NEUROMYELITIS OPTICA

A REVIEW OF THE LITERATURE AND A REPORT OF A CASE WHICH FOLLOWED TRAUMATIC PARAPLEGIA

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INTRODUCTION

NEUROMYELITIS optica is a type of encephalomyelitis which is characterised by massive demyelination of the optic nerves and spinal cord. The disease usually runs a subacute course, though its progression may cover the whole spectrum from fulminating to chronic. It is also known as Devic's disease, acute disseminated myelitis, diffuse myelitis with optic neuritis and ophthalmoneuromyelitis, but it is most commonly known as neuromyelitis optica, particularly in recent years. The usual presentation is with a sudden blindness in one eye, followed a few days later by blindness in the other eye, and days or weeks later by a rapidly ascending spinal paralysis which may end in death from respiratory failure only weeks from the onset of the first symptom. Sometimes the spinal paralysis separates the onset in the two eyes, and less commonly the paralysis occurs before the onset of optic neuritis in either eye. The pathology is that of acute necrosis of the spinal cord and optic nerves, and histologically this is seen to be due to a massive destruction of the myelin sheaths and to a lesser extent of the axon cylinders, with accumulation of large numbers of macrophages (often bulging with fat) and smaller numbers of polymorpho-nuclear leucocytes and plasma cells. There is usually only a moderate astrocytic reaction. In severe cases cavitation is common.

REVIEW OF THE LITERATURE

In the opinion of most authors, Allbutt (1870) was the first person to describe a case of neuromyelitis optica. In this paper, changes in the optic fundus are described in 14 cases of spinal cord disease of varying pathology; these include eight cases of spinal cord trauma out of 13 who survived longer than a few weeks. No eye changes were observed in 17 other patients who died within a few weeks of the injury. In only one of the 14 patients who developed optic neuritis could a diagnosis of neuromyelitis optica be seriously considered, but on the information given, even this is uncertain. Erb (1880) gave the first thorough description of the condition, and Seguin (1880) reported two cases, but it was Devic (1894) and his pupil Gault (1894) who first reviewed a series of cases and gave a detailed description of the clinical and pathological features of neuromyelitis optica. Since then many more cases have been reported in the French, German, English and American literature, of which important reviews were made of 52 cases by Goulden (1914), 70 cases by Beck (1927), 22 cases by McAlpine (1938), 12 cases by Putman and Forster (1942), 200 cases by Stansbury (1949), 12 cases by Scott (1952) and Hughes (1961).

Neuromyelitis optica is generally classified as one of the demyelinating diseases. Multiple sclerosis, the commonest of these diseases, was noted by Dreschfeld (1894) to be similar to neuromyelitis optica. Since this observation there has been controversy as to whether the two conditions should be regarded as separate clinicopathological entities or as variants of one disease. Goulden (1914), Beck (1927), Walsh (1935), Balser (1936), Hassin (1937), McAlpine (1938), Kohut and Richter (1945), Stansbury (1949), and others, view them as separate entities because of the very different clinical course and symptomatology of 'typical' cases of each—neuromyelitis optica with its fulminating course of acute blindness, sudden spinal paralysis and, often, early death, compared to multiple sclerosis with its typically chronic relapsing course over many years. They also point out the gross pathological differences between the two conditions—the massive demyelination of large areas of the spinal cord and optic nerves, and rarely of the brain, in neuromyelitis optica, compared to the discrete, small, perivascular, widely disseminated foci of demyelination seen in multiple sclerosis. Others, such as Brain (1962), feel that neuromyelitis optica may be a variant of acute disseminated encephalomyelitis, while Symonds (1924), Putman and Forster (1942) Ferraro (1944), and Hughes (1966) maintain that all of the demyelinating diseases are but variants of each other. A number of writer have emphasised that neuromyelitis optica is not necessarily a fulminating disease with a rapidly fatal termination, but may take other forms, such as a chronic and relapsing course, or a course in which there is rapid and permanent recovery. Scott (1952) reviews 10 cases of his own and 50 other cases from the literature, most of which are mild and who recover. He is critical of Stansbury (1949) and others who include in their series only fulminating cases which led to rapid death and, hence, to autopsy confirmation of the diagnosis. He feels that the disease is commoner than is generally thought because of a failure to diagnose many mild cases. One of Dreschfeld's (1882) case reports is interesting in this context. A 28-year-old male developed a right optic neuritis, followed by gradually ascending paralysis, followed soon after by optic neuritis in the other eye. This appeared to be a typical history of neuromyelitis optica but, at autopsy, an irregular distribution of myelitic patches was found. These were irregular in size and location, perivascular in distribution, and there were marked changes in both optic nerves. The pathology was more like that of multiple sclerosis, except that it was confined to the spinal cord and optic nerves. A case reported by Beck (1927) is also of interest. He describes a chronic relapsing history of spinal cord and optic nerve changes in a 15-year-old girl, a history more like that of multiple sclerosis, but the pathology in this case was typically that of neuromyelitis optica with massive demyelination of spinal cord and optic nerves. If the diagnosis of neuromyelitis optica be confined to cases of demyelination in the spinal cord and optic nerves, a problem arises in those numerous cases in the literature where there is a typical clinico-pathological presentation of neuromyelitis optica but also scattered areas of demyelination in the cerebrum. These cases include Devic's (1894) original cases. If the diagnosis of neuromyelitis optica be confined only to the fulminating, classical case which leads to early death, another problem arises from the well-authenticated cases of chronic relapsing multiple sclerosis which terminate years later with a fulminating relapse, and at post mortem demonstrate massive demyelination in the spinal cord and optic nerves.

