Accepted 10 March 1989

**Psychiatric disturbance in mitochondrial encephalomyopathy**

Sir: Luft et al.1 reported a case of muscular disorder which was considered as mitochondrial myopathy because of abnormal existence of muscular mitochondria revealed by the ultrastructural, histochemical and biochemical assays. The term mitochondrial encephalomyopathy was introduced by Shapira et al.2 to represent various types of neuromuscular disorders which showed defects in the oxidative metabolic system for energy production in the muscular mitochondria. There have been, however, no studies to our knowledge to investigate the psychiatric disturbance of mitochondrial encephalomyopathy. This case report describes psychiatric features of mitochondrial encephalomyopathy.

The patient was a 35 year old male. His short stature had been remarkable since the age of 10 years. At the age of 19 years he complained of severe abdominal pain with vomiting. General muscle atrophy had developed gradually since then. At the age of 25 years, he had a sudden abdominal pain and showed schizophrenia-like symptoms: auditory hallucination, delusion of reference and persecution, delusional mood, loosening of association and disorganised behaviour. He was admitted to a mental hospital and the symptoms disappeared after treatment with various antipsychotics for about three weeks. At the ages of 28 and 30 years, he was admitted to the same mental hospital with symptoms such as illogical thought, psychomotor excitement and impulsive behaviour. After 2 months in the hospital, these psychiatric disturbances were

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improved each time. At the age of 31 years he became again restless and agitated with delusional ideas. During the stay in the hospital at that time, there was an insidious development of dementia with memory impairment, dyscalculia, loss of intellectual abilities of social functioning and euphoric personality change. The episode of unconsciousness sometimes recurred. At the age of 35 years, he suffered from acute disturbance of consciousness and showed dysartria, weakness of all the limb muscles, akinetic mutism and myoclonus in the right upper and lower extremities. The patient was referred to Tsukuba University Hospital for detailed neurological, psychiatric and physical examinations.

He was short, 156 cm in height, and extremely emaciated, 31.5 kg in body weight. Remarkable general muscle atrophy in the whole body was observed without muscular fascination. He was alert but immobile. Vocalising and spontaneous activity were lacking. Myoclonus in the right extremities and a generalised convulsion were observed. Paralytic ileus was diagnosed radiologically. Hypertrophic cardiomyopathy was revealed by ultrasonic cardiography (UCG) and ECG showed nonspecific ST-T changes. EGG showed diffuse slow background activity with paroxysmal spikes in the left central and occipital areas. Brain CT demonstrated diffuse cerebral atrophy with ventricular dilatation and enlargement of ambient and supracerebellar cisterns. Cerebellum and brain stem were also atrophic. The spin-echo scan of MRI examination revealed an increased T2 region in the left parieto-occipital areas. Routine haematologic examinations, urinalysis and serum enzyme tests were normal except for high values of CK and LDH. The former was 392 IU/l (normal, less than 190) and the latter was 648 IU/l (normal, 120–520). Liver and renal functions were normal. Serum lactate and pyruvate showed high values of 26 mg/dl (normal, 0.4–10) and 1.5 mg/dl (normal, 0.3–0.9), respectively. The value of serum tryptophan, 63.3 nmol/ml (normal, 43.0–67.2), the urinary concentrations of δ-ALA, 1.3 mg/l (normal, 0.8–2.8), of uroporphyrin, 5.0 