RELAPSING NEUROPATHY DUE TO TETANUS TOXOID

Report of a Case

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SUMMARY

A unique case history is presented, of a 42-year-old patient who has suffered three episodes of a demyelinating neuropathy, each of which followed an injection of tetanus toxoid. The clinical features on each occasion were characteristic of acute idiopathic polyneuropathy; a rapid onset of a mainly motor neuropathy with eventual recovery. Nerve conduction studies performed during the second and third episodes demonstrated grossly slowed motor conduction velocities. The sural nerve was biopsied after the third episode, and the features seen on light and electron microscopy included prominent hypertrophic changes, mononuclear cells associated with most “onion bulbs” and macrophage mediated demyelination. Studies of blastogenesis and macrophage migration inhibition, showed T lymphocyte responsiveness to both peripheral nerve myelin and tetanus toxoid. Typing for antigens of the HLA system indicated that the patient was homozygous for HLA B8.

INTRODUCTION

Acute idiopathic polyneuropathy (Landry-Guillain-Barré-Strohl syndrome) (AIP) is commonly associated with some antecedent event, such as an upper respiratory tract infection or exanthematous reaction; occasionally it follows surgery, malignant disease, certain vaccinations or the administration of foreign sera. The precise manner by which the antecedent events are related to the pathological changes is unknown but it is generally believed that they trigger an immune response against nerve in the host.

In the majority of cases, idiopathic polyneuropathy (AIP) is a uniphasic disease,
but in some patients the disease follows a chronic relapsing or progressive course (Roger and Boudouresques 1957; Thomas, Lascelles, Hallpike and Hewer 1969). Recurrence of disease has been reported further exposure to some known antecedents such as surgery (Borit and Altrocchi 1971) or vaccination (Barnworth 1948), although we are unaware of any detailed description of such a case. Because the precise precipitating agent is usually not known, it is uncertain whether chronic relapsing cases may sometimes follow re-exposure.

Experimental allergic neuritis (EAN) is widely considered to be a model of AIP, and chronic and relapsing forms of EAN have been described following repeated injections of peripheral nerve antigen (Schröder and Krücke 1970; Pollard, King and Thomas 1975). It might therefore be expected that repeated exposure to the agent which precipitates peripheral demyelinating disease in man may likewise cause recurrent disease.

In this paper we describe a unique case history of a patient who inadvertently received three separate injections of tetanus toxoid over a period of 14 years and developed an acute demyelinating polyneuropathy soon after the injection on each occasion. The pathological findings in this case are of interest as they are very similar to those seen in relapsing EAN.

Case history

The patient (J. P.) a male of 42 years was first seen by one of us (G.S.) in September 1971, because of a rapidly progressive limb weakness. He gave a history of admission to a London hospital 9 years previously with a similar illness, where he developed progressive limb weakness 3 weeks after receiving tetanus toxoid for a minor laceration to the foot. The full details of this first hospital admission are not known, but after 2 months hospitalisation the patient recovered virtually completely and a diagnosis of post-infective polyneuropathy was made.

In September 1971, he again sustained a laceration to the foot and was treated with tetanus toxoid; he was unaware at this stage of any association between the injection and his previous illness. Two weeks later the patient developed tingling and numbness in the feet and fingers and these symptoms ascended over a few days. Examination revealed mild peripheral weakness, absence of all tendon reflexes except the triceps, impaired two point discrimination in the fingers, loss of postural sensibility in the toes, and a markedly ataxic gait. CSF protein was 250 mg/100 ml, but the fluid was otherwise normal. Nerve conduction studies showed gross slowing of motor conduction velocities (see Table 1). The patient admitted to a moderate alcohol intake at the time of this admission, but his diet was adequate. Other screening tests for possible causes of neuropathy such as diabetes, porphyria, uremia and carcinoma were negative. Without specific treatment recovery had occurred 8 months later and when examined at that time the only abnormalities found were slight tremor of the hands and absent ankle reflexes. Sensation and power had recovered completely.

In June 1976, the patient sustained further minor trauma and was given tetanus toxoid at the local district hospital. Ten days later numbness and weakness of hands and feet developed and within 2 days the patient was unable to walk. Examination 12 days after the onset of symptoms showed mild weakness of hand muscles only; severe loss of postural sensibility in upper and lower limbs, loss of two-point discrimination in the fingers and diminished pain sensation below the knees. No tendon reflexes could be elicited, and the plantar responses were flexor. The CSF protein on this occasion was 300 mg/100 ml.

