REFSUM'S SYNDROME AFFECTING A BROTHER AND TWO SISTERS*

BY

E. M. ASHENHURST, M.B., M.R.C.P.Ed.
*Registrar, Department of Neurology, Royal Victoria
Hospital, Belfast*

J. H. D. MILLAR, M.D., M.R.C.P.
Consultant Neurologist, Royal Victoria Hospital, Belfast

AND

T. G. MILLIKEN, M.D., M.R.C.P.
*Consultant Physician, South Tyrone Hospital,
Dungannon, N.I.*

A familial syndrome with the descriptive title "heredopathia atactica polyneuritiformis" was first described by Sigvald Refsum (1946) in Norway. Five cases in patients ranging in age from 25 to 41 years occurred in two unrelated families. A similar condition occurring in children was reported by Refsum *et al.* (1949); four cases in three unrelated families were described. A single case report has been published in this country (Clarke and Critchley, 1951), but, so far as we can discover, no other instance of this rare condition has been reported in the British Isles.

This paper records three further cases occurring in a single family.

The Clinical Syndrome

The syndrome is characterized by the following components: (a) Atypical retinitis pigmentosa—pigmentary changes are usually insignificant or absent—with night blindness and concentric limitation of the visual fields. (b) A chronic polyneuritic-like picture with progressive pareses of the limbs distally. This is associated with cytoalbuminological dissociation in the cerebrospinal fluid, very high levels of protein being achieved in many cases. (c) Ataxia, nystagmus, and other cerebellar manifestations. These may be very pronounced, so that a diagnosis of Friedreich's ataxia is often mistakenly made. (d) Other neurological abnormalities, which are not constantly found, include a neurogenic type of deafness, abnormalities of the pupillary reactions, and anosmia.

Among other findings, which are frequently associated with the retinal and neurological pictures, are ichthyotic skin changes and abnormalities in the electrocardiogram. These latter are of many varieties and include increase of the P-Q interval, nodal and auricular extrasystoles, alterations in the QRS complex, and sinus tachycardia. Sudden death is not infrequent in cases of Refsum's syndrome, and a cardiac basis has been postulated. In no case has there been clinical or x-ray evidence of cardiac enlargement. Consanguinity has been present in practically every instance. The high incidence of consanguineous marriages is strong evidence in favour of recessive heredity.

Differential Diagnosis.—Among the differential diagnoses which have to be considered are the hereditary ataxias of the Friedreich type, peroneal muscular atrophy, and hypertrophic interstitial polyneuritis (the Dejerine-Sottas syndrome). The Laurence-Moon-Biedl syndrome can be readily ruled out, the only common factor in the two conditions being retinitis pigmentosa. The juvenile form of amaurotic familial idiocy (Tay-Sachs disease) also comes under consideration because of the retinal changes which occur.

Pathology.—Understandably, few necropsies have been carried out (Refsum, 1946; Reese and Bareta, 1950). The

main abnormalities have consisted of fibrous thickening and infiltration of the leptomeninges by lipid macrophages, moderate fatty degeneration of peripheral nerves, with axonal changes in the anterior horn cells of the spinal cord, and degeneration of the fibre tracts from the pontobulbar region to the cerebellar white matter. No inflammatory changes have been described. In one adult case in which the peripheral nerves were examined, changes characteristic of hypertrophic interstitial neuritis were found (Reese and Bareta, 1950).

Case 1

In May, 1953, a man aged 21 developed an influenza-like illness of sudden onset characterized by general malaise, anorexia, pains in the limbs and back, productive cough, and low-grade pyrexia. These symptoms persisted for two weeks before he observed any muscular weakness, pain being the dominant feature, increasing in severity and causing insomnia. Weakness appeared simultaneously in all four limbs, although the legs were more severely affected than the arms, so that in a few days he was unable to stand or walk. He was admitted to hospital.

Physical examination showed a normally developed man of 21. There was nothing remarkable on general examination except for slight thickening and scaling of the skin of the hands and feet. There was bilateral pes cavus but no other skeletal abnormality.

Examination of the cranial nerves revealed the presence of anosmia, bilateral optic atrophy, concentric constriction of the visual fields on testing by confrontation, and fine horizontal nystagmus on lateral gaze to right and left sides.