From a review of the literature it is considered that there is such a variability

in the clinical and pathological features of both neuromyelitis optica and multiple sclerosis, together with borderline cases such as those of Dreschfeld (1882) and Beck (1927) that neuromyelitis optica is best regarded as a variant of multiple sclerosis, and akin to other members of the group of demyelinating diseases. However, there is a danger in such an assumption, and this is that there is a tendency to look only for one cause if a number of diseases are grouped together. There is a trend towards regarding the mechanism of demyelination in this group of diseases as being the same, but, even should there be the same final cause for demyelination, different factors may initiate the final common pathway.

The available literature of neuromyelitis optica has been reviewed: Allbutt (1870), Seguin (1880), Dreschfeld (1882, 1894), Firth (1886), Drake-Brockman (1892), Taylor and Collier (1901), Holden (1911, 1914), Goulden (1914), Beck (1927), Perritt (1934), Cone, Russel and Harwood (1934), Walsh (1935, 1957), Berliner (1935), Balser (1936), Hassin (1937), Fralik and De Yong (1937), Rosenbaum (1937), McAlpine (1938), Dolgopol (1938), McKee and McNaughton (1938), Fetterman and Chamberlain (1940), Haynes (1940), Noran and Polan (1942), Putman and Forster (1942), Kohut and Richter (1945), Dennis and Calkins (1949), Stansbury (1949), Armentrout and Peasley (1950) Scott (1952), Markham and Otenasek (1954), Hierons and Lyle (1959), Field (1961), Kemp and Van Rossum (1963) and Rose and Pearson (1963). Seventy-five cases have been selected in which it is possible clearly to separate the diagnosis of neuromyelitis optica from that of multiple sclerosis. Of the 75 patients, 46 (61 per cent.) were female, a proportion which agrees with that recorded by most other authors. Twenty-four (32 per cent.) of the 75 case reports describe a febrile illness, with or without upper respiratory tract symptoms, which precede or coincide with the onset of neurological signs. In seven (9 per cent.) of the patients there was a preceding gastro-intestinal illness (including two cases of acute appendicitis). It is not clear whether these febrile disturbances should be regarded as antecedent to the neurological disease or whether they are prodromal symptoms of the disease. Other preceding incidents recorded include surgical trauma, gastro-intestinal diseases of various types, syphilis, gonorrhoea, lead poisoning, diabetes, epididymo-orchitis, childbirth, trauma to an eye and heredity.

In the seventy-five cases reviewed there was no record of a patient who had sustained traumatic paraplegia prior to the onset of neuromyelitis optica, nor is there any reference to such a case in any of the detailed reviews of the disease. It is necessary to go back to Allbutt (1870) to find any reference to optic neuritis following spinal cord trauma. Taylor and Collier (1901) also described an association between optic neuritis and spinal cord diseases in twelve case reports—one of which was a case of spinal cord trauma. In a review of 154 case records of spinal cord disease of varying pathology at the National Hospital between the years 1893 and 1899, they found nineteen with optic neuritis. Of these only two followed trauma to the spinal cord. It is doubtful if the description of optic neuritis which is given in both these papers is of the acute, severe form which is seen in fulminating neuromyelitis optica.

