THYROTOXIC PERIODIC PARALYSIS

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Various types of somatic muscle involvement have been described in association with thyrotoxicosis: these include myopathy (acute and chronic), encephalopathy, exophthalmic ophthalmoplegia, myasthenia gravis and periodic paralysis (Millikan and Haines, 1953; Adams, Denny-Brown and Pearson, 1962).

Periodic paralysis complicating thyrotoxicosis was first reported by Rosenfeld in 1902 according to Mora (1932). It would appear from reports in the world literature that thyrotoxic periodic paralysis is rare except in Japan. The first four cases in America were described by Dunlop and Kepler in 1931 from the Mayo Clinic followed by the fifth by Mora in 1932. Up to 1963 only a total of 20 cases have been reported (Bartels and Pouget, 1963). In England, 5 cases have been described (Petch, 1964; Dyde, 1965) and in Australia, 4 cases by Robertson (1954). In contrast, Okinaka et al. (1957) found 119 patients with hyperthyroidism and periodic paralysis in a series of 6,333 cases of hyperthyroidism admitted to three hospitals in Japan over a 20 year period, and Itahara (1961) had 71 cases of thyrotoxic periodic paralysis in 126 patients with periodic paralysis. Engel (1961) noted that 205 out of the 228 reported cases of thyrotoxic periodic paralysis have come from Japan. Recently, its occurrence has been reported in Chinese in Taiwan by Chen, Hung and Lin (1965) and in 25 Chinese in Hong Kong by McFadzean and Yeung (1967).

This paper reports 8 Chinese patients with thyrotoxic periodic paralysis seen at the Thyroid Clinic, Department of Medicine, General Hospital, Singapore in the period 1961-7.

CASE REPORTS

Patient No. 1

C.K.L. a male Chinese aged 40 years was admitted to hospital with a history of weight loss (27 lbs), excessive sweating, palpitations, tremors of hands and irritability of 6 months duration. Since one and a half months ago he began to experience attacks of weakness of lower limbs. The attacks occurred at night, after his evening meal, at about 7-9 p.m. There was numbness then weakness and finally paralysis of the lower limbs which could not be lifted from the bed. He remained in bed and was quite well and fully recovered by the next morning. He had 4 attacks in all. The upper limbs were never involved. On clinical examination he was found to be toxic with a pulse rate of 132 per minute, proptosis of the eyes and lid retraction. The thyroid gland was diffusely enlarged, soft and with a bruit heard over the left lobe. While in hospital he developed a fifth paralytic attack involving again the lower limbs which began at 7 p.m. after a normal evening meal. The attack lasted for seven hours with spontaneous recovery. During the paralytic period the tendon reflexes were present. The serum electrolytes taken during the attack gave a low potassium level of 2·8 mEq. per litre. Thyroid function tests showed a basal metabolic rate of plus 38% and plus 40%. The blood cholesterol was 86 mgm%. He was treated with Carbimazole for 9 months followed by partial thyroidectomy. He has had no further attacks of paralysis and is well after 5 years.

Patient No. 2

Y.K.M. a male Chinese aged 34 years, attended hospital with a history of palpitations, sweating, tremors of hands and weight loss for 1 year. A few months after onset of above symptoms he had an attack of paralysis of the upper and lower limbs on waking up in the middle of the night to pass urine. Several months later he had a similar attack of paralysis, again occurring in the middle of the night. During each attack the lower limbs were more involved than the upper limbs. Each attack lasted for 3-4 hours and he recovered spontaneously with no residual weakness. On examination he was found to be clinically toxic. The pulse rate was 120 per minute. The thyroid gland was small and diffusely enlarged, with a soft bruit heard over both lobes. The central nervous system showed no abnormality. The basal metabolic rate was plus 29% and the serum electrolytes were within normal limits. He was treated with carbimazole for 2 years: a few months after treatment he had a transient attack of weakness of the lower limbs for 10-15 minutes. He had a relapse of thyrotoxicosis 4 months after stopping antithyroid therapy, but did not have any further attacks of

