Membranous glomerulonephritis and Grover disease with diverse neurological abnormalities; an immunological disorder due to poliovirus infection?

Sir: Guilain-Barré syndrome associated with the nephrotic syndrome was reported and the immunological pathogenesis was suspected in the early 1970s.1,2 We here report a case of membranous glomerulonephritis and transient acantholytic dermatosis (Grover disease) with unique neurological abnormalities. This appears to be the first reported case of such a combination of disorders.

A 32 year old Japanese man was well until July 1984 when he gradually developed a low grade fever of 37.5°C, general malaise, occipital headache, and severe dysaesthesia in the lower extremities. Neurological examination on admission in late August revealed signs of meningeal irritation, diminished deep tendon reflexes, hypesthesia in the distal parts of the extremities, positive nerve stretch signs of the sciatic and femoral nerves, and mild gait ataxia. Signs of cerebellar dysfunction such as gaze nystagmus, scanning speech, and limb ataxia appeared in late September. All of the neurological abnormalities progressed gradually. In early October small vesicular papules appeared on the face, trunk, and proximal parts of the extremities. Past history was negative except that he had had the trivalent oral poliovirus vaccine at 12 years of age. His 2 year old daughter had this vaccination in the autumn of 1983.

On admission he had the nephrotic syndrome with proteinuria ranging from 2 to 4 g/day. At the height of the illness, ESR was 88 mm/hour, and CSF contained 30 lymphocytes/μl, 250 mg/dl protein, and 29 mg/dl IgG. Peripheral nerve conduction velocity and short latency sensory evoked potential studies indicated abnormalities in the spinal nerve roots and peripheral nerves. Although complements level was low, the immune complex, cryoglobulin, LE test, anti-nuclear antibody, anti-DNA antibody, anti-RNP antibody, and anti-Sm antibody were repeatedly negative in the serum. There was marked elevation of the poliovirus type 2 antibody titre in the serum: neutralisation test (NT) was 1:2048 and complement fixation test (CF) was 1:16 in early September. Other viruses showed no remarkable elevation of the antibody titres.

The diagnosis of stage 2 membranous glomerulonephritis was made by kidney biopsy, which revealed electron dense deposits along the subepithelial aspects of the basement membrane. Skin biopsy showed intra-epidermal vesicles with acantholytic changes, with suprabasal clefs at acro- syringium. Direct immunofluorescence revealed deposition of IgG at the dermo-epidermal junction. Muscle biopsy of the gastrocnemius showed a mild degree of mononuclear cell infiltration of small blood vessels in the perimysium, a finding of non-specific vasculitis.

Prednisolone 60 mg/day was started in mid October, and all of the abnormalities subsided rapidly. The skin lesions were diagnosed as Grover disease from the clinical course and the biopsy findings retrospectively. The poliovirus type 2 antibody titre declined gradually; NT was 1:128 and CF was <1:4 in November.

Membranous glomerulonephritis is a well known immune complex disease. Grover disease is a rare vesicular skin disease first described in 1970,3 and although the aetiology is still unknown, immunological disturbance has been suspected to play an important role.4 This case is unique in that the hitherto undescribed neurological abnormalities developed almost simultaneously with these disorders, and in that all responded dramatically to prednisolone. The neurological abnormalities of this case can be summarised as involving the lepto- meninges, cerebellum, and spinal nerve roots and peripheral nerves, indicating a dissemi- nation of the lesions throughout the nervous system. Under these circumstances, it would be reasonable to speculate that the neurological abnormalities were also due to the same immunological disturbance that caused both the renal and dermatological abnormalities, although the reason is unclear why the neurological abnormalities preceded the others.

It is of particular interest in this case that the level of the CSF protein fluctuated in parallel with that of the urinary protein. The anatomical and physiological similarity of the choroid plexus and renal glomerulus has been pointed out by several workers,5,6 and the immune complex deposition in the choroid plexus has been observed in such immunological disorders as systemic lupus erythematosus, acute serum sickness, and experimental allergic encephalomyelitis.7,8 Although the precise mechanism of the elevation of CSF protein cannot be determined, choroid plexus damage due to the immunological disturbance mentioned above may have contributed in this case.

