APHONIA AND DEAFNESS IN HYPERPARATHYROIDISM

BY

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The role of calcium in variations of the excitability of nervous tissue is generally accepted. A relatively small decrease in the serum ionized calcium causes hyperexcitability of sensory and motor nerve fibres, and spontaneous activity may be sufficient to cause paraesthesiae and muscular spasm, which is the basis of tetany. Conversely, increased ionized calcium in the blood might be expected to decrease nerve excitability. The muscular weakness commonly found in cases of hyperparathyroidism has been so explained (Albright and Reifstein, 1948), but surprisingly few sensory symptoms have been reported. Aphonia and deafness were noted by a patient (Case 1) at a time when hypoexcitability of nerves was certainly present. Cases 2 and 3 were seen two years after operation, so data are not complete. It is suggested, however, that they closely resemble Case 1 in the type of symptoms exhibited, and in the prompt and permanent relief after removal of a parathyroid adenoma. They are reported by courtesy of Mr. J. Hinton Robertson.

Case 1

A married woman aged 58 was admitted to the Western Infirmary, Glasgow, under Mr. R. Barnes in October, 1952. In 1947 she had complained of weakness of the right leg sufficient to prevent her lifting the foot. This gradually improved, but once again deteriorated in March, 1951. She then became easily tired and both legs felt "slow and stiff," so that she was bedridden. In February, 1952, vomiting, associated with eating greasy food, and right subcostal pain were attributed to cholecystitis. Thereafter she complained of increasing weakness, pains in the legs, headache, anorexia, thirst, polyuria, and severe constipation. About the same time her voice became almost inaudible, she noted difficulty in opening her eyes and she had severe deafness, associated with sensations of being cut off from people—"as if my ears were blocked" and "as if the whole head was shutting

FIG. 1.—Case 1. Audiogram. O—O Rt. ear. X—X Lt. ear. Inset, bone conduction.

in." Deafness was severe for about a month, then gradually cleared. It was absent when she was examined at the orthopaedic clinic by Mr. T. Gardner, who diagnosed hyperparathyroidism as the cause of her limb pains.

Mr. Barnes kindly allowed me to investigate the case in the Gardiner Institute. There was generalized weakness with hypotonia but normal reflexes, the serum calcium was 15.0 mg. per 100 ml., serum inorganic phosphate 2.8 mg. per 100 ml., and serum alkaline phosphatase 145 K.-A. units. The serum calcium level slowly dropped to 13.6 mg. per 100 ml. Hearing was good and the ears were apparently normal. Dr. J. C. McKinley found the drum-heads normal, Rinné test positive, and bone conduction good in each ear. Whispered voice was heard at 6 ft (1.8 m.) from each ear, and conversational voice at 18 ft. (5.5 m.). An audiogram was within the normal range in relation to the patient's age (Fig. 1). The response of

FIG. 2.—Case 1. Accommodation curve of right ulnar nerve. The slope is 31; the time-constant of accommodation (reciprocal of slope) is 32.3 msec. The shaded area shows the normal range for women (Solandt, 1936).

the right ulnar nerve to exponentially rising electric currents of variable time-constant was tested, as described by Solandt (1936), with Andrew's (1952) stimulator to estimate its time-constant of accommodation (λ) (Hill, 1936). It was found to be 32.3 msec. (Fig. 2).

A large parathyroid adenoma was removed from the upper mediastinum by Professor C. F. W. Illingworth on November 27, 1952. Symptoms and signs of latent tetany developed and were controlled by calcium gluconate injections, with calcium lactate and calciferol orally. A normal biochemical picture has been maintained. Strength was rapidly increasing, the patient was able to walk unsupported, and the bones were recalcifying. There has been no recurrence of aphonia or of deafness.