METHODS

Immunological studies

Blastogenesis of the patient’s lymphocytes was studied in response to tetanus
toxoid and an aqueous extract of sciatic nerve homogenate. The response was compared to that of lymphocytes from both a positive and a negative control patient. The positive control had received regular tetanus toxoid injections over the recent ten years and had high antibody levels. The negative control had received no tetanus toxoid for the last seven years and had no detectable antibody. The blastogenesis technique has been described previously (Stewart, Basten, Guinan, Bashir, Cameron and McLeod 1977).

Production of macrophage inhibition factor (MIF) was assessed after incubating lymphocytes from the patient and the positive control separately with dialysed tetanus toxoid and an aqueous extract of peripheral nerve homogenate. The details of MIF production and preparation of the nerve antigen have been cited elsewhere (Rocklin, Sheremata, Feldman, Kies and David 1971; Marsman, Van der Hart, Walig and Eijssvoogell 1972).

Histological

Sural nerve biopsy was performed at the level of the lateral malleolus. A portion of the nerve was fixed in Flemming’s solution and transverse sections were stained with Kultschitzsky’s haematoxylin and counterstained with Van Gieson. Another portion was fixed in 10% formaldehyde stained in 1% osmic acid and single nerve fibres teased out. The section of nerve for electron microscopy was fixed in 3% glutaraldehyde in a 0.1 M cacodylate buffer for 3 hr followed by 2% osmium tetroxide for 1 hr. Specimens were dehydrated in graded concentrations of ethanol and embedded in epoxy resin (spurs). Sections were stained with lead citrate and uranyl acetate and examined in an electron microscope (Philips EM201).

Nerve conduction studies

Motor conduction studies were performed on the median, ulnar and lateral popliteal nerves; sensory action potentials were recorded in the median and ulnar nerves and mixed nerve action potentials were recorded in the ulnar and lateral popliteal nerves (Walsh and McLeod 1970).

TABLE 1
NERVE CONDUCTION STUDIES

<table>
<thead>
<tr>
<th></th>
<th>A. 1971</th>
<th>B. 1976</th>
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<tr>
<td>Sensory action potentials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>right median</td>
<td>absent</td>
<td>absent</td>
</tr>
<tr>
<td>right ulnar</td>
<td>absent</td>
<td>absent</td>
</tr>
<tr>
<td>Motor latencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>right median</td>
<td>15.0 msec</td>
<td>15.5 msec</td>
</tr>
<tr>
<td>right ulnar</td>
<td>10.0 msec</td>
<td>12.2 msec</td>
</tr>
<tr>
<td>right lateral popliteal</td>
<td>—</td>
<td>33.0 msec</td>
</tr>
<tr>
<td>Motor conduction velocities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>right median</td>
<td>10 m/sec</td>
<td>7 m/sec</td>
</tr>
<tr>
<td>right ulnar</td>
<td>8 m/sec</td>
<td>7 m/sec</td>
</tr>
<tr>
<td>right lateral popliteal</td>
<td>—</td>
<td>6 m/sec</td>
</tr>
</tbody>
</table>
TABLE 2
IMMUNOLOGICAL STUDIES

<table>
<thead>
<tr>
<th></th>
<th>Tetanus toxoid</th>
<th>Nerve homogenate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Blastogenesis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. P. (patient)</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>L. A. (+ve control)</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>E. F. (-ve control)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>B. Macrophage inhibition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. P. (patient)</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>L. A. (+ve control)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>E. F. (-ve control)</td>
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RESULTS

Electrophysiological studies

The results of nerve conduction studies performed in 1971 and 1976 are summarised in Table 1. Gross slowing of conduction was recorded in each nerve tested on both occasions.

Immunological studies

Blast transformation occurred with the patient’s lymphocytes and those from the positive control, in response to tetanus toxoid. The negative control did not respond to the antigen. No response was obtained when peripheral nerve homogenate was used as antigen. In an assay for the production of macrophage inhibition factor significant inhibition was seen when the patient’s cells were incubated with peripheral nerve homogenate, but not with cells from either the positive or negative control patients (Table 2).

Histological studies

Sural nerve biopsy was performed 5 weeks after peak disability during the most recent episode.

Light microscopy

It may be seen from Fig. 1 that there is a reduction in the normal density of myelinated fibres and that only small or medium-sized fibres remain which are mostly thinly myelinated.

Electron microscopy

The prominent feature was the inclusion of virtually all myelinated fibres in onion bulb formations (Fig. 2). Onion bulbs in all stages of development were present in the one section; some central fibres had been recently demyelinated, others were partially remyelinated and some more fully myelinated (Fig. 3). The onion bulb lamellae were composed of layers of circumferentially orientated basement membrane containing processes of Schwann cell cytoplasm (Figs. 3 and 4) and within some of these lamellae, axonal sprouts were seen (Figs. 3 and 4).
Another notable feature was the association between mononuclear cells and most onion bulbs: macrophages or lymphocytes separately or together were incorporated within the lamellar structure of the majority of onion bulbs (Fig. 4). Fibroblasts were also commonly seen. Other mononuclear cells were active in the removal of myelin in a fashion similar to that described in EAN (Fig. 5); myelin was stripped from fibres by macrophage processes, while the Schwann cell appeared to play no active role in this process. Some fibres so demyelinated were at the centre of well developed onion bulbs, a finding which clearly illustrated the chronicity of the demyelinating process.

