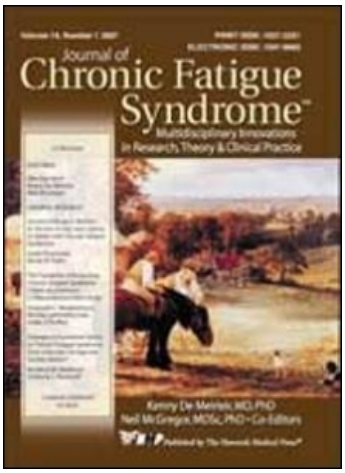

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CASE REPORT

Viral Isolation from Brain in Myalgic Encephalomyelitis

J. Richardson

Much has been written and debated about this condition, but this is a report on a case which sadly came to autopsy.

HISTORY

A married man with young children and a good caring wife. He had a responsible job and was satisfied with life. His wife gave me the following written history prior to my seeing him.

His problems started in October 1986 with swelling of the face, neck and shoulder areas, which were very red and looked as if they had been burnt. Intense heat appeared to have been generated, and this affected his eyes and mouth, and he could only eat or drink though a straw. After a few days the skin would crack and open and peel off, and this recurred after 2 or 3 weeks. He was seen in a dermatology department, and at first it was thought to be psoriasis. Later it was thought to be streptococcal, but this was disproven and it did not respond to any antibiotic. He had patch tests for allergy, and none was found. This severe stage lasted about three months on and off and then subsided, but

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he still had times when his skin was extremely sensitive, especially when he washed. He then started to have 'sudden fast feelings of movements throughout his limbs, upon which areas of swelling developed.' The swellings were hot and hard and could last up to an hour or more, and after they disappeared the area felt spongy. His muscles then began to twitch even when he was asleep, and he had considerable loss of strength and stamina–even short walks and simple tasks were exhausting, and he found it difficult to walk in a straight line, and at times could barely focus. He lost 2 stones in weight, mostly from neck, hips, shoulders, thighs and buttocks, and it appeared to be muscle loss. Sometimes he had difficulty with breathing, as though it was an effort. His circulation seemed sluggish and his legs, feet and arms were cold, whereas he used to be a very hot individual. His bladder and bowel tended to be erratic, and he passed furry cotton wool type of substance with his motions. His sleep pattern changed, and he could hardly sleep at night, and his hair and eyelashes began to fall.

Despite this, he was diagnosed as suffering from depression, and was given tablets which did not help him, and his own doctor changed them to a more potent antidepressant, but these did not help him either. Despite this he managed to work, but his wife took him to and fro until he eventually had to surrender due to a feeling of gross inadequacy. For a good while he had only left the house to go to work, and had lost interest in the TV and newspapers, undoubtedly due to the fact that he could not concentrate.

In the interview I found him a pleasant, quiet, ill man. The history, which his wife had given to me, was substantiated, but on direct questioning he also admitted that he had the anomia and vivid dreams which were more characteristic of peduncular hallucinosis. He denied depression, but admitted to oppression by the illness and said that he felt he would rather die than live as he was. I had a good letter from his doctor, which stated that it was felt that there was more to it than 'depression.' The dermatologist also felt there was more to it, and could not adequately explain the skin manifestation.

ON EXAMINATION

He scored only 2 on the Hamilton scoring chart for anxiety.

However, he scored 18 out of 25 on the ME scoring chart (which is a chart I formulated by taking the symptoms which occurred 80% of the time in hundreds of letters and case histories). This was a definitive score. He had a head thick with seb. Capitis. BP.120/80 mmHg and although no murmurs were heard, there was pericardial friction rub. His calf and thigh muscles had the softened tender areas we palpate in some of these cases, and there was 2 cms

wasting of the left calf. On flexing and extending the legs he displayed the coarse, uneven fibrillatory movements seen in these patients.

CNS. Fundi hyperaemic. He had mild bilateral nystagmus of the abducting eye. Facial sensation was very poor in the T1 and T2 areas on the left side. He had a left-sided tensor tympani syndrome, i.e., on audiometry, he was intolerant to high frequencies above 50 dbs. His reflexes were normal, but he had an impaired sensation for temperature, in that warmth was slow to be felt, and cold produced a stinging feeling.

Serology showed high neutralizing titres of 1/512 to Coxackie B group 1 and titres of 1/128 to group 4. He had a positive IgM (ELISA) to CBV as well as positive IgM to EB virus. The special VPI test done by Professor J. Mowbray, Department of Immunology, St. Marys Hospital, London (to whom we owe a debt of gratitude)–was positive likewise.

However, by this time like others he was extremely ill and appeared to me to have lost faith in doctors, and in ever being well again. I had a call to say he had been dissuaded from attending for follow up. Shortly after this I was told he had committed suicide by hanging. The pathologist who did the post mortem examination was most helpful, and brain tissue which was given to me was sent to Professor Mowbray, who had done the previous VPI testing.

Pathology reports are as follows: Paraffin section from cerebral cortex; Immunoperoxidase staining with monoclonal D8-1 against enteroviral VPI protein.

