Neurological and psychiatric manifestations in idiopathic hypoparathyroidism: response to treatment

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Patients with hypoparathyroidism may develop psychiatric symptoms. Others, like the two patients we present here may have symptoms which are more typical of organic brain disease. A feature common to the two patients is that the symptoms were only controlled when the hypocalcaemia was abolished; less specific forms of treatment failed.

CASE 1

Miss V.C., aged 54, had attacks of tetany for 34 years but was otherwise well. From about May 1965 she became increasingly confused and her personality deteriorated. A psychiatrist who examined her in April 1966 diagnosed presenile dementia and gave her chlorpromazine 25 mg q.d.s. Within a few weeks she was jaundiced and was admitted to another hospital. The jaundice disappeared on withdrawal of the drug, the serum bilirubin falling from 11 mg/100 ml. to 2 mg/100 ml., but she remained mentally confused and had continuous gross involuntary movements. None of the members of the patient's family were known to have had symptoms of mental confusion or involuntary movements. On examination her hair was dry and brittle and when the knee and ankle jerks were elicited there was plantar flexion of both feet with adduction of toes. Trousseau's test was positive. The serum calcium was 6.4 mg/100 ml. A radiograph of the skull showed extensive intracerebral calcification. She was thought to have idiopathic hypoparathyroidism, and in order to examine the relation between this and the confusional state she was transferred to Leeds General Infirmary.

Her mental condition was one of disorientation in time and space, with impairment of memory and concentration. She had flights of ideas with occasional perseveration and continuous choreiform movements of the face, head, and all four limbs. These movements had a hemiballismic character. Figure 1 shows a specimen of her handwriting. The reflexes were brisk and symmetrical, and the plantar responses were flexor. There were no opacities in the lenses. Trousseau's test was positive at one minute.

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INVESTIGATIONS The serum calcium was 4.9 mg/100 ml., serum magnesium 1.45 mg/100 ml., and the serum inorganic phosphorus 6.6 mg/100 ml. The serum alkaline phosphatase was 14 KA u./100 ml., with a heat stability index of 0.27. The blood urea was 18 mg/100 ml. Electrocardiography showed rather flat T waves, and long Q-T intervals; these findings are compatible with low serum calcium.

The plasma protein content was normal, as was the composition of the cerebrospinal fluid. The only radiological abnormality was extensive intracerebral calcification, distributed throughout the basal ganglia. The electroencephalograph was normal and was not altered by hyperventilation.

A sample of trabecular bone, by trephine from the iliac crest, was histologically normal.

TREATMENT AND PROGRESS Her involuntary movements stopped immediately after intravenous diazepam (10 mg).

FIG. 1. Specimen of the patient's handwriting on admission (5 May 1966).

FIG. 2. Specimen of the patient's handwriting when her choreiform movement was controlled (10 June 1966).

They recurred two hours later although not to the same extent as before. In view of this improvement she was given diazepam by mouth, at first 20 mg and later 75 mg per day. Although this treatment partly controlled the involuntary movements she remained agitated and depressed. She also had attacks of tetany with laryngeal stridor and on one occasion with a generalized convulsion. The tetany was abolished by an intravenous injection of calcium gluconate. She was then given calciferol 2 mg/day (80,000 u.) with 2.4 g effervescent calcium (Sandoz). Her serum calcium rose and at the same time her involuntary movements diminished. Figure 2 shows a specimen of her handwriting one month after beginning calciferol, when her serum calcium was 9.5 mg/100 ml. By this time she was less confused and she required only 2.5 mg diazepam per day. Her memory had improved, she appeared more intelligent, and her involuntary movements had ceased. Her behaviour continued to improve while her serum calcium was maintained at 9.5 to 10.5 mg/100 ml. with 1 mg vitamin D₂ daily. In March 1967, the diazepam was stopped without any immediate deterioration in her mental state.

By July 1967, she was hyperactive and much more talkative. Her serum calcium was then 8 mg/100 ml. A month later she was admitted to hospital, and on examination her serum calcium was found to have fallen to 7.2 mg/100 ml. She had motor restlessness with an associated tremor, a marked increase in tone, and some cog-wheel rigidity. Psychiatric opinion was that the patient was hypomanic, most probably related to some metabolic disturbance in a setting of long-standing organic deterioration. She was given benzhexol 2 mg t.d.s. and haloperidol starting at 0.75 mg t.d.s. and increasing to a maintenance dose of 1.5 mg t.d.s.