He had generalized wasting of the upper and lower limbs of slight degree and weakness of all muscle groups, most marked distally. The respiratory musculature was not involved. Fibrillation was not seen in the weakened muscles. Muscular hypotonia was present in both arms and legs. Slight ataxia was observed in the upper limbs on performing finger-nose-finger tests and a terminal intention tremor was demonstrable. Weakness was too pronounced in the lower limbs to enable any assessment of co-ordination to be made. The tendon reflexes were universally absent. Abdominal cutaneous reflexes were easily obtained and the plantar responses were flexor in type. Sensory changes were absent except for loss of vibration sense in the legs and impairment of joint-position sense in both feet. The sphincters were controlled. He was thought at that time to be a case of Friedreich's ataxia with an exacerbation of symptoms following an attack of influenza.

During the next four to five months he improved considerably, and by the end of that period could discern no weakness in his upper limbs. Power had also improved in the legs and was virtually normal, except at the ankles. There was bilateral foot-drop, and active dorsiflexion at the ankle was absent. The tendon reflexes had returned in the arms, but knee- and ankle-jerks were unobtainable. Nystagmus was no longer present, and the fundi, which had been clearly visualized before, were no longer visible because of lens opacities.

On reply to direct questioning he now admitted to inability to see in the dark. This symptom had been present for many years.

Ophthalmological Report.—"There are opacities in the posterior part of each lens. The disks show waxy pallor and there is a fine retinal degeneration in all areas in both fundi. There is not a marked degree, but fine pigmentation is visible. The case is considered to be one of retinitis pigmentosa."

On August 28 lumbar puncture was performed and clear fluid obtained under normal pressure. Considerable elevation of protein content without concomitant rise in leucocytes was revealed (see Table).

A triple athrodesis, with bilateral tendo-Achillis lengthening, was carried out with considerable benefit to the patient.

He was seen from time to time as an out-patient and remained in good health until December, 1956, when he

*Based on a communication given to the Association of British Neurologists, November, 1957.

Cerebrospinal Fluid Analysis in Case 1

August 28, 1953	..	R.B.C. 0/c.mm.; W.B.C. 2/c.mm.; protein 450 mg./100 ml.; globulin ++; W.R. negative; Lange 1122342100.
August 3, 1954	..	R.B.C. 123/c.mm.; W.B.C. 2/c.mm.; protein 150 mg./100 ml.; globulin ++; Lange 112210000.
August 6, 1955	..	R.B.C. 0/c.mm.; W.B.C. 2/c.mm.; protein 60 mg./100 ml.; globulin trace; Lange 112210000.
August 20, 1957	..	Cells nil; protein 120 mg./100 ml.; globulin ++; Lange 1112233100.

Electrophoresis of C.S.F. protein showed the relative proportions of the various fractions to be within normal limits.

had a recurrence of weakness and root pains in the upper limbs with aggravation of the existing weakness in his legs. There was no history of any preceding upper respiratory infection on this occasion. Over a period of four to five months power gradually returned, and in May, 1957, there was virtually no change from the previous examination except for the disappearance once more of the tendon reflexes in the upper limbs. Examination of the cerebrospinal fluid at this time revealed that this clinical exacerbation had been accompanied by further elevation of protein content of the fluid. It was felt that he was a case of the syndrome described by Refsum.

He has remained in good health and was able to get about quite normally wearing surgical boots.

Other Investigations.—Serum calcium, 10.3 mg.; serum phosphorus, 4.6 mg./100 ml.; blood urea, 32 mg./100 ml.; serum lipids, 680 mg./100 ml. Urinary porphyrins, no evidence of abnormal porphyrin excretion. Urinary chromatogram, normal amino-acid pattern. Serum electrophoresis, serum protein distribution within normal limits and the pattern normal. Electrophoresis of C.S.F. protein: very marked rise in beta- and gamma-globulin (July 24, 1957). E.C.G., normal. Predicted Q-T, 0.383 sec.; actual Q-T (average), 0.34 sec. Audiogram normal.

Comment.—This case demonstrates some of the pitfalls in the diagnosis of the syndrome. The patient was originally thought to be a case of Friedreich's ataxia in spite of the history of acute onset of the condition. Following examination of the C.S.F. the diagnosis was altered to one of acute idiopathic polyneuritis and retinitis pigmentosa. It was not until his second attack of polyneuritis that the correct diagnosis was made and examination of the siblings arranged.

Case 2

A married sister, aged 23, of the above patient was first seen in June, 1957, when an ophthalmological examination was carried out and a clinical examination performed. She had no complaints whatever at this time and had come to hospital at our request. On direct questioning she admitted to poor vision at night for many years. She had been unable to ride her bicycle after dark since about four years previously.