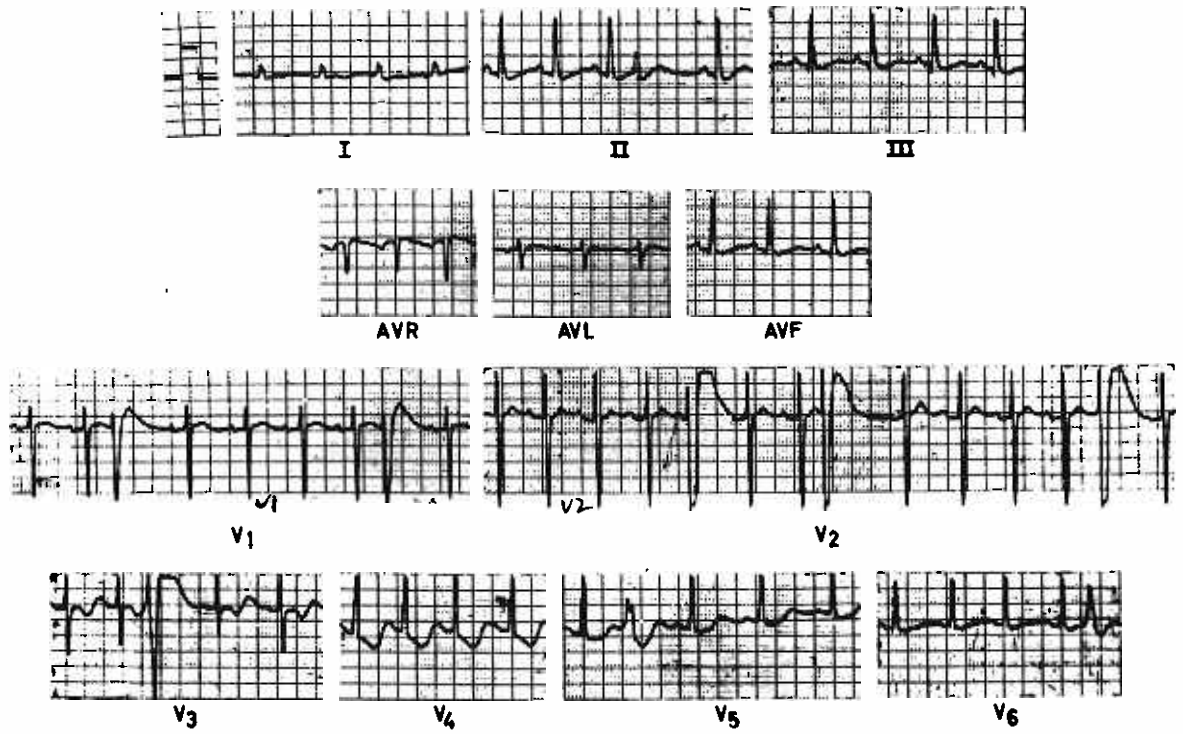

Fig. 1. Electrocardiograph showing depressed ST segment, flattened T waves and extrasystoles in a patient with low serum potassium level during an attack of paralysis.

