PERIODIC PARALYSIS

BY

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Though a comparatively rare disease, periodic paralysis, familial or sporadic, has been reported at intervals since the middle of the last century, so that in 1941 Talbott was able to record over 400 cases from the world literature, while there is little doubt that many more have been seen but never published.

Two families are reported in this paper. In the first the disease has appeared in six members of three generations; in the second, one member only is known to have been affected, but the high incidence of other morbid conditions makes the family history of interest. The study emphasizes the remarkable similarity of symptomatology in the different individuals, the good prognosis which may be possible, the permanent changes which may occur, and the dangers of injustice due to mistaken diagnosis. The first family includes one of the three patients studied by Aitken, Allott, Castleden, and Walker (1937) and Allott and McArdle (1938) when they demonstrated the close relationship between the serum potassium level and muscle paresis.

Cases of periodic paralysis have previously been reported in this country by Singer and Goodbody (1901), Buzzard (1901)—the first familial cases—Gardner (1913), Adie (1927), MacLachlan (1932), Aitken and others (1937), Allott and McArdle (1938), Holmes (1941), and Lewis (1950), while Talbott (1941) believes that the earliest account of the disease is given by William Musgrave in 1687.

The "H" Family

The pedigree of the family is shown in Fig. 1.

Generation I

I.1.—Male, died aged 52. I.2.—Female, died aged 89.

Generation II

II.1.—Female, died aged 73.

II.2.—Male, died aged 63 of pneumonia. Had three attacks of leg weakness early in the third decade.

II.3.—Male, died aged 67. II.4.—Female, died aged 59.

II.5.—Male, alive and well, aged 73. At age 15 he developed frequent attacks of total paralysis of the

limbs, mainly in the early hours of the morning, lasting from two to 30 hours, and recovering spontaneously. Attacks became less frequent in his late 20s, and ceased entirely after the age of 32. Twice during hospital admissions the patient was considered hysterical.

II.6.—Male, alive and well aged 68.

II.7.—Male, died aged 52.

Generation III (Offspring of II.2)

III.1.—Male, alive and well, aged 51. Attacks of total paralysis of the limbs began when the subject was aged 15, occurring very frequently and often lasting over 24 hours. They were usually precipitated by alarm, emotion, or exposure to extreme cold, the weakness developing in the early hours of the next morning. One attack, involving the legs, was of exceedingly rapid onset, and came on while he was wading in very cold water. The frequency decreased after the age of 25 and the attacks ceased entirely after 41.

The patient was examined twice when aged 51. The facial muscles bilaterally were weak, and the quadriceps were slightly wasted. The arm reflexes on the first occasion were normal, but knee and ankle jerks were completely absent. One week later the arm reflexes were barely perceptible and knee and ankle jerks were obtained on reinforcement. Blood chemistry and an E.C.G. were normal.

FIG. 1.—Genealogical table for the "H" family.

These attacks had been variously diagnosed as "epilepsy", "hysteria", and "familial hysterical trances".

III.2.—Male, alive and well, aged 50.

III.3.—Female, alive, aged 48. Subject to severe migraine.

III.4.—Male, alive and well, aged 47. He had had six attacks of weakness of the limbs, one incapacitating, between the ages of 17 and 37. The attacks were precipitated by excitement, they occurred in the early morning, but the patient was usually able to "walk them off".

He was examined aged 47. Slight weakness of the facial musculature and marked facial asymmetry were noted. All tendon reflexes were very sluggish. Blood chemistry was normal.

III.5.—Female, died of tuberculosis, aged 15.

III.6.—Male, alive and well, aged 41 (Case 2 of Allott and McArdle, 1938).

Attacks of total paralysis of the limbs began when the patient was aged 13, increased in frequency to age 24, usually developing in the early morning and lasting from two to 24 hours. A heavy meal at night, emotion, and excitement were the main precipitating factors especially if accompanied by exertion. He was able to "walk off" mild attacks. He was given potassium salts from the age of 28 and attacks ceased entirely after age 34.