It is believed, after a careful study of the available literature, that the case report which follows is unique in that unequivocal neuromyelitis optica followed closely upon traumatic paraplegia.

CASE REPORT

A previously healthy timber worker, aged 49 years, was rendered immediately paraplegic on 2 November 1965 when a large tree fell on him in Tasmania. He was treated initially at the Royal Hobart Hospital, but received no specific treatment for the 52 hours before his transfer to the Spinal Injuries Centre for Victoria. Before his admission to the Centre he had several episodes of haemoptysis, and some dyspnoea.

Examination revealed a flexion-compression fracture-dislocation of the twelfth dorsal vertebra on the first lumbar, with complete flaccid paraplegia below the twelfth dorsal segment. There were also fractures of three upper lumbar transverse processes, two fractured ribs on the right, one fractured rib on the left, and a right-sided pulmonary contusion. A successful postural reduction of the spinal fracture was achieved within 24 hours. A paralytic ileus was treated by naso-gastric aspiration and intravenous fluids, and he was taking oral fluids by the fourth day. Over this period he complained of upper abdominal pain. He was febrile for the next two and a half weeks, despite the exhibition of prophylactic antibiotics for the chest. This fever was never satisfactorily explained.

A week after admission he had two spontaneous epistaxes. Coagulation time, bleeding time, prothrombin time and platelet counts were within normal limits.

At four weeks after the injury there was a return of reflex activity below the lesion, but there was never any motor or sensory recovery.

On 14 December, six weeks after admission, he developed a left femoral vein thrombosis which was treated with anticoagulants (heparin and ethylidene dicoumarin). Twenty-four hours after the commencement of this treatment he appeared, clinically, to have a pulmonary embolus, and over the next week he had a number of cyanotic episodes. He also developed a friction rub in the right axilla. Over this week he had febrile episodes, abdominal pain, nausea, vomiting and haematuria (even though his prothrombin time did not fall below 20 per cent.). Despite the absence of radiological signs he probably had had multiple small pulmonary emboli.

A few days later he developed a right epididymo-orchitis, which was treated with streptomycin and nalidixic acid. He continued to run a fever with further cyanotic episodes. Chest X-ray and electrocardiogram were normal.

A week later, on 26 December, he developed an acute cholecystitis. A cholecystogram showed a non-functioning gall-bladder, but in view of his many other problems he was treated conservatively. His febrile state continued over the next three weeks, even though the mass under the right costal margin and the epididymo-orchitis subsided. Repeated chest X-rays failed to reveal a pulmonary or mediastinal basis for his fever, and three consecutive blood cultures were negative.

Vague abdominal discomfort continued, together with pain, anorexia, nausea and vomiting. Finally, on 19 January 1966, a laparotomy was performed at which time anticoagulants were discontinued. Cholecystectomy was performed for chronic cholecystitis. No other abnormality was found in the abdomen. Because of the recurrent pulmonary emboli the inferior vena cava was plicated below the renal veins. He remained afebrile only for three days post-operatively. Although his fever returned after this he looked well and did not have any more abdominal pain or other gastro-intestinal symptoms.

In addition to the acute epididymo-orchitis he had recurrent urinary tract infections, but these were mild, with the exception of a *Pseudomonas pyocyanea* infection on 10 January 1966, which was treated with a three-week course of sulfamethizole and methenamine mandelate, and nalidixic acid, and a mixed *pseudomonas*, *E. Coli* infection on 21 February 1967, treated by framycetin bladder washouts.

On 1 February, two weeks after the laparotomy and three months after the initial injury, the patient complained of deterioration of vision and right retro-orbital pain. Two days later the pain in the right eye became much worse, and simultaneously the vision began also to fail in the left eye. After four days he was completely blind in the

right eye and able to perceive only light and movements with the left eye. On clinical examination of the eyes, the only abnormalities were tenderness of the eyeballs and dilated pupils which reacted sluggishly to light. Intra-ocular tensions and the fundi were normal. The patient was fully conscious and had no neurological signs other than those of his paraplegia below D12. Cisternal puncture was normal, and the cerebro-spinal fluid showed no abnormality. Over the next few days the blindness became more complete and bilateral papilloedema with swelling of the retinal veins and retinal haemorrhages was observed. Over the next few days papilloedema subsided and the discs became pallid, now presenting the features of optic atrophy.

Investigations performed during this period included:

X-ray of the skull—No abnormality seen.