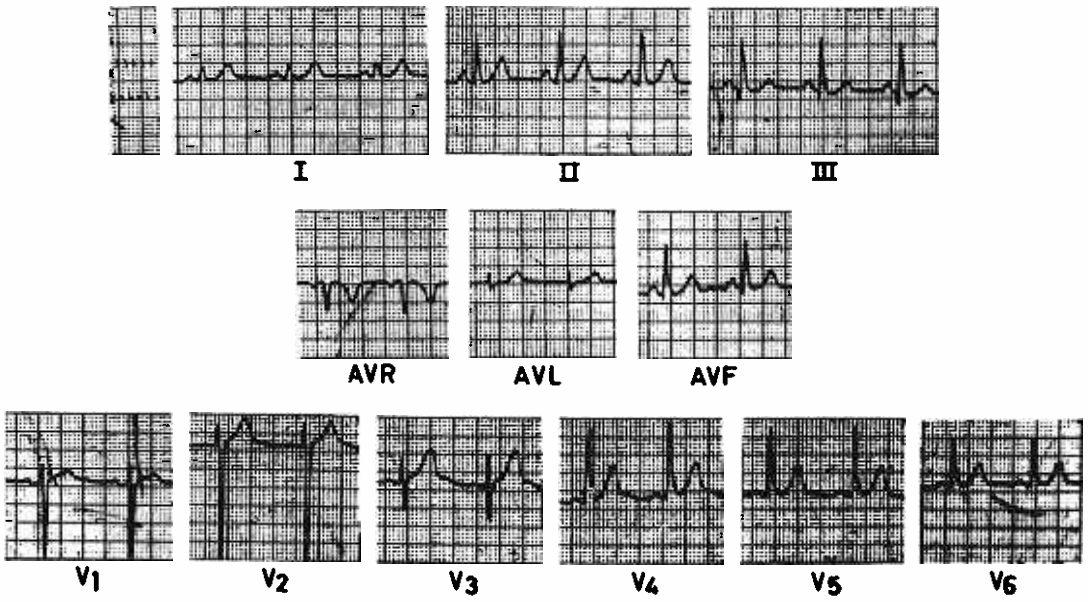

Fig. 2. Showing normal electrocardiograph following treatment with potassium chloride. Serum potassium level was 3.9 mEq./litre.

paralysis. He received a further course of carbimazole followed by a partial thyroidectomy. He has remained well since.

Patient No. 3

O.C.B. a male Chinese aged 39 years was admitted to hospital with a history of paralysis of upper and lower limbs since 2 a.m. in the morning when he woke up to empty his bladder. He has had three similar attacks during the past 4 months but there was only weakness of the limbs and he recovered after an hour or so. During the last 3 years he recollected having had palpitations, sweats and tremors of the hands which had become more marked during the last month. On examination he had the typical signs of thyrotoxicosis with a small diffusely enlarged thyroid gland: a bruit was present over both lobes. There was weakness of the upper and lower limbs but more of the lower limbs, sluggish deep tendon reflexes and no sensory loss. The tensilon (edrophonium) test was negative. A basal metabolic rate of plus 32% was obtained. The serum electrolytes taken during the attack was within normal limits with a potassium level of 3·6 mEq./litre. He was treated with carbimazole and improved with no further attacks of paralysis. He recently completed 3 years therapy with carbimazole and is well.

Patient No. 4

G.J.W. a male Chinese aged 29 years, who presented with a history of nervousness, palpitations and sweating for 3 years and bouts of diarrhoea for 1 year with loss of weight (50 lbs) for 6 months. Since the last 1 year he has had several attacks of weakness of the upper and lower limbs on waking up in the early hours of the morning. The weakness improved after a few hours and he was normal again. He came to hospital during an attack which was the most severe and prolonged. On examination he was found to be completely paralysed in the lower limbs and in the upper limbs he was only able to move his hand and forearm. All the deep tendon reflexes were absent, with no plantar response. There was no sensory loss. The thyroid gland was diffusely enlarged with a bruit heard over the lobes, and he had obvious signs of thyrotoxicosis clinically. The serum potassium taken during the attack was 2.2. mEq./litre with sodium at 133 mEq./litre and chloride at 109 mEq./litre. The electrocardiograph showed depressed ST segment and flat T waves with extrasystoles, which became normal after potassium therapy (Figs. 1 & 2). The basal metabolic rate was plus 31 %. He was given oral potassium chloride mixture (2 gms t.d.s.) and by the next day had fully recovered with return of power and reflexes to all four limbs. The serum electrolytes also showed a return of the potassium to normal levels (3·9 mEq./litre). He received carbimazole therapy and has had no further attacks of weakness.

Patient No. 5

W.Y.K. a male Chinese aged 30 years, began to have recurrent attacks of weakness of the lower limbs usually on waking up in the morning, but sometimes in the evening as well, during the last 10 months. The attacks would last from half to 2 hours and he recovered spontaneously. On the day before he was seen at the hospital, he had attended an evening show at the local cinema. During the show he sat with his knees placed against the back of the seat in front of him. At the end of the show he found difficulty in getting up from his seat because of weakness of the lower limbs. When he finally could, he had to be helped out and his knees buckled under him several times when he attempted to walk. He was still weak in the legs the next afternoon when he was seen at the hospital. During the last 10 months he had also noticed gradual loss of weight with insomnia, intolerance to hot weather, palpitations, irritability and bouts of loose stools. On examination he was hyperkinetic and clinically toxic with a small, diffusely enlarged thyroid gland and slight proptosis of the eyes. There was weakness of the quadriceps muscles, and the deep tendon reflexes were brisk and equal. The basal metabolic rate was plus 32% and plus 28%. The serum electrolytes were within normal limits. He was given carbimazole therapy and is now euthyroid after 6 months of therapy. He is on a maintenance dose of carbimazole and remains well with no further attacks of weakness.