Examination between attacks was recorded by Allott and McArdle as normal. Paralysis was induced by insulin and glucose, and by adrenaline, during which the serum potassium level fell to below 6 mg. per 100 ml. Potassium chloride, 10–12 g., at the onset would prevent an attack developing.

Generation IV

IV.1.—Male, aged 19, the son of III.1, was admitted to the Queen Elizabeth Hospital, Birmingham, on April 13, 1951 (Case No. 3945150332).

He was subject to migraine, but otherwise was well until the age of 16 when following unusual exertion he developed weakness of the legs spreading upwards until he was unable to move any part of the body below the neck. Recovery was spontaneous after several hours. Attacks had recurred many times since, varying in duration from three to 24 hours, and in severity from weakness of the ankles to total paralysis below the neck. The muscles feel tight and swollen during paralysis. Physical exertion and high carbohydrate meals are the main precipitating factors, the paralysis developing in the early hours of the morning. The patient can "walk off" mild attacks. In one attack in Sweden the serum potassium level was recorded as 7 mg. per 100 ml., and the E.C.G. showed absent T waves.

A general and neurological examination on admission gave entirely normal findings, except for a small, unsuspected, and unexplained spontaneous pneumothorax. Extensive blood and cerebrospinal fluid, cytological, biochemical, and serological examinations were normal. A glucose tolerance test and an E.C.G. were normal.

Paralysis was induced by the administration of 300 g. of glucose in a pint of water orally. Six hours later the

patient woke completely paralysed below the neck, excepting the respiratory muscles and the gastrocnemii, which were normal. The disorder was entirely motor, and all tendon reflexes except the ankle jerks were absent. Though the limbs were quite flaccid, the muscles had a firmness to touch quite different from that in a denervated limb. The limb circumference was 1–1½ cm. greater than earlier measurements. Power returned gradually, in six hours being 50% normal, and in 12 hours entirely normal, all reflexes having returned.

Fig. 2 shows serum potassium readings both before and during paralysis together with a diagrammatic representation of the degree of paralysis. It will be

FIG. 2.—Serum potassium levels in Case H.IV.1 before, during, and after an induced attack of paralysis. Block diagrams represent degree of paralysis, the shaded area indicating proportional loss of muscle strength. 12 N = noon; 12 M = midnight.

noted that a lower figure was obtained during recovery than at the height of the paralysis. An E.C.G. at the stage of 50% paralysis showed lower T waves than on the previous day, and a U wave in lead II. Potassium output in the urine during the day of paralysis was 2.12 g. per litre compared with 2.64 g. the previous day.

On one further occasion marked weakness of the anterior tibial muscles developed three hours after the ingestion of 200 g. of glucose, but the serum potassium level was unchanged.

On 9 to 12 g. of potassium acetate per day he has remained well since discharge except for one severe attack following omission of treatment on an evening devoted to dancing.

Re-examination on several occasions has shown very slight permanent weakness of the right anterior tibials but the knee and ankle jerks have become increasingly difficult to obtain, and at the end of 1951, despite six months' freedom from attacks of paralysis, were absent altogether.

IV.2.—Male, aged 26. Son of III.2. Normal.

IV.3. and IV.4.—Male, aged 20, and female aged 16. Offspring of III.4. Both had the same facial asymmetry as III.4, both were free from attacks, and the blood chemistry was normal. IV.4 subject to migraine.

IV.5.—Male, aged 18. Son of III.6. Normal.

Generation V

V.1.—Infant daughter of IV.2. Normal.

With the aid of Dr. J. N. Hawthorne, two-dimensional partition chromatography was performed on the urines of H.IV.1, both before and during an attack of paralysis, and on H.III.1, H.III.4, H.IV.3, and H.IV.4. The amino-acid pattern was normal in all, and the spots were of normal intensity, though cysteic acid was rather unusually prominent in each.

The "F" Family

The pedigree is shown in Fig. 3.

FIG. 3.—Genealogical table for the "F" family.