Case 2

A married woman aged 49 was admitted to the Victoria Infirmary, Glasgow, with spontaneous fracture of the femoral neck in April, 1950. A radiological diagnosis of hyperparathyroidism was confirmed by the biochemical findings. The serum calcium content was 15.8 mg. per 100 ml., serum inorganic phosphate 2.85 mg. per 100 ml., and serum alkaline phosphatase 59 K.-A. units. For one year previously she had complained of spells of deafness and tinnitus in the left ear. She was discharged from hospital after a negative exploration of the neck, but was readmitted in May, 1951. Her symptoms were as before, with the addition of dyspnoea on slight exertion, tiredness, mental depression, spells of tingling of the hands, and marked huskiness of speech. Serum calcium was now

12.2 mg. per 100 ml., serum inorganic phosphate 3.05 mg. per 100 ml., serum alkaline phosphatase 31 K.-A. units. A parathyroid adenoma was removed from the mediastinum by Mr. J. Hinton Robertson; signs of latent tetany developed, but spasm was prevented by injection of calcium gluconate. Fatigue, deafness, and tinnitus disappeared after operation, and had not returned when I examined the patient in March, 1953, and found no evidence of aural abnormality.

Case 3

A spinster aged 49 years was admitted to the Victoria Infirmary in December, 1950, with cardio-renal failure due to hypertension and with auricular fibrillation. She complained also of pains in many parts of the body, present for several years, and of weakness of the muscles. She had very bowed legs, kyphoscoliosis, and early lenticular cataract. Radiology suggested a diagnosis of hyperparathyroidism, which was confirmed by the biochemical findings (serum calcium 14.5 mg. per 100 ml.; serum inorganic phosphate 2.18 mg. per 100 ml.; serum alkaline phosphatase 62.8 K.-A. units). The reflexes were recorded as "physiological." A parathyroid adenoma was removed by Mr. J. Hinton Robertson in February, 1951, transient post-operative tetany being readily controlled. The patient was well when I examined her in March, 1953. In response to questioning she stated that she had noticed attacks of singing in the ears when muscle weakness was present before the operation, but had had no auditory disturbance since (without any specific treatment). In March, 1953, hearing was normal.

Discussion

Since 1937 five cases of hyperparathyroidism have been investigated in the Gardiner Institute, including Case 1 above. Of the other four, deafness was recorded in two. Unfortunately the deafness was not further investigated, and the case notes do not record the post-operative hearing state. The two patients who were admitted in 1937 and 1942 cannot now be traced.

The three cases presented exhibit the classical symptoms of hyperparathyroidism, including muscular weakness and hypotonia, which are attributed to diminished nerve excitability caused by hypercalcaemia (Albright and Reifenstein, 1948). Though the husky voice of Case 2 is no doubt due to previous trauma, the aphonia described by Case 1 is thought to be due to muscle weakness of the same type. Gutman, Swenson, and Parsons (1934) report the case of a patient who was "almost aphonic," with a serum calcium content of 13.9 mg. per 100 ml. On laryngoscopy no abnormality was noted, except oedema of the mucous membrane.

Motor symptoms are alarming enough to a patient to be reported, but sensory symptoms other than pain tend to be ignored if thought irrelevant by both patient and examining physician. At any rate, a review of the literature on hyperparathyroidism reveals few references to disturbances of function of afferent nerves. Vertigo and dizziness are common complaints which are too indefinite to analyse. Gutman, Swenson, and Parsons (1934) also report a case in which the patient complained of occasional numbness of the extremities and pruritus, and the case records sometimes mention deafness without giving details—for example, Werner, 1942. Nevertheless, Cantarow (1947) finds that in late cases of hyperparathyroidism complaint of muscle weakness is made in 15%, paraesthesiae in 2%, and deafness in 1%. Reifenstein (1950) states that decrease in auditory acuity occurs in hyperparathyroid patients, and Albright and Reifenstein (1948) suggest that nerve deafness should be expected, but the case they quote as evidence was believed by Hunter and Turnbull (1931), who report it, to have otosclerotic deafness. It is common to find increased auditory acuity in tetany (Ucko, 1951), but this is always of short duration.