On examination there was no pes cavus, but the second and third toes of both feet were webbed with "hammer-toe" deformity, the fourth toes being abnormally short. The skin of the extensor surface of the arms and legs was thickened, rough, and scaling, and there was extensive ichthyosis of the anterior thorax and abdominal wall. Neurological examination was normal except for absent ankle-jerks and concentric contraction of the visual fields.

Ophthalmological Report.—"Posterior lens opacities. Fundi rather atrophic. No pigmentation, but fine pepper-and-salt appearance. Slit-lamp—opacities in posterior cornea. Rounded nodule just behind nucleus and radiating striae." Fields plotted on the perimeter showed marked concentric contraction.

The patient was admitted to another hospital on July 16 with the following history. About six weeks previously she had developed an illness which was diagnosed as influenza. This consisted of cough without sputum or haemoptysis but associated with anorexia and loss of weight. A week later she observed weakness and paraesthesiae in the form of "pins and needles" in her legs. At first the weakness was

evident only after heavy exercise such as cycling or walking uphill. It was, however, steadily progressive, so that by the end of a month she was quite unable to stand or walk. At this time weakness also occurred in the upper limbs and progressed. Within 10 days voluntary power had been lost completely in the arms.

The weakness was accompanied by severe shooting pains in the arms and legs. These kept her awake at night and at times caused her to weep. They flitted from limb to limb, not remaining in any one site for more than a few minutes. She was transferred to the Royal Victoria Hospital on July 29.

Physical examination at that time revealed that the patient was an ill, anxious-looking woman of 23 years. She had obviously lost weight. The ichthyosis previously noted, the retinal changes, and constriction of the visual fields were confirmed. General examination showed nothing remarkable except for a regular tachycardia of 120 beats a minute. The blood pressure was 115/70.

Examination of the central nervous system gave the following results. Cranial nerves—there was bilateral facial weakness of lower motor neurone type. Fibrillation was noted in the tongue, which was poorly protruded. There was weakness of the sternomastoids. She appeared to have no difficulty in swallowing or in clearing secretions. There was no palatal weakness. Flaccid paralysis of the limbs was present. The only voluntary movements possible were a few degrees of hip flexion and abduction of the shoulders. The muscles were generally wasted, with marked global wasting of the small muscles of the hands. Fibrillation was seen in the thenar and hypothenar eminences but not elsewhere. There did not appear to be any intercostal weakness. The tendon reflexes were all absent.

There was a "stocking and glove" area of diminution of light touch and pain sensation extending to the wrists and in the legs to the mid-calf. Vibration sense was impaired in the left hand and both feet. Muscle joint sense was lost in the hands and feet and impaired at the ankles and wrists. The plantar responses were not obtainable.

There was no change whatever in the patient's condition over the next week. She was greatly distressed by root pains, which were only partially relieved by injections of methadone ("physeptone"). It was decided to try the effect of steroid therapy. This was given in the form of prednisone, 5 mg. t.i.d. There was almost immediate relief of pain. On the second day of treatment she had an attack of coughing, collapsed suddenly, and died in a few minutes. A post-mortem examination was not permitted.

Investigation.—Blood urea 30 mg./100 ml.; serum cholesterol, 213 mg./100 ml.; serum lipids, 643 mg./100 ml.; serum electrophoresis, normal pattern with normal total protein. C.S.F.: clear fluid; protein 600 mg./100 ml.; globulin ++; W.B.C. 1; Lange 1112220000; W.R. negative. Urinary chromatogram, marked general amino-aciduria of cystinuric pattern. X-ray examination: spine, pelvis, left femur and humerus, and skull normal; chest showed normal pulmonary vascular pattern, but there was some increase in the size of the heart shadow, mainly on the left side. E.C.G., sinus tachycardia 120 a minute. T wave flat in limb leads and V3-6. Myocardial change.

Comment.—This case illustrates an acute onset of the condition, which might easily be diagnosed as acute infective polyneuritis both on clinical grounds and on cerebrospinal fluid findings. It also demonstrates the sudden and unexpected death which may occur, presumably cardiac in origin. An interesting finding was the cystinuric pattern of amino-aciduria.

Case 3

An unmarried sister aged 20 of the first two patients attended hospital with her sister in June, 1957, at our request. She was the youngest member of the family and had no complaints and no visual disturbance.

On examination she was small and thin. The feet were high-arched, with hammer-toes. Thickening and scaling of

the skin of the hands was noted. Neurological examination revealed no abnormality apart from bilateral absence of the biceps, triceps, and ankle-jerks.

Ophthalmological Examination.—R.V. 6+/36. L.V. 6+/36. Lenses clear. Retinae showed atrophic appearance with narrowed arteries. Disks slightly blurred but no pallor. Slit-lamp: slight exaggeration of sutures and few granular opacities in posterior halves of lenses. Fields of vision on perimetry showed gross concentric contraction.