In generations I and II there were 20 members, none being subject to periodic paralysis: II.4, II.12, and II.13 died in infancy of unknown causes; II.9 was a stillborn twin, an abnormal foetus; II.11 died aged 21 from a cerebral abscess, and II.14 aged 29 from jaundice; II.10, the father of III.1, suffered in youth from migraine.

Generation III (Offspring of II.7 and II.10)

III.1.—A man, aged 30, was admitted to the Queen Elizabeth Hospital on November 23, 1951 (Case No. 2931211121).

The patient was one of a twin pregnancy, the other being an abnormal foetus. He was well until July, 1949, when he developed mild weakness of the legs in the early morning following unusual exertion. Two weeks later he had an attack in which the legs and trunk were completely paralysed and the arms weakened. He recovered spontaneously in 12 hours. Several similar episodes in the next six weeks were interspersed with milder attacks which he was able to "walk off". He was twice examined elsewhere during attacks and found to have very weak tendon reflexes, but all investigations, including measurement of the serum potassium, were normal, and he was thought to be hysterical. He was well from January, 1950, to October, 1951, when he had a severe attack following a rich supper.

Examination on admission showed no abnormality in any system, and extensive blood and cerebrospinal fluid, cytological, biochemical, and serological examinations were normal, except for a serum cholesterol level of 96 mg. per 100 ml. An E.C.G. was normal.

Paralysis of the legs to about 50% of normal developed six hours after the oral administration of 300 g. of glucose in a pint of water, and all tendon reflexes except

the ankle jerks were greatly reduced. Recovery occurred gradually over the next 12 hours. Serum potassium readings are recorded in Fig. 4. It will be noted that the level remained low even when power returned to normal.

FIG. 4.—Serum potassium levels before, during, and after an induced attack of paralysis in Case F.III.1. Block diagrams represent degree of paralysis, the shaded areas indicating proportional loss of muscle strength. 12 N = noon; 12 M = midnight.

Attempts to re-precipitate paralysis by giving insulin and glucose were unsuccessful. E.C.Gs. showed slight depression of the T waves during paralysis.

On another occasion, after careful examination, the patient's right hand and wrist were immersed in water at 14° C. for 45 minutes. At 15 minutes the interossei were weak; at 30 minutes there was marked weakness of the interossei and lumbricals and the opponens pollicis was practically paralysed; at 45 minutes there was also weakness of dorsiflexion of the wrist. Tendon reflexes were unchanged. Twenty minutes after removal from the bath, when the hand had been at a normal temperature for over 15 minutes, there had been practically no return of power. The serum potassium level was unchanged throughout.

The patient was unable to remain for further investigation and was discharged to take potassium acetate prophylactically.

III.2.—Still-born twin; abnormal foetus.

III.3.—Male. Alive and well, aged 28. He had diphtheritic polyneuritis aged 6, and an isolated, severe attack of typical migraine at the age of 13. He was normal on examination except for a left-sided Holmes-Adie pupil.

III.4.—Female, died aged 6 months. She was a healthy child, found dead one morning, and not asphyxiated. Death was unexplained, despite a necropsy.

Comment

In the "H" family, the condition, once it appeared, seems to have been transmitted as a simple dominant. Though F.III.1 may be a sporadic example, there was so high a degree of unexplained infant mortality in his family that it is possible that

other members might have become affected had they lived to adult life. All affected members in both families were males.

Course and Prognosis.—The age of onset in the "H" family was between 13 and 17, attacks increased until the age of 25 then decreased spontaneously, and stopped entirely in the fourth decade. One affected member only is dead, and he died of other causes, 40 years after his last attack, while H.II.5 has been well for 41 years. Talbott (1941) showed this good prognosis in the majority of cases and at least one of Buzzard's cases of 1901 was known to be well 47 years later (G.D.H., 1948). Talbott (1941) found, however, more than 35 examples of death in an attack, and Holtzapple (1905) records this six times in one family, respiratory obstruction being a frequent cause.