E.C.G.—Generalized ischaemic changes.

Full blood examination—Haemoglobin 12.2 gm. per cent., W.C.C.

11,000/c.mm. (82 per cent. polymorphonuclears), Platelets 830,000/c.mm. (Previously within normal limits), E.S.R. 110 mm. in 1 hr. (this had remained high since his admission).

On 25 February, three weeks after the onset of blindness, complete flaccid tetraplegia below the fifth cervical segment developed over a period of 24 hours. The level of this lesion rose steadily over the next week and he died of respiratory failure on 5 March 1966, four months after becoming paraplegic and 33 days after the first ocular symptoms. Serum electrophoresis, just prior to his death, demonstrated only a moderate elevation of the gamma-globulin fraction.

AUTOPSY

General

There was slight atheroma of the coronary vessels, which were patent, and an old pericarditis with moderately firm adhesions. The retinal arteries and veins were normal. The lungs showed bilateral bronchopneumonia. The gall-bladder bed was a mass of dense fibrous tissue, and the cholecystectomy stump was intact. The inferior vena cava was thrombosed up to the level of the plication just below the renal veins. There was no abscess or any free pus within the abdominal cavity. The bladder was of normal size, but its mucosa was congested and slightly trabeculated. There was a small infarct in the upper pole of the right kidney.

Nervous System

Brain. The surface of each cerebral hemisphere showed congested surface vessels, but there was no atheroma of the thin-walled cerebral arteries. Microscopic sections of each cerebral hemisphere showed generalised capillary congestion of the white matter. There were a few small, well-demarcated islets of grey matter scattered in the superficial zone of the white matter in all lobes, but no areas of demyelination. At the chiasma, a single small focus of demyelination of slightly paler appearance was seen, and this extended more into the right optic nerve. The mid brain and hind brain were of normal appearance, but a small demyelinated patch was found in the medulla.

Optic Nerves. The optic nerves were partially liquefied from the bulbs almost to the chiasma. The small pale patch in the chiasma connected with more extensive pale areas in the optic nerves. Microscopic sections through the optic nerves showed a general preservation of the nerve structure and fibrous stroma, but scattered swelling and demyelination of the nerve fibres. There were also more extensive zones of myelin destruction, which were well demarcated and packed with large histiocytes laden with fat (fig. 1 A, B and C).

Spinal Cord. The spinal cord was also semi-liquefied from the upper cervical level to the mid-dorsal level. The lower cord and the roots of the cauda equina were firmly embedded in a mass of new bone and fibrous tissue around the site of the healing fracture-dislocation. The surface of the spinal cord was covered with congested venules. Sections of the spinal cord showed a poorly defined central zone of softening in the upper

FIG. 1

A, Optic nerve. Increased cellularity, many of the cells being macrophages. (H and E. $\times 62$). B, Optic nerve. Foaming macrophages. (H and E. $\times 155$). C, Optic chiasma. Myelin stain showing area of demarcation between normal chiasma and demyelinated patch. (Luxol Fast Blue. $\times 75$).

cervical and lower dorsal regions. The area of softening was larger and more sharply defined in the upper dorsal region and, in the mid-dorsal region, necrosis of the cord was complete. These necrotic areas were continuous with each other. The pial surface was, however, well defined. In the region of the old injury the filum terminale was well defined, surrounded by the roots of the cauda equina. There was dense fibrous dura

FIG. 2

Spinal cord. Anterior horn neurones showing chromatolysis in an area of liquefaction. (H and E. $\times 62$).

A

B

FIG. 3

A, Spinal cord. Demyelinated area. (Luxol Fast Blue. $\times 75$). B, Spinal cord. Demyelinated area. (Luxol Fast Blue. $\times 300$).

adherent anteriorly and laterally. Microscopic sections through the cord showed extensive central necrosis, extending right through the cord in the mid dorsal region, but confined centrally in the cervical, upper dorsal and lower dorsal regions. The necrotic areas were packed with histiocytes, laden with fat, and only a few plasma cells were visible. Axonal tissue was still present (fig. 2). Extensive demyelination was also demonstrated (fig. 3, A and B). There was considerable capillary congestion within the cord and in the surrounding arachnoid. No specific changes were seen in the blood vessels, and there was no evidence of thrombosis (fig. 2).