Bellin and Gershwin (1935) report severe deafness and decrease of muscle tone in a patient with hyperparathyroidism. "She was absolutely definite in stating that her hearing was markedly impaired since all these peculiar

things were happening to her." The serum calcium was 19.5 mg. per 100 ml., rising to 22 mg. before operation, and the serum inorganic phosphate was 6.8 mg. per 100 ml. The authors state that both eardrums showed calcification—more on the right side, "where almost complete deafness existed." Unfortunately they included no tests of bone conduction. After parathyroidectomy the serum calcium levelled out at about 11.6 mg. per 100 ml., muscle tone increased to normal, and hearing returned completely in the left ear and partially in the right. At the same time they observed disappearance of the calcific deposits in the eardrums. One hesitates to deny the possibility that metastatic calcification of the eardrums could be responsible for deafness in this case, yet it should be noticed that the authors found no other evidence of metastatic calcification and no renal calculi. Metastatic calcification most commonly affects those tissues in which acid secretion takes place (kidneys, stomach, lungs), or in scar tissue (Cantarow, 1947), so that it would be surprising to find that both eardrums were the only sites of metastatic calcification in hyperparathyroidism. Further, after removal of a parathyroid adenoma there is no tendency for resorption of metastatic deposits of calcium—indeed, they may increase—especially when the serum calcium level remains abnormally high.

On the other hand, the symptoms are strikingly like those of Case 1 of the present report, and comparison with Cases 2 and 3 suggests that auditory disturbance is greater when muscular weakness is severe, and so may have the same cause. The serum calcium level fluctuates considerably in untreated hyperparathyroidism (Cope, 1948) and may even return temporarily to a normal level (cf. Case 2), and symptoms are correspondingly variable. The serum calcium level was falling and muscle power improving when Case 1 was admitted to hospital. It may be presumed that the serum calcium had been higher than the recorded level at the time of maximum weakness, vomiting, aphonia, and deafness, yet even when the serum calcium was 15 mg. per 100 ml. and there was no deafness (Fig. 1), the accommodation of the motor fibres of the right ulnar nerve was greatly increased, with a time-constant of 32.3 msec. (Fig. 2), the lower limit in normal women being 50 msec. (Solandt, 1936).

The "time-constant of accommodation" (λ) of a nerve (Hill, 1936) is an index of its excitability by an electrical stimulus. It is lowered by increasing the calcium in the nerve's environment (Solandt, 1936). Increased accommodation (decreased λ) reduces the frequency of response of a nerve to a stimulus. Galambos and Davis (1943) have shown that alteration of loudness of a sound at the ear is signalled by the auditory nerve as variation in impulse-frequency so that the effect of increasing accommodation would be to decrease the apparent intensity of sound.

The possibility that deafness is determined by the bone changes rather than the biochemical changes must be examined, as at one time otosclerosis was widely believed to be due to hyperparathyroidism (Mayer, 1917), and deafness is also associated with other bone diseases. In osteitis deformans (Paget's disease) it is often attributed to nerve compression in the auditory canal, but otosclerosis is said to be common in advanced cases (Hunter, 1944), though Lindsay and Perlman (1936) and Wilson and Anson (1936) found no conclusive evidence for a close relationship. Anson and Wilson (1937) found that the deafness was usually due to damage of the inner ear from involvement of the petrous temporal bone. Otosclerosis also occurs in 60% of cases of osteogenesis imperfecta (Hunter, 1944), apparently as an associated genetic abnormality, and van der Hoeve and de Kleyn (1918) described degeneration of the labyrinth in this condition. It might seem, then, that deafness in hyperparathyroidism was of the same nature, but in these bone diseases, which are unaccompanied by hypercalcaemia, the deafness shows no tendency to spontaneous remission. It is inconceivable that otosclerosis can explain the loss of hearing in the cases of hyperparathyroidism in which deafness closely follows excessively high blood calcium levels, and is promptly and permanently relieved after parathyroidectomy.

The evidence cited cannot be regarded as conclusive, as the cases were all seen after recovery from deafness, but it is highly suggestive of a close relationship between reversible deafness, aphonia, muscular weakness, increased nerve accommodation, and hypercalcaemia. It is perhaps relevant to note that other causes of "chemical deafness" are quinine, which is well known to block nerve conduction (Cooper, 1924), and analgesics such as salicylates and acetanilid (Macht, Greenberg, and Isaacs, 1919). The latter drug at least has been shown to depress muscle-nerve excitability (Macht, 1919). Hyperparathyroidism is rare and is usually diagnosed at orthopaedic clinics. It is hoped that this paper will stimulate interest so that the occurrence of deafness can be fully investigated before and after operation.