Patient No. 6

N.T.S. a male Chinese aged 31 years. He presented with 2 attacks of paralysis of the lower limbs separated by an interval of 6 months. Both attacks occurred in the early hours of the morning. The first attack occurred at 5 a.m. when he woke up to go to toilet and lasted for 3-4 hours before full recovery. The second attack occurred at 7 a.m. when he woke up, and lasted for over an hour before full recovery. The upper limbs were slightly weak on both occasions. During both attacks the left limbs were observed to be weaker than the right. He could not recall having symptoms of any kind before the first attack. About 2-3 months after the first attack he

noticed excessive sweating, weight loss, tremors of the hands and a swelling over the front of the neck. On examination he was clinically toxic. The thyroid gland was diffusely enlarged and a bruit was heard over the lobes. He had slight weakness of the lower limbs especially the quadriceps muscles and the reflexes were present. The basal metabolic rate was plus 51%. Radioiodine studies using an oral tracer dose of 10·9 microcuries I^{131} showed hyperfunction of thyroid gland. Uptake over the thyroid gland at 4 hours was 62·5% of dose and at 24 hours was 68·0% of dose. The protein bound I^{131} at 48 hours was 0·64% of dose per litre and at 72 hours was 0·97% of dose per litre. He has been given Carbimazole and is being followed up.

Patient No. 7

N.C.L. a young Chinese boy aged 18 years was admitted to hospital with a history of paralysis of the lower limbs since 3 a.m. followed by weakness of the upper limbs several hours later. He recalled having had a heavy meal for dinner consisting of rice, mee and satay. He had a similar attack of weakness of the lower and upper limbs 2 months ago which recovered spontaneously after three days. He has had a history of palpitations and sweating for over 1 year with nervousness and irritability for 8 months: there was no weight loss. On examination he was found to have paralysis of the lower limbs with weakness of the upper limbs. The reflexes were present and brisk and there was no sensory loss. The thyroid gland was diffusely enlarged with a bruit heard over the lobes. The pulse rate was regular at 100 per minute and the blood pressure was 140/40 mm.Hg. There was fine tremors of the hands. He was also noted to be of tall slim build with arachnodactaly and high arched palate but without lens subluxation. He gave no family history of similar attacks. The basal metabolic rate was plus 6% and plus 4%. The serum electrolytes taken during the attack gave a serum potassium value of 2·0 mEq./litre. The electrocardiograph showed presence of U waves. He was given an intravenous dose of potassium chloride (2 gms) and the paralysis improved dramatically. The electrocardiograph returned to normal and the serum electrolytes taken the next day when he was fully recovered showed normal level of serum potassium. Protein bound iodine was over 12 micrograms%. Radioiodine studies were done using an oral tracer dose of 5·4 microcuries of I^{131}. The uptake over the thyroid gland at 2 hours, 4 hours, 24 and 48 hours was 67·7%, 72·0%, 70·8% and 67·5% of dose respectively and th protein bound iodine^{131} at 48 and 72 hours was 0·725% and 0·71% of dose per litre of plasma respectively. He is being treated with carbimazole.