Permanent changes may also occur in the muscles. These were of mild degree in the "H" family, consisting of slight wasting of thigh muscles, weakness of facial muscles, and absent reflexes. In 1891 Oppenheim described wasting of thighs and buttocks, absent reflexes, and pseudohypertrophy of calves, the last feature also being reported by Tyler, Stephens, Gunn, and Perkoff (1951). Holtzapple (1905) and MacLachlan (1932) mention permanent weakness and areflexia, and Biemond and Daniels (1934) had one child who developed wasted shoulder girdles, another permanent paralysis of the legs, and the eldest child, when his attacks stopped at age 38, had wasted legs and absent reflexes, the wasting later progressing to involve the rest of the body, leaving him bedridden. There was no muscle fibrillation. Oliver, Ziegler, and McQuarrie (1944) found one child permanently paralysed, but it is not necessarily the patients most severely affected who develop the permanent changes.

The Paralysis.—Predisposing factors in both families were exertion, emotion, high carbohydrate intake, and exposure to severe cold. As is usual, paralysis did not occur until four to six hours after the exciting cause, excepting a very rapid onset during exposure to cold. The ability to walk off mild attacks was prominent. The paralysis usually spread proximally from the legs, did not extend above the neck, and might leave groups of muscles entirely unaffected.

During total paralysis the muscles in H.IV.1 were strikingly firm, a feature stressed by MacLachlan (1932) and Zabriskie and Frantz (1932) while there was an increase in limb circumference, a fact found frequently by Talbott (1941) and

notably by Neel (1928) who reported 8 cm. enlargement. The tendon reflexes in all paralysed muscles were abolished, the superficial reflexes preserved.

Electrocardiography.—The changes in our patients during paralysis were slight, consisting of lowering of the T waves and the appearance of a U wave. Stewart, Smith, and Milhorat (1940), Perelson and Cosby (1949) and McAllen (1951) have classified the E.C.G. changes as prolongation of the PR interval, QRS complex and Q-T interval, depression of the T waves, and appearance of a U wave, and have stressed the variability in different patients.

Biochemical Changes.—The widely recognized lowering of the serum potassium level was present in three of our patients investigated during severe attacks, and was the only significant biochemical change discovered. In milder, but still definite, attacks of paralysis there was no significant change in the serum potassium. Pudenz, McIntosh, and McEachern (1938), Watson (1946), and Ziegler (1949) report attacks of paralysis with no lowering of serum potassium levels, and four cases of Tyler and others (1951) had major attacks without such changes. In H.IV.1 and a patient of Gammon, Austin, Blithe, and Reid (1939) the serum potassium level was lower during recovery than at the height of the paralysis. Conversely, Allott and McArdle (1938) point out that reductions of serum potassium to 7.6 mg. per 100 ml. may occur in patients not suffering from periodic paralysis without loss of muscle power.

Association with Migraine.—Three members of the "H" family and two of the "F" family suffered from migraine. Association of the two conditions was considered important by Holtzapple (1905), Gardner (1913), and MacLachlan (1932).

Errors of Diagnosis.—The commonest error is to consider the attacks of paralysis hysterical, as occurred in three of our patients and to many cases from the literature, sometimes with tragic results. H.III.1 was called an epileptic. Attacks occurring during a poliomyelitis epidemic may cause confusion of diagnosis, and the permanent muscle and reflex changes may, in later life, give rise to diagnoses such as muscular dystrophy, motor neuron disease, or tabes (Biemond and Daniels, 1934).

Discussion

The biochemical basis for this disease is still unknown. The serum potassium is usually, but not

invariably, low during an attack. Theories as to the causation of this fall have been discussed in detail by Talbott (1941) and by Gass, Cherkasky, and Savitsky (1948), and though it is known that potassium does not move into the red cells, nor is lost from the body in the urine, yet does move from the extracellular to the intracellular phase (Danowski, Elkinton, Burrows, and Winkler, 1948), its site of transfer remains uncertain, the muscles or the liver being the most likely. The production of paralysis by water diuresis (Gammon and others, 1939) and, in Addison's disease, by excessive administration of D.O.C.A., both measures causing generalized depletion of body potassium, and the E.C.G. changes in periodic paralysis, being those of potassium depletion of heart muscle, make accumulation of potassium in the muscles unlikely. The knowledge that potassium is required in the process of liver glycogenesis and glycogenolysis, the association of attacks with heavy carbohydrate intake, involving the former, and administration of adrenaline, involving the latter, favour a "hepatic drain" on serum potassium. These theories do not explain the mechanism of development of the paralysis, nor the numerous reports of paralysis with a normal or even very high serum potassium level (Finch and Marchand, 1943).