Summary

Disturbances of hearing are reported in five cases of hyperparathyroidism, and aphonia in one case.

In three cases these symptoms disappeared after removal of a parathyroid adenoma, and examination showed no defect of hearing.

Increased nerve accommodation, demonstrated in one case, is suggested as a possible cause of these symptoms.

The cases are reported so as to draw attention to an unusual cause of nerve deafness.

I wish to thank Professor Sir John McNee, Mr. Roland Barnes, and Mr. J. Hinton Robertson for permission to study their cases; Mr. A. M. Andrew, of the department of physiology, for the use of his stimulator; and Dr. J. C. McKinley for the audiogram in Case 1.

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The National Multiple Sclerosis Society has published a 32-page booklet on *Psychological Factors in the Care of Patients with Multiple Sclerosis*, written by M. P. Harrower and R. Herrmann. A brief summary of facts on the nature of the disease and its management in the U.S.A. is followed by a discussion on the personality of the patient, the psychological aspects of his relations with the doctor, and the psychological difficulties peculiar to those with disseminated sclerosis. The use of psychological testing in diagnosis and as an adjunct to therapy is described. Group therapy for patients and relatives is advocated; occupational therapy in the home is important, and rehabilitation centres are also of value. The booklet may be had free of charge from the Society at 270, Park Avenue, New York, 17, U.S.A.

SKIN LESIONS AND DEAFNESS IN DISSEMINATED TUBERCULOSIS

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Skin lesions which form part of a clinical complex produced by the dissemination of active foci of tuberculosis in various organs of the body are comparatively infrequent, so that when they are encountered their significance may be overlooked. Early recognition of these lesions is desirable when the tuberculous disease is chronic. When it is acute, skin involvement may provide the earliest means of identifying the nature of a disease in which prompt administration of appropriate treatment is of vital importance.

In the first four cases of disseminated tuberculosis reported below cutaneous lesions were either prominent presenting features of the disease or were or might have been of diagnostic assistance; and it is interesting that deafness was recorded in two of them. In Cases 5-8 abnormalities of the skin produced by subcutaneous tuberculous lesions were important clinical features, and increasing deafness was a presenting symptom in the only one in which the disease was of an overwhelming nature.

Case 1

A man aged 50 was admitted to Ruchill Hospital on March 21, 1951, with a diagnosis of erysipelas. He had been in another hospital from December 15, 1950, to January 29, 1951, with a left lower lobe pneumonia which had failed to respond to penicillin, but showed complete resolution clinically and radiologically after treatment with aureomycin. Subsequently he remained well until March 18, when he developed what he thought was a sty on the left upper eyelid; on the 19th the inflammation involved the peri-orbital skin, and later other cutaneous lesions developed on the back of the neck.

On admission to Ruchill Hospital he was moderately ill. His pulse was 80 and respirations 16. His temperature was normal on admission but rose a few hours later to 103° F. (39.4° C.) and continued swinging to 103-104° F. (39.4-40° C.) until death. He had a purplish swelling round the left eye, with numerous small papules and pustules in the affected skin. On the back and right side of the neck were several infiltrated bluish plaques with surrounding erythema and scaling and also numerous small papules and pustules. A linear, infiltrated purplish lesion on the right malar region and several small crusted papules on the front and back of the chest were seen. The tip of the spleen was just palpable. The urine contained a trace of albumin. Blood examination showed: leucocytes, 6,000 per c.mm. (polymorphs 44%, lymphocytes 46%). A chest x-ray film on March 28 showed marked right hilar enlargement; the lung fields were clear except for a calcified primary focus in the right upper lobe with associated calcification in the right paratracheal glands. Sputum examinations were negative for *Mycobacterium tuberculosis*. Penicillin was given on admission, followed by aureomycin, and, from April 4, streptomycin, 1 g. daily, but there was no response.

Repeated blood examinations during the illness showed a steady decline in the leucocyte count from 6,000 on admission to 1,000 per c.mm. a few days before death; the erythrocytes declined in that period from 3,200,000 to 2,100,000 per c.mm. The patient died on April 11.