The patient's serum calcium rose to 9 mg% during the next three months on calciferol (vitamin D₂) 1 mg/day. Her mental state improved gradually, she became less agitated, and her involuntary movements disappeared. Haloperidol was withdrawn without a recurrence of her symptoms. She was discharged on vitamin D₂ 1 mg a day and 2.4 g effervescent calcium (Sandoz); her serum calcium was 10 mg/100 ml. Her last admission was in March 1969 when she was found to be restless, agitated, and unable to sit quietly; there were continuous choreiform movements of all four limbs. Her serum calcium was 8.3 mg/100 ml. Intravenous diazepam produced no apparent effect. In order to alleviate her mental condition while her vitamin D therapy was being adjusted, she was given large doses of tranquilizers and unfortunately developed bilateral hypostatic pneumonia. Because of her weakened physical condition, vitamin D therapy was difficult to administer, and her serum calcium fell further, to 7.5 mg%. After her chest infection improved with antibiotics and physiotherapy, she was started on dihydrotachysterol (DHT) 0.5 mg per day, her serum calcium rose steadily and was maintained at 10 mg/100 ml. At the same time her choreiform movements disappeared and have not since recurred. Concurrently, her acute hypomania was treated with increasing doses of haloperidol. At the time of writing her serum calcium is 9.5 mg/100 ml. on DHT 0.5 mg/day, and the dose of the haloperidol is being reduced. She is

mentally and physically well and able to carry out her daily duties.

CASE 2

A.P., aged 16, had his first fit after a 'flu-like' illness when he was 14 years old. The fits, which occurred frequently during the next two years, took the form of loss of consciousness lasting about 30 seconds and clonic movements of limbs lasting half to one hour. As the attacks recurred he became an anxious child and began to lag behind his classmates so that in September 1966 he was transferred to a lower form at school. He was referred to a neurologist in 1967 for investigation of his fits. Extensive neurological examination and investigation, including electroencephalography, lumbar puncture, and air encephalography failed to reveal any cause for the fits. He was given diazepam 10 mg q.d.s. and phenytoin 50 mg t.d.s. and sent home. However, he continued to have fits and was readmitted in November 1967. When the serum calcium was measured for the first time it was found to be 5.8 mg/100 ml. He was transferred for further investigations with the following results. The serum calcium was 5.5 mg/100 ml., the serum inorganic phosphorus was 11.2 mg/100 ml., the serum magnesium was 1.94 mg/100 ml., the serum alkaline phosphatase 39 KA units, and the blood urea 15 mg/100 ml. The urine calcium was 15 mg in 24 hours. The Ellsworth-Howard test showed a response of the renal tubules to an injection of parathyroid hormone with an increase in the rate of excretion of phosphate. Xylose absorption was normal. Faecal fats were within the normal range. A radiological skeletal survey was normal, as was the bone biopsy.

It appeared that this boy had idiopathic hypoparathyroidism. As a first measure in the correction of the hypocalcaemia we attempted to reduce the serum phosphorus. He was given aluminium hydroxide, 15 ml. four times a day, in an attempt to diminish phosphate absorption, but there was no change in the serum calcium or phosphorus. A week later he was given, in addition, probenecid 2 g a day with the aim of increasing the excretion of phosphorus in the urine. There was little change in the patient's serum phosphorus, but the serum calcium increased. When dihydrotachysterol (DHT) was given in addition to aluminium hydroxide and the serum calcium rose to within normal values, the serum phosphorus fell and he had no more fits. Progressive withdrawal of aluminium hydroxide, probenecid, and the anti-epileptic therapy produced no recurrence of his symptoms or a change in the serum calcium or phosphorus. He has made a complete recovery; he is more placid and a much less troublesome child. The standard of his work at school has improved immensely.

DISCUSSION

Gross mental retardation and symptoms of hypomania and hallucinations, as encountered in our first case, have been observed in a few patients with idiopathic hypoparathyroidism (Simpson, 1952; Rose and Vas, 1966). These were usually patients

who had escaped diagnosis for many years. However, 80% of the cases studied by Denko and Kaelbling (1962) had intellectual impairment (IQ 40 to 90) as the sole or major psychiatric finding. Mental impairment is reversed in about 50% of the patients (Berezin and Stein, 1948; Treusch, 1957; Denko and Kaelbling, 1962) when the serum calcium is brought into the normal range, as was the case in both of our patients.

Calcification of the basal ganglia is a reflection of long-standing hypocalcaemia (Eaton and Haines, 1939; Danowski, Lasser, and Wechsler, 1960) and its presence should lead one to look for abnormalities of calcium metabolism. Naef and Adle (1959), in a discussion on calcification of the basal ganglia, state that the calcification is bilaterally symmetrical and is dense in the caudate nucleus and globus pallidus. There is hyalinization and deposition of calcium within the walls of the small blood vessels, chiefly in the media and adventitia. Profound involvement of the vessels is associated with degeneration and loss of ganglion cells. The crystalline form of the pathological deposits of calcium is that of the natural apatites—that is, $3\text{Ca}_3(\text{PO}_4)_2\text{Ca} \cdot x\text{H}_2\text{O}$, where x may represent a variety of substances. The apatite of bone is probably a hydroxyapatite, $3\text{Ca}_3(\text{PO}_4)_2\text{CaOH}_2$, but its composition is modified by the ions substituted at the surface of the crystals in particular, carbonate may substitute for phosphates. Presence of calcification in the basal ganglia is not necessarily accompanied by central nervous system disorder (Naef and Adle, 1959; Muentner and Whisnant, 1968) and the condition is not unique to hypoparathyroidism. It has also been noted in enceph-