Patient No. 8

L.H.N. a female Chinese aged 24 years. Since 1 year ago she has had many attacks of weakness of the lower limbs, usually in the evenings at the end of a day's work, but sometimes in the morning. These attacks improved spontaneously after a day. She had one attack of complete paralysis of the lower limbs which lasted for several days. During the same period, she also had palpitations, nervousness, sweating and irritability with swelling over the front of the neck. On examination she was found to have obvious signs of thyrotoxicosis. The thyroid gland was moderately enlarged with a marked bruit heard over the upper poles of both lobes. The lower limbs were weak but there was no evidence of wasting of the muscles: the deep tendon reflexes were present and there was no sensory change. The basal metabolic rate was plus 77%. The serum electrolytes were within normal limits with the serum potassium at 3·6 mEq./litre. Radioiodine studies were performed with an oral tracer dose of 10 microcuries of I^{131} and showed increased thyroid function. The 4 hour uptake over the thyroid gland was 69·2% of dose and the 24 hour uptake over the thyroid gland was 56.2% of dose. The protein bound radioiodine at 48 hours was very high at 2·49% of dose/litre of plasma. She was treated with carbimazole and is now euthyroid. She has had no further attacks of weakness or paralysis. She is being referred for thyroidectomy.

DISCUSSION

Periodic paralysis is a clinical syndrome which may be due to various aetiological factors. The majority of cases are familial (Talbot, 1941) or asscciated with thyrctoxicosis (Okinaka, 1957). Other less common causes include primary aldosteronism, potassium losing nephritis, renal tubular acidosis and Fanconi's syndrome, recovery phase from diabetic acidosis and following chlorothiazide and para-amino salicylic acid therapy (Engel, 1961; Chen, Hung and Lin, 1965).

Although the clinical picture during attacks is similar, thyrotoxic periodic paralysis differs from the familial form in several respects. In the former, manifestations of thyrotoxicosis are present and only 2% have a family history: the

age at onset is commonly in the third and fourth decade and the sex incidence is predominantly male, as high as 20:1 in favour of males (Okinaka et al. 1957). In the familial form, there is no evidence of thyrotoxicosis, a family history is obtained in 80% of cases, the age at onset is earlier and usually in adolescence, while the male preponderance is less striking, about 3 males to 1 female (Talbot, 1941).

During the period 1961 to early 1967, 460 patients with thyrotoxicosis were seen. Of these 350 are females and 110 males. Eight patients gave a history of more than one attack of paralysis. This gives an incidence of 1.7% with thyrotoxic periodic paralysis comparable to that of 1·9% reported by Okinaka et al (1957) and 1·8% by McFadzean and Yeung (1967). Of these eight patients, seven (6·4%) are males and only one (0·3%) female. This gives a strikingly high male incidence in a condition more commonly seen in females. Okinaka et al (1957) had 99 cases of thyrotoxic periodic paralysis in their 1214 male patients (8·2%) and 20 cases in their 5119 female patients (0·4%) while McFadzean and Yeung (1967) had 23 cases in their 178 male patients (13%) and 2 cases in their 1188 female patients (0·17%). In the present series all the patients are Chinese, with age at onset of paralytic attacks ranging from 18 to 40 years (Table 1). In none was there a family history. Although the population of Singapore is predominantly Chinese, the fact that all the patients are Chinese suggests a high incidence among the Chinese as was found by McFadzean and Yeung (1967) and this may be significant, especially in the light of the high incidence in Japan, of possible racial and dietary influences in the aetiology of thyrotoxic periodic paralysis.

TABLE I

SHOWING RACE, SEX AND AGE AT ONSET OF 8 PATIENTS WITH THYROTOXIC PERIODIC PARALYSIS

No. Patient	Patient's Name	Race	Sex	Age in Years
1.	C.K.L.	CH.	M	40
2.	Y.K.M.	CH.	M	34
3.	O.C.B.	CH.	M	39
4.	G.J.W.	CH.	M	29
5.	W.K.Y.	CH.	M	30
6.	N.K.S.	CH.	M	31
7.	N.C.L.	CH.	M	18
8.	L.H.N.	CH.	F	24

The diagnosis of thyrotoxic periodic paralysis is made from the history of one or more episodes of partial or complete paralysis of the muscles of the extremities in a patient with manifestations of thyrotoxicosis. The attacks usually occur at the same time or following after the onset of hyperthyroidism as was found in 7 out of the 8 patients in this series and in 73% of Okinaka's (1957) series. One patient had manifestations of thyrotoxicosis after the first attack of paralysis as did 17% in Okinaka's group.