There is staining of cytoplasm of fibroblasts around small vessels. In addition there is patchy distribution of stain in isolated glial cells throughout the section. Only a small fraction of all the glial cells are stained. Specificity confirmed by absence of staining of glial cells or perivascular fibroblasts with either normal mouse serum or a control mouse monoclonal antibody to dengue virus.

DNA probe report: Enterovirus-specific cDNA probes labelled with biotin and hybridized *in situ* on formalin fixed and paraffin-embedded 5 micron sections of autopsy material from cerebral hemispheres.

Results: Positive hybridization signals were observed in the form of dense brown staining of glial cells and fibroblasts in the adventitia of small blood vessels. No hybridization was observed in control adjacent sections hybridized with a control biotin labelled vector plasmid clone.

Conclusion: Enterovirus specific genomic sequences were detected in this specimen, indicating active infection of these cells.

REMARKS

Myalgic encephalomyelitis has been a provocative subject and much has been written both by antagonists and protagonists alike, often treating it in iso-

lation, either as a myth or as a separate entity unrelated to other pathology of the same aetiology. This has resulted in a combination of misconceptions as follows:

1. Any concomitant illness of the same aetiology, e.g., myocardial, glandular, thyroid, pancreatic, renal, etc., . . . is assumed to be the reason for the malaise. The reasoning then is, when this is corrected the patient should be better. In these patients it is not so.
2. The corollary to 1. That if there is no concomitant illness definable by the doctor, then it must be all in the mind. Varying hypotheses have been put forward to explain this. None of these are really convincing to those of us who have worked in the field for many years, and indeed cause us considerable distress, though this must be minimal compared to the distress felt by the patient when the effects of the illness are compounded by a negative approach, sometimes amounting to a denial of the illness itself.

This has resulted in suicides in some cases, and the very act itself is then seen as verification of the original 'all in the mind' diagnosis. There is conclusive evidence of the viral aetiology in myocarditis by Archard et al. There is also abundant evidence showing the effects of virus in the CNS. However, this may be the first time that virus has been sought and discovered in the brain of a patient with ME, albeit in other CNS syndromes it has been recorded. Moreover, the post mortem isolation in this case is of importance, as it supports the previous serological evidence of viral infection. In our series the VPI test which Professor Mowbray has pioneered has been a useful indicator, but like the mantoux and many other serological tests, it does not indicate how ill a patient may be, nor was it meant to define which organ or system is affected. Professor Mowbray has made it abundantly clear that, when positive, it only indicates ongoing persistent enteroviral infections. Thus, as with all other tests, it has to be interpreted in the light of the clinical findings, which as shown may vary.

Finally, it may be well to consider that we do not have "poliomyelitis" in this part of the world, at least not in the way in which it is remembered, but, for those who can remember, the diagnosis was obvious and the results long lasting–but that was the anterior variety. Many have forgotten that 'posterior poliomyelitis' was also a defined entity 'affecting the posterior graey horns of the spinal cord' (Dorland American illustrated Medical dictionary). This was not so obvious to the beholder, but just as real to the victim, as the anterior variety; the aetiological agent however was the same. After immunization the scene changed, and it is probable that the word 'changed' is the correct definition, for this did not eradicate the virus, but changed or modified the host response. In

the literature polioencephalitis is described as well as the spinal and bulbar syndromes. Harrison makes mention of one epidemic where 'most patients had this type of disease.' The diffuse form is characterized by confusion, agitation, anxiety with a feeling of impending doom, or somnolence. Quivering and jerking of the facial muscles and extremities, flushing of the face, tremor of the hands and restless movements occur.

INSOMNIA MAY BE SEVERE

In fatal cases confusion is marked, and progresses to lethargy and death. In focal polioencephalitis, there may be clinical evidence of brain damage, or the lesions may be silent and demonstrable only at necropsy. Visual-verbal agnosia, myoclonic jerks, grand mal convulsions, which occasionally persist for a long time after recovery; spastic hemiparesis, ataxia of one arm or leg–all were observed. If the medullary respiratory centre was involved then the rhythm, rate and depth of breathing was affected and the cold, mottled, clammy skin was seen. This is so reminiscent of ME, albeit more severe, yet I could recognize these features in the case reported.

We should now stop and consider more than we have done, the various implications of viral infections, and also stop and consider the effect that immunization has had in changing or modifying the pattern of host response. Viral illnesses are patently increasing both in number, severity and diverse pathology, and it is the latter which poses the challenge, as many are unaware of this changing pattern or disease. The reason for this as shown earlier, is the way in which host response can be modified for good or ill by either active or so called 'passive' immunization. From the work of Prussiner and his colleagues it should be evident that the host can replicate prions or virions, the former having no nucleic acid. Moreover, the concept of the virus taking over the replication system of the cell should be challenged. From my study of a few hundred families and the sequelae of viral illness, it appears logical that the host both replicates and mutates the virus, no doubt trying to make it 'more like self.' In the process other members of the family, sharing similar genetic features, who have had the infection as demonstrated by high serological titres, but were not ill, are then at more risk and in fact may later succumb, because their autoimmune system is disadvantaged by the modified 'virus' which has been mutated by the previous host.