DISCUSSION

There is little doubt that the three clinical episodes of demyelinating neuropathy resulted from the administration of tetanus toxoid. The only other common factor was minor skin lacerations. AIP has been described following surgery and even the relapses in more chronically afflicted patients have been attributed to surgery (Borit and Altrocchi 1971) but not to such minor trauma.

Peripheral nerve involvement after vaccination is well recognised and although it is most commonly seen after typhoid–paratyphoid inoculation (Peacher and Robinson 1945; Miller and Stanton 1954) it has also been described following the use of tetanus toxoid (Wooling and Rushton 1950; Tsairis, Dyck and Mulder 1972). Miller and Stanton (1954) collected from the literature all the neurologic sequelae of typhoid–paratyphoid vaccination and found that 40% of patients had signs of CNS disorder, 36% a symmetrical peripheral neuropathy and 24% a plexus neuropathy. Although reference has been made in the literature to repeated neurologic involvement following a second or even third inoculation (Barnworth 1948), we are unaware of any such case which has been described in detail. Information concerning the possibility of recurrence with
repeated vaccination is clearly important in these days of widespread international travel and prophylactic inoculations.

The pathological and immunological studies in this patient indicate that similar pathogenetic mechanisms are involved in the demyelination seen in this post-inoculation polyneuropathy as in the more usual post-infective variety (Wiśniewski, Terry, Whitaker, Cook and Dowling 1969; Prineas 1972). This pattern of demyelination
effected by macrophages in the presence of lymphocytes has been described in experimental allergic encephalitis (EAE) (Lampert 1965), EAN (Waksman and Adams 1955; Lampert 1969), chronic relapsing EAN (Pollard et al. 1975), acute idiopathic polyneuropathy (Wiśniewski et al. 1969; Prineas 1972), chronic relapsing polyneuritis (Prineas 1971; Prineas and McLeod 1976), recurrent and progressive demyelinating neuropathy (Dyck, Lais, Ohta, Bastron, Okazaki and Groover 1975), Marek's disease (Prineas and Wright 1972) and possibly in canine distemper encephalomyelitis (Wiś-
niewski 1975). Numerous precipitating events have been associated with both the acute and chronic idiopathic demyelinating neuropathy in man; these include viral, bacterial and mycoplasmal infections, inoculations with foreign sera or proteins, surgery and neoplasia (Arnason 1975). It is difficult to propose any one mechanism by which such varied events could precipitate the same disease state. However, one common feature
Fig. 5. Myelin is removed from axon (A) by a macrophage (M). a: Schwann cells appear as passive bystander cells. Chronicity is proven by demyelination occurring in a well developed “onion bulb”. × 15,500. b: Myelin lamellae being stripped by a macrophage process (M.P.). The fibre being demyelinated is central within an onion bulb, the outer lamellae of which can be seen (L). × 35,000.
of these precipitating events is their relationship to the cell-mediated immune system. The bodily defence against the infectious agents associated with AIP, depends on the cell-mediated immune system rather than on antibody production; likewise activity within the immune system after vaccination and inoculations is principally a cell-mediated phenomenon. After sera administration AIP is seen occasionally but brachial or lumbosacral neuropathy is much more common and the aetiology in these entities is considered to be different and to involve immune complex disease. The associated malignancies, mainly Hodgkin's disease and the other lymphomas all display abnormalities of cell-mediated immunity. Indeed, Wiśniewski (1975) has demonstrated that demyelination may occur non-specifically in areas of haematogenous cell infiltrates which result from local application of PPD (purified protein derivative) in primed animals.

It is by no means clear, however, why this non-specific arousal of cell mediated immunity by such different causes should evoke destruction of host myelin. Delayed (cell-mediated) hypersensitivity against basic protein of peripheral nerve myelin in cases of AIP has been shown by many workers (Behan, Lamarche, Feldman and Sherrmata 1970; Currie and Knowles 1971; Caspary, Currie, Walton and Field 1971). In our case also, delayed hypersensitivity to peripheral nerve extract was shown by a positive MIF assay. Hypersensitivity to tetanus antigen was also demonstrated by blast transformation. However, despite the demonstration of hypersensitivity to these two antigens, we have no further understanding as to why tetanus toxoid antigen should result in cellular hypersensitivity to myelin. Theories of cross-reactivity or shared antigens clearly provide unsatisfactory explanations for this event considering the relative rarity of such breakdowns in immunological tolerance and the great variety of antigens which can evoke this response.