TABLE II

SHOWING INVOLVEMENT OF LIMBS AND NUMBER OF ATTACKS IN EIGHT PATIENTS WITH THYROTOXIC PERIODIC PARALYSIS

No. Patient	Patient's Name	No. of Attacks	Limb Involved Upper	Lower
1.	C.K.L.	5	0	+
2.	Y.K.M.	2	+	+
3.	O.C.B.	4	+	+
4.	G.J.W.	several	+	+
5.	W.Y.K.	several	0	+
6.	N.T.S.	2	+	+
7.	N.C.L.	2	+	+
8.	L.H.N.	> 10	0	+

The muscles of the limbs are most commonly affected and both the upper and lower limbs or either the upper or lower limbs may be involved although the lower limbs are more frequently and more severely affected than the upper. Of the 8 patients reported here, 5 had involvement of both upper and lower limbs while 3 had only lower limb involvement (Table II). The degree of paralysis varied from weakness of the muscles to complete paralysis as in patients numbers 1, 4 and 7. In none were the muscles of the head, respiration, speech and swallowing affected and no changes in mental function or sensory loss were noted. In most reports the tendon reflexes are described as absent during the phase of complete paralysis but in two patients (Nos. 1 and 7) the deep tendon reflexes of the completely paralysed lower limbs were present and brisk and the muscles firm and not flaccid. The significance of this is not clear. In the series reported by Chen, Hung and Lin (1965), they also noted that the tendon reflexes did not always disappear completely even at the height of paralysis as was seen in 5 of their patients. The paralytic attacks typically occur at night or in the early hours of

the morning or on waking up in the morning, and 5 out of the 8 patients developed attacks during this period. The duration of an attack may last a few minutes or may persist for several hours to several days with eventual complete recovery. The paralysis may be asymmetrical in distribution. In patient No. 6, there was more severe involvement of the left limbs than the right limbs. The number of attacks may vary from one to more than two attacks. 3 patients had 2 attacks, one 4 and another 5, while two had several and one had more than 10 attacks (Table II).

During the attacks of paralysis, the level of serum potassium in the majority of patients has been found to be below the normal value of 3 mEq./litre (Satoyoshi et al., 1963). However, MacArdle (1956), Chen, Hung and Lin (1965) as well as McFadzean and Yeung (1967) have reported normal serum potassium levels during the paralytic attacks in their patients. Cases of periodic paralysis have also been described with high serum potassium values during paralytic attacks (Bull, Carter and Lowe, 1953; Gamstorp, 1957) and some patients with low serum potassium values do not develop paralysis (Chen, Hung and Lin, 1965). The serum potassium level in the present series was found to be low in 3 patients and normal in 1 patient who was seen during the attack of paralysis. In the other four patients the serum potassium levels were normal; one of these was seen soon after an attack and with still some residual weakness while the other 3 were seen after an attack and without any weakness of the limbs (Table III).

TABLE III

SHOWING SERUM ELECTROLYTE LEVELS IN 8 PATIENTS WITH THYROTOXIC PERIODIC PARALYSIS

No. Patient	Patient's Name	Serum Electrolytes mEg./L. Pot.	Sod.	Chloride
1.	C.K.L.	* 2.8	137	108
2.	Y.K.M.	4.0	139	109
3.	O.C.B.	* 3.6	146	113
4.	G.J.W.	* 2.2	133	109
5.	W.Y.K.	4.1	134	108
6.	N.T.S.	3.6	132	104
7.	N.C.L.	* 2.0	134	103
8.	L.H.N.	3.6	134	104

* Patients seen during attack of paralysis.

McFadzean and Yeung (1967) found that the fall in serum potassium was proportional to the extent and severity of the paralysis and in the more extensive as well as more severe paralysis there was invariably a fall to hypokalaemic levels, but when the paralysis was restricted in extent and in severity the serum potassium level was in some instances within normal limits at the height of the paralysis. The hypopotassaemia during paralytic attacks has been shown to result from a shift of potassium from the extracellular to the intracellular fluid compartments. Both Zierler and Andres (1957) as well as Grob, Johns and Liljestrand (1957), demonstrated a large net uptake of potassium from arterial plasma by skeletal muscle during an attack of paralysis and movement of potassium out of skeletal muscle into venous plasma during spontaneous recovery from an attack. Shizume et al. (1966) studying the arterio-venous serum potassium and sodium changes during an induced attack of paralysis, found that in both idiopathic and thyrotoxic periodic paralysis, a constant positive arterio-venous difference was obtained. This finding supports further the theory that cellular migration of potassium from the extracellular space is the mechanism of hypokalaemia in periodic paralysis. Conn and his co-workers (1957) found that before the paralytic attacks in their 2 patients there was a large increase of urinary aldosterone excretion with a retention of sodium and concluded that sodium retention is the primary factor which sets into motion the potassium migration into the muscle cells. Jones et al. (1959), however, failed to duplicate these results in their 2 patients.