Investigations.—C.S.F. clear fluid with normal constituents. Protein 30 mg./100 ml. Electrophoresis of C.S.F. protein showed a normal pattern. Urinary chromatogram normal.

Unfortunately we have not been able to examine the fourth sibling.

Discussion

The exact position of this syndrome among the heredo-familial ataxias is not altogether clear, nor has its position as a nosological entity been firmly established. It appears to be a familial condition with a recessive mode of inheritance; consanguinity has usually been demonstrable. In this family no evidence of consanguinity has been found (Fig. 1).

FIG. 1.—Family tree of the three cases of Refsum's syndrome. There was no evidence of consanguinity.

These cases also differed from the original description in some other respects. Progressive polyneuritis with distal paresis was not a feature. The attacks were of acute and subacute onset with considerable recovery in the first patient after each of two episodes. Clinical exacerbations were paralleled by elevation of the C.S.F. protein. In the third case, with no symptoms and few signs, the protein content of the fluid was normal.

An additional finding, which does not appear to have been described previously—namely, a complicated type of posterior lens opacity—was noted. This was felt to be a complication of the retinitis pigmentosa. The discovery of amino-aciduria in the second patient was of interest, and again this had not been noted in other cases (Fig. 2). It was not present in the other siblings tested, and would therefore appear to fall into the group of cystinuria where the abnormality is inherited in a Mendelian recessive fashion (Harris *et al.*, 1955). The amino-aciduria is not likely to be related to the neurological disorder, as its presence was not demonstrable in other cases showing the full clinical picture. One is reminded of the cases of cerebellar ataxia of a reversible type associated with photosensitivity of the skin and amino-aciduria, so-called "H" disease, which have been described recently (Baron *et al.*, 1956). The resemblance between the two syndromes is, however, purely superficial, the skin lesions being quite different and the pattern of amino-aciduria dissimilar. Cytoalbuminological dissociation was present in some of the cases of "H" disease and all the cases affected showed the typical urinary excretion of amino-acids.

The differential diagnosis has been discussed at length in the original communications and will not be gone into fully here. The condition which Refsum's syndrome may most closely resemble appears to be chronic hypertrophic interstitial neuritis or progressive hypertrophic neuritis (Dejerine-Sottas disease). This latter condition in addition to showing the classical features of polyneuritis has, in not a few instances, exhibited nystagmus, intention tremor, kyphoscoliosis, and sluggish or fixed pupils. Furthermore, a special variety is distinguished by remissions and exacerbations (Rossolimo, 1899; Natrass, 1921; Harris and Newcomb, 1929); and in a few cases elevation of the C.S.F. protein without concomitant increase of cells has been discovered (Wolf *et al.*, 1930; Wilson, 1954). The

FIG. 2.—Amino-acids in Case 2. 1, valine; 2, taurine; 3, cysteic acid (from cystine); 4, β -amino-isobutyric acid; 5, histidine; 6, hydroxyproline; 7, alanine; 8, glycine; 9, glutamic acid; 10, arginine; 11, "nephrosis peptide." The circle areas are proportional to the densities of the spots on the developed chromatogram.

C.S.F. findings in most cases have been entirely normal. The post-mortem findings in one case of Refsum's syndrome have been typical of progressive hypertrophic neuritis. There was no palpable thickening of nerves in any of the present cases, and nerve biopsy was not carried out. It should be remembered, of course, that absence of nerve thickening by no means excludes the diagnosis of hypertrophic neuritis.

In spite of the close resemblance to other neurological disorders, and, in particular, the syndrome of progressive hypertrophic neuritis, the constant association of retinitis pigmentosa and elevated C.S.F. protein in Refsum's syndrome seems to distinguish it from other conditions.

There was radiological and electrocardiographic evidence of myocardial disorder in the second case. While we feel that treatment was of too brief duration to have had any contributory effect to the fatal outcome, it might be wise to use steroid hormones cautiously in these cases.

Summary

Three cases of Refsum's syndrome in a family are described. The differential diagnosis, particularly with regard to Dejerine-Sottas disease, is discussed.

Cystinuria was present in one patient, and was thought to be unrelated to the main condition.

We are grateful to Professor A. C. Stevenson, department of social and preventive medicine, Queen's University, Belfast, for the family tree; to Mr. J. A. Corkey for ophthalmological reports; and to Mr. D. W. Neill, department of biochemistry, Royal Victoria Hospital, Belfast, for biochemical investigations.

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