical cases had been reported and these have been admirably reviewed by Talbott.[1] The main interest in the pathogenesis of classical periodic paralysis has been focused on the role of potassium.

Biemond and Daniels[4] (1934) were the first to report a diminution in concentration of potassium during a spontaneous attack. Its significance, however, was not appreciated until 1937, when Aitken *et al.*[5] confirmed the finding and purposely terminated an episode by giving KC1. Metabolic balance studies showed that potassium excretion was not increased during the attack—in fact it was decreased, thus showing that K^+ must be transferred from the intravascular to the extravascular compartment.

Fairly recent studies based on arteriovenous differences in serum-K^+ concentration have shown that potassium moves from the intravascular compartment into the skeletal muscle cells themselves. Zierler and Andres[6] have shown that the rate of movement of K^+ into muscle cells during the development of a spontaneous attack of paralysis is approximately 1 mEq./hour/kg. of muscle—enough to explain the observed decrease in serum-K^+ concentration. During spontaneous recovery, K^+ moved from the muscle at a rate of about 4 mEq./hour/kg. of muscle, thereby raising the serum-K^+ concentration and terminating the attack. Both these rates are at least 5 - 10 times greater than those seen in normal subjects.

This presented an apparent paradox; if the episode of paralysis was associated with an increased intracellular K^+ concentration, why should the administration of extra potassium terminate the episode?

Changes in neuromuscular function following alteration in plasma-K^+ concentration and movement have indicated that the membrane potential of the resting muscle varies with the concentration gradient of K^+ (intra- to extracellular).

Grob *et al.*[7] have shown that the lowered serum K^+ that occurs in periodic paralysis is associated with a marked reduction in the action-potential response of muscle to nerve stimulation, and also a reduction in the depolarizing action of acetylcholine and other depolarizing agents; these changes were much greater than occurred in normal subjects with comparable hypokalaemia. They concluded that the loss of strength in periodic paralysis was due to the fact that the large uptake of K^+ by muscle resulted in a greater K^+ gradient, hyperpolarization of the muscle membrane, and consequent lowered excitability. If this is so, it is quite feasible that, despite high intracellular levels, the administration of KC1 terminates an attack by reducing the concentration gradient.

The role of K^+ has not yet been fully elucidated and the reason for the abnormal mobility of K^+ across the muscle-cell membrane has yet to be explained. The pathogenesis of the normokalaemic and hypokalaemic types of periodic paralysis also remains problematical.

The role of carbohydrate metabolism in the pathogenesis of periodic paralysis has also received attention. It is known that paralysis can be precipitated with glucose or glucose *plus* insulin. It is also well known that the deposition of glycogen is accompanied by the movement of K^+ from the extracellular to the intracellular compartments. McArdle[3] mentions that in periodic paralysis a good correlation was found between levels of serum K^+ and inorganic phosphate, the two tending to rise and fall together during and between attacks. These and other studies were tentatively interpreted as indicating a partial block at the hexose-phosphate stage of carbohydrate metabolism.

On the other hand, collateral data obtained by Zierler and Andres[6] revealed associated disturbances in glucose,

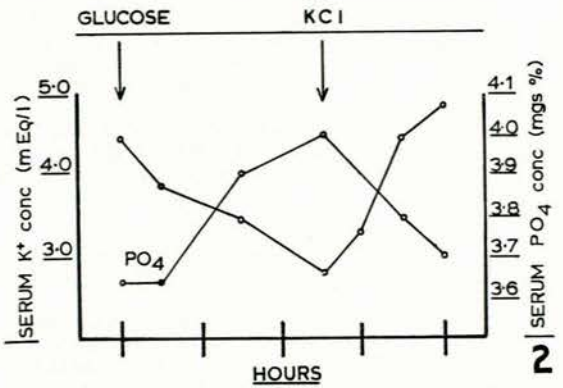

Fig. 2. Case 5. Graph showing inverse relationship between serum potassium and inorganic phosphate levels during an episode of paralysis induced by 50 G. of glucose orally and terminated by 15 G. of KCl.

lactate and CO_2 metabolism, but they concluded that these did not appear to be aetiologically related to exaggerated K^+ movement. Our inorganic phosphate studies (Fig. 2) are directly contradictory to those mentioned by McArdle, and clarification is required.

More recently, Doak and Eyre[8] have made the interesting suggestion that the paralysis may be due to intracellular deficiency of adenosine triphosphate (ATP), which implies a deficiency of high-energy phosphate bonds; research in this direction may prove very interesting.

The differential diagnosis of reversible temporary paralysis has been tabulated by Eales *et al.*[9] To this list we might add the periodic flaccid paralysis that occurs during cold weather in patients with chronic hypertrophic polyneuropathy.[10]

The prognosis in periodic paralysis must be guarded. The mortality is about 10%, death being due to respiratory paralysis, cardiac failure, or inhalation pneumonia associated with inability to clear the trachea of aspirated vomitus.

SUMMARY AND CONCLUSIONS

1. Seven cases of classical periodic paralysis were observed; all are members of one Durban family, whose family tree is presented.

2. The clinical features and electrolyte studies are presented.

3. The pathogenesis is discussed. The view is held that exaggerated permeability of muscle membrane to potassium is a fundamental defect in classical periodic paralysis. The increased mobilization of K^+ from the intravascular to the intracellular compartment results in a greater K^+ gradient, hyperpolarization of the muscle membrane, and consequent lowered excitability.

4. The role of carbohydrate metabolism in the disease is not clear.

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