Five of the eight patients were treated with carbimazole and two by subtotal thyroidectomy. In these 7 patients, no further attacks of paralysis have occurred after treatment was started and the patients became euthyroid. The period of follow-up ranged from 6 months to 5 years. The remaining patient (No. 7—N.C.L.) was started on carbimazole therapy at the time of writing. Similar experiences have been reported by all workers of the effect of treatment of thyrotoxicosis on the paralytic attacks. McFadzean and Yeung (1967) furthermore found that in the euthyroid state attacks of paralysis could no longer be induced even when hypokalaemia was produced by priming with 9-x-flurohydrocortisone. Relapse of the thyrotoxicosis has been found to result in recurrence of attacks of periodic paralysis (Dunlap and Kepler, 1931; Okinaka et al., 1957; McFadzean and Yeung, 1967). The adverse effects of thyroid medication on thyrotoxic periodic paralysis have also been described by Robertson (1954).

Attacks of paralysis may be induced by large amounts of glucose and carbohydrate (Aitken

et al., 1937), by a combination of high carbohydrate intake and insulin (McFadzean and Yeung, 1967) or by the injection of epinephrine (Talbot, 1941; Chen, Hung and Lin, 1965). In one patient (No. 7—N.C.L.) the second attack of paralysis developed after a heavy carbohydrate meal. The paralytic attacks usually recover spontaneoulsy but in the more severe and prolonged attacks, treatment with oral or intravenous potassium salts may speed recovery from the attack as in two patients (Nos. 4 and 7). Aldosterone antagonists (spironolactone) have been also found effective in preventing the induction of paralysis in a proportion of patients with thyrotoxic periodic paralysis (Okinaka et al., 1957; McFadzean and Yeung, 1967).

While there appears to be a definite and true relationship between attacks of periodic paralysis and hyperfunction of the thyroid gland, the exact role of the thyroid gland and the thyroid hormones in producing the attacks of paralysis is still not clear. Evidence in favour of direct influence of the thyroid gland include; firstly, attacks of paralysis cease when the thyrotoxicosis is controlled and recurs when thyrotoxicosis relapses: secondly, the adverse effect of thyroid administration on thyrotoxic periodic paralysis and not on the familial type and thirdly, factors which induced attacks in the toxic state could not be made to do so during the euthyroid state even when hypokalaemia was produced by first giving 9-flurohydrocortisone. However, not all thyrotoxic patients develop periodic paralysis nor is the occurrence of attacks related to the duration or severity of the thyrotoxicosis. Also in those without a history of paralysis attempts to induce paralysis fail to produce an attack. McFadzean and Yeung (1967) have noted the high incidence among mongoloids and suggested that the basic defect in thyrotoxic periodic paralysis may be genetically determined.

SUMMARY

Of 460 patients with thyrotoxicosis (350 females and 110 males), eight (1·7%) gave a history of attacks of periodic paralysis. All the eight are Chinese patients. Seven (6·4%) are males and one (0·3%) female and their ages at onset of paralysis ranged from 18 to 40 years. In none was a family history obtained.

Two patients had rather brisk reflexes during the period of paralysis which is rather atypical as most reports describe the reflexes to be absent.

Four patients were seen during the paralytic attack. Three showed low levels of serum potassium while the fourth had normal levels. The other four patients who were not seen during a paralytic attack had normal serum potassium levels.

Seven of the patients were treated for their thyrotoxicosis by either carbimazole therapy or subtotal thyroidectomy and had no further attacks with control of their thyrotoxicosis.

The main features of periodic paralysis are discussed.

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