The primary cause of this immunological disturbance could not be determined: the antigen was not identified. The antibody titre of the poliovirus type 2, however, was remarkably elevated in the early phase of the illness, and declined gradually thereafter. Although this might represent only a coin-

References

occidental infection or the non-specific elevation of the antibody titre due to polyclonal activation of the memory B cells, there remains a possibility that this virus triggered the immunological derangement of this unusual case.

Kiichiro Matsumura*, Manabu Sakuta*, Tomoyuki Ichikawa†, Kumiiko Jitsukawa‡, Department of Neurology,* Department of Medicine,† Department of Dermatology,‡ Japanese Red Cross Medical Center, 4-1-22 Hiroo, Shibuya, Tokyo 150, Japan.

References

Accepted 22 September 1987

Visual evoked potentials and neopterin: biotin ratio in urine show a high correlation in Alzheimer's disease

Sir: Tetrahydrobiopterin is the rate controlling co-factor in the synthesis of the neurotransmitters dopamine and noradrenaline. Alzheimer's disease is associated with decreased tetrahydrobiopterin levels. Analysis of postmortem cerebral spinal fluid, postmortem temporal cortex and serum of patients with Alzheimer's disease has shown that an elevated neopterin: biotin (N:B) ratio is a measure of this reduced conversion rate.

In Alzheimer's disease, measurement of the visual evoked potential (VEP) shows that the major positive, or P2, component of the flash VEP is delayed, while the P100 component of pattern reversal VEP is unaffected. This unusual combination of results is believed to indicate that the pathology is at the level of the visual association areas. Reduction of the latency of the pattern reversal P100 component from the flash P2 component, therefore gives a value which is elevated in Alzheimer's disease. The magnitude of this flash-pattern latency difference has been shown to increase with increasing severity of dementia.

Ten patients suffering from Alzheimer's disease were diagnosed and referred for the study by a consultant psychogeriatrician. All were diagnosed as presenting with primary dementia of the Alzheimer type with no evidence of cerebrovascular disease. All had significant memory loss but were capable of fixing pattern reversal stimulus and providing a urine sample. The degree of dementia was moderate. Urine samples, taken directly into ascorbic acid to give a final ascorbic concentration of 1%, were measured for neopterin, biotin and creatinine. Flash and pattern visual evoked potentials (VEPs) were recorded. The mean age of the patients was 77 years (standard deviation 8-21 years). The nine controls were paid volunteers, with a mean age of 81 years (standard deviation 4-39 years) with a binocular visual acuity of 6/9 or better and a Royal College of Physicians mental test score of 29 or better. Ophthalmoscopic was carried out on all patients and controls and a medical history obtained. No one with evidence of ophthalmic pathology or diseases affecting the immune system was included as these would affect the pattern VEP and neopterin: biotin ratio respectively.

The table shows that the mean values of N:B ratio, flash P2 latency and flash-pattern difference were all significantly elevated in the group with Alzheimer's disease compared with the controls. The relationship between the urine and VEP results was investigated by the determination of the correlation coefficient. There is a highly significant correlation between the urine N:B ratio and both flash P2 latency and the flash-pattern difference (table).

The correlation between the N:B ratio and the VEP measures shows that with increasing disease severity there is decreasing conversion of dihydronopterin triphosphate to tetrahydrobiopterin.

References

N:B ratio | Flash P2 latency (ms) | Flash P2-pattern P100 difference (ms)
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Alzheimer's disease (± SD) n=10 | 2.43±1.56 | 156±7±17.1 | 60±4±7.8
Control group (± SD) n=9 | 1.51±0.62 | 136±6±7.3 | 31±4±9.9
T test: statistical significance | p<0.05 | p<0.01 | p<0.002
Correlation with N:B ratios | 0.63(p<0.001) | 0.92(p<0.001) |