DISCUSSION

In the case reported, the history of acute optic neuritis with rapid development of blindness in one eye, followed by similar changes in the other eye only 48 hours later, and then by a rapidly ascending transverse myelitis only two weeks later, is characteristic of neuromyelitis optica in its most fulminating form. Similarly, the massive demyelination in a large segment of the spinal cord and both optic nerves, with no suggestion of spinal, retinal artery or vein thrombosis, is also characteristic of the condition. However, the development of neuromyelitis optica in this man is particularly interesting because of its occurrence only three months after severe injury to the spinal cord below the site of these demyelinating changes. Also of possible significance in the history are the recurrent chronic infections, the unexplained fever, and the tendency to thrombotic episodes. It is proposed to discuss whether the traumatic paraplegia was coincidental to the onset of neuromyelitis optica or whether it might be of any significance in elucidating the aetiology of the disease.

In the literature there is much to be studied concerning the aetiology of multiple sclerosis, but little thought has been given to the aetiology of neuromyelitis optica. The only features which recur with any regularity in the case reports which were reviewed were upper respiratory tract infections and unexplained fevers (in 32 per cent. of the cases reviewed), occurring before or at the onset of the disease. If neuromyelitis optica is a variant of multiple sclerosis it is possible to make the cautious suggestion that the demyelination might be due to an auto-immune process. In theory, auto-immune diseases may evolve

1. By a change in an antigen so that it stimulates the production of an antibody;
2. An antigen may be hidden from the immune processes of the body until some accident exposes it to them for the first time;
3. The immune defences of the body may undergo some change and fail to recognise their own body antigens.

It seems likely that the aetiology of neuromyelitis optica will be found to be the result of multiple factors, acting as initiating and secondary factors producing extensive demyelination. It might be argued that the process is self-potentiating once it is initiated because of the short delay in the time between the development of lesions at different sites—*i.e.* each eye and the spinal cord separately. Damage at one site might lead to the further production of immunologically competent cells or proteins which, in turn, could continue the process of demyelination at the same or other sites.

In the case reported, as a result of injury to the spine, myelin antigens may have been altered and, hence, antibodies to myelin formed, or myelin may have

been exposed to the immune processes of the body for the first time as a result of the trauma. But if this be so, it is surprising that this is the first reported case of a traumatic paraplegic having developed neuromyelitis optica. Kabat *et al.* (1947, 1949) showed that brain extracts injected into experimental animals produced encephalomyelitis much more readily if they were combined with various adjuvants, such as paraffin oil containing killed tubercle bacilli. It is conceivable that the chronic infections in this man acted as adjuvants in the evolution of the immune process against his own myelin but, again, it seems strange that this coincidence has never before been reported. It has been clearly demonstrated that thrombosis is not involved in any of the demyelinating diseases, so it is unlikely that the thrombotic episodes in this case are relevant to the demyelinating disease, particularly as there was no evidence of spinal or retinal thrombosis.

Thus there is, on the one hand, a speculation as to whether in the case described trauma to the spinal cord might have acted as an initiating factor in the patient's later development of neuromyelitis optica. This speculation is itself contingent upon another unproved theory, namely that the demyelinating diseases are caused by an auto-immune process. On the other hand, the facts that an association between spinal cord trauma and neuromyelitis optica has never before been reported, and that the case was complicated by so many systemic disturbances, together make it much the more likely that the relationship between the spinal cord trauma and the subsequent neuromyelitis optica was coincidental rather than causal.

None the less, the case is reported not only for its intrinsic interest but also because its publication may lead others to speculate upon the aetiology of demyelinating diseases, and to initiate both retrospective and prospective investigations into the possible association between trauma to the nervous system and demyelination. There are none better placed to pursue this line than those who are working in Spinal Injuries Centres.

ACKNOWLEDGEMENT

We would like to thank the following colleagues for their contributions to the investigation and treatment of this case: Mr. L. T. Stretton, General Surgeon; Dr. B. D. Coote, Ophthalmic Surgeon; Dr. P. F. Bladin, Neurologist; Mr. W. L. Elrick, Neurosurgeon, and Drs. J. D. Hicks, J. Riddell and Ross Anderson, Morbid Anatomists.

SUMMARY

1. The literature of neuromyelitis optica is reviewed.
2. A case is presented in which neuromyelitis optica followed three months after traumatic paraplegia. It is believed that this case is unique.
3. This case raises possibilities concerning the aetiology of neuromyelitis optica, and may suggest possible future lines of investigation.

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