There is much accumulated evidence to suggest that EAN is a useful model for AIP. Certain striking similarities between the present case and the animal model are evident. Both result from sensitisation to a relatively simple protein, and follow a similar time course. Repeated administration of the antigen to the patient has resulted in pathological changes identical to those seen in chronic relapsing EAN. T lymphocyte responsiveness has been demonstrated to the inciting antigen in both situations. It is pertinent that susceptibility to EAE (and presumably EAN) is strongly influenced by the H2 type of the animal (Bernard 1976). No HLA association has been reported in acute idiopathic polyneuropathy, but Stewart, Pollard and McLeod (1978) have shown an increased incidence of HLA B8 in patients with the chronic relapsing form of idiopathic polyneuropathy. This patient is homozygous for HLA B8, a type known to be associated with autoimmune disease (Mackay and Morris 1972; Fritze, Hermann, Smith and Walport 1973).

Finally this case adds to the already ample evidence which suggests that onion bulb formation or hypertrophic neuropathy is the result of repeated episodes of demyelination and remyelination.

It is clear that the simple repetition of such episodes does not necessarily produce hypertrophic change. In a large series of 53 cases of chronic progressive and relapsing inflammatory polyneuropathy Dyck et al. (1975) reported that only 4 of 26 biopsied
cases showed onion bulb formation. Prineas and McLeod (1976) reported occasional small onion bulbs among 27 biopsied cases but in none of this group (which contained few cases with multiple relapses) did the onion bulbs approach the size of those seen in Charcot–Marie–Tooth or Dejerine–Sottas disease. Onion bulbs produced experimentally by repeated tourniquet application, for example, have all been of small size. The evidence seems conclusive that the density and size of onion bulbs depends on the frequency of episodes and the time over which they occur (Dyck et al. 1975). Pathological examination of animals who have been paralysed by EAN shows that 6 months after the event the appearance of the peripheral nerve is virtually within normal limits (Pollard et al. 1975). In animals which develop a chronic relapsing form of the disease true hypertrophic changes are seen and close examination of the peripheral nerves in these animals shows changes very similar to those seen in this patient, a chronic grumbling cellular reaction which apparently flares into clinical expression with reintroduction of the antigen. Without such an interpretation it is difficult to imagine how 3 episodes in 13 years should produce the pronounced changes seen in this patient.

It is often stated that onion bulb formation is a non-specific feature seen in many disease states where repeated or continuing demyelination and remyelination occurs. Nevertheless specific features may often been seen on electron microscope examination of the onion bulbs. Dyck (1966) and Dyck and Gomez (1968) described distinctions between the onion bulb of hypertrophic Charcot–Marie–Tooth and Dejerine–Sottas neuropathies. Low (1977) has clearly defined this distinction with particular reference to the hypertrophic neuropathy of the trembler mouse and discussed the evidence for a primary Schwann cell abnormality in the neuropathies of Dejerine–Sottas and the trembler mouse. The onion bulbs of Refsum's disease and the leukodystrophies can be distinguished by various Schwann cell inclusions. The characteristic features of the immune-mediated hypertrophic neuropathy are illustrated by this case: the presence of numerous mononuclear cells and macrophage-mediated demyelination (Prineas 1971) and relatively well myelinated fibres at the centre of even multi-lammellated onion bulbs. This latter feature, not seen for instance in Dejerine–Sottas neuropathy, presumably reflects the relative normality of Schwann cell function in the inflammatory or immune neuropathies (Low 1977).

It is apparent that onion bulbs are seen in at least three pathological categories. In the first type, previously healthy myelin is repeatedly destroyed by an extraneous agent such as an auto-immune process (chronic relapsing or progressive neuropathy of the inflammatory type). In the second type, some systemic disorder affects the function of the cell of Schwann amongst other cells; as a consequence myelin cannot be maintained (the leukodystrophies, Refsum's disease). A third category includes conditions where there is reason to suppose Schwann cells alone are defective and continuing demyelination results (Dejerine–Sottas neuropathy, and hypertrophic neuropathy of the trembler mouse (Aguayo, Attiwell, Trecarten, Perkins and Bray 1977; Low 1977).

This case is of particular interest in that after three episodes there can be little doubt about the antigen responsible for the clinical attacks. Further immunological studies are being undertaken to investigate possible mechanisms by which tetanus
toxoid acts antigenically in this patient to provoke macrophage mediated demyelination.

ACKNOWLEDGEMENTS

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REFERENCES