Could it be that the fundamental abnormality lies primarily in the muscle, rather than in the chemical constituents of the blood? That there is during paralysis a defect in the muscle itself rather than in the nerve supply seems apparent from numerous reports (e.g., Pudenz and others, 1938; Zabriskie and Frantz, 1932; Talbott, 1941) showing absence of response to electrical stimulation applied direct to the muscle. During paralysis the muscles have a firmness to the touch quite different from that associated with the flaccidity of denervation, and measurements have shown increase in the bulk of the limb. Most reports of muscle biopsy during paralysis refer to vacuoles and unidentified droplets and granules (Talbott, 1941) and these were stressed in the careful studies of Tyler and others (1951).

It is possible also to produce localized muscle paralysis by exposing local muscle groups to low temperatures, and the paralysis develops actually during the exposure to cold and not some hours later as in other methods of inducing an attack. Zabriskie and Frantz (1932) produced rapid paralysis of their patient's forearm by immersing it in water at 10-14° C., the paralysis being limited to the muscles immersed which became inexcitable to electrical stimuli. Neel (1928) demonstrated the same phenomenon. Our patient, H.III.1, had an attack of leg paralysis of very rapid onset while

wading in very cold water, and mild paralysis was experimentally produced in the muscles immersed of F.III.1.

The extensive work of Szent-Györgyi (1948) may have some bearing in this respect. He and his colleagues suggest that muscle contractility depends upon the combination of two substances, actin and myosin, to form the protein actomyosin, which, in association with adenosine triphosphate is capable of physical contraction. If dissociation of these substances occurs the muscle not only ceases to contract but becomes incapable of contraction. Experimentally changes in ionic context of the surrounding media above or below certain limits and exposure to cold are factors which bring about this dissociation. Actin changes from fibrous strands to globules, there is increased water content, and muscle fibres containing the dissociated substances become stiff and rigid instead of supple and elastic. In attacks of periodic paralysis the muscles are not flabby, but firm; they may increase in size; they may be incapable of contraction even when directly stimulated; they may show granules and droplets on biopsy. The attacks are produced by cold and often by, or associated with, changes in serum electrolytes.

One cannot draw too close a parallel between Szent-Györgyi's experimental work and the clinical features of this disease, but if there were in familial periodic paralysis some genetically determined structural abnormality in the elements responsible for contractility, the biochemical findings might assume rather less importance, the irregularity of their appearance be less confusing, while it would be easier to understand the permanent muscle changes with paralysis, progressive wasting, and pseudohypertrophy which on some occasions have resembled the hereditary muscular dystrophies.

There are a number of features of the disease which this suggestion does not explain, for example, the therapeutic value of potassium and the spontaneous cessation of attacks, but it is hoped that it may indicate another line of approach to a difficult and obscure problem.

Summary

Periodic paralysis is reported in two families. One member from each family has been studied in detail, both while normal and during induced paralysis.

Emphasis is placed on the usually benign prognosis, and on the permanent muscle and reflex changes which may occur.

Reference is made to current theories of pathogenicity, and attention drawn to the possibility of

the fundamental defect lying in the structural elements of the muscle itself.

The patients investigated in detail were under the care of Professor P. C. Cloake and Dr. G. S. Hall. Professor Waldenström of Malmö, Sweden, supplied details referring to H.IV.1, and extracts from the case history of H.III.6 are reproduced with the permission of Drs. E. N. Allott and Brian McArdle. Serum potassium estimations were carried out by Dr. Ronald Fletcher, and charts photographed by Mr. T. F. Dee.

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