litis lethargica, carbon monoxide poisoning, hypoxia, tuberous sclerosis, paralysis agitans, old intracerebral thrombosis, and spinal tumor (Bennett, Maffly, and Steinbach, 1959; McKinney, 1962; Muentner and Whisnant, 1968).

Chorea is a very rare manifestation in hypoparathyroidism associated with calcification of the basal ganglia, and only one case has been reported by Simpson (1952) in the British literature. McKinney (1962) reviewed the literature of cases with either idiopathic hypoparathyroidism or pseudohypoparathyroidism and found 17 cases of patients who demonstrated abnormal movement, but only four of these cases demonstrated choreiform movement. One of the cases had evidence of calcification of the basal ganglia. The four cases are summarized in Table 1. Muentner and Whisnant (1962), in a review of cases from Mayo Clinic between 1935 and 1966, found 38 patients with bilateral calcification of the basal ganglia of whom nine patients had hypoparathyroidism and evidence of neurological disorder. The neurological abnormalities were movement disorders, seizures, retinal degeneration, hemianopia, cranial nerve deficit, cerebellar dysfunction, and dementia. They noticed that in the majority of cases of calcification of the basal ganglia associated with neurological disorder, the latter abnormality could be reversed in cases of hypoparathyroidism (five out of nine) in contrast with those without hypoparathyroidism (0 out of 12). Our patient, Miss V. C., who had hypoparathyroidism and calcification of the basal ganglia, developed choreiform movement only when her serum calcium values were outside the normal ranges.

TABLE
SUMMARY OF CASES OF HYPOPARATHYROIDISM WITH CHOREIFORM MOVEMENT

Author	Patient's age (yr)	Sex	Disease	Type of movement	Basal ganglia calcification	Serum Ca level (mg/100 ml.)	Remarks
Bronsky <i>et al.</i> (1958)	16	F	Idiopathic hypoparathyroid	Chorea	Yes	5.8-7.4	Choreiform movements disappeared when serum calcium was 9.9 mg/100 ml. No recurrence of chorea
Forbes (1956)		M	Idiopathic hypoparathyroid	Chorea with head nodding and nystagmus	None	6.2-8.8	Treatment with vitamin D and oral calcium produced satisfactory response—movements became less awkward, head nodding and nystagmus markedly lessened
McKinney (1962)	68	F	Hypoparathyroid after total thyroidectomy	Chorea	None	5.2	Treated with parenteral and oral calcium, her chorea improved considerably
Simpson (1952)	9	M	Idiopathic hypoparathyroidism	Chorea	None	5.0-7.2	Choreiform state subsided in about a week. No recurrence with treatment

The appearance of involuntary movements in our patients suggests that the cells of the basal ganglia cannot function adequately with low levels of serum calcium. The disorder affects inhibitory influences on thalamocortical pathways concerned in the control of voluntary movement, but the condition is reversible when normal calcium levels are restored.

Epileptic attacks are frequent in about 40 to 50% of patients with idiopathic hypoparathyroidism (Willison and Whitty, 1957; Dickson, Morita, Cowser, Graves, and Myer, 1960). The frequency of attacks is less after post-operative hypoparathyroidism, presumably because the hypocalcaemia is less severe. Despite this, epilepsy may manifest itself in patients with hypoparathyroidism without any evidence of overt tetany (Eaton and Haines, 1939; Rose and Vas, 1966). A characteristic of the epileptic seizure in hypocalcaemia is resistance to anticonvulsant therapy (Frame and Carter, 1955; Rose and Vas, 1966). Seizures after hypocalcaemia diminish in frequency initially and finally stop when the level of serum Ca^{++} is raised to normal levels (Eaton and Haines, 1939; Rose and Vas, 1966). Our patient, A.P., showed all these features.

The two patients, taken together, demonstrate the specific and probably causative relation between the serum calcium and symptoms, whatever the form of the symptoms (Eaton and Haines, 1939; Rose and Vas, 1966). Neither the state of agitation, anxiety, and chorea as illustrated in our first patient nor the fits in our second patient could be controlled except by bringing the serum calcium into the normal range.

SUMMARY

Two patients with idiopathic hypoparathyroidism who developed symptoms of dementia and chorea (as in case 1), and epilepsy (as in case 2) only when their serum calcium was low are described. The symptoms more or less disappeared when their serum calcium was maintained in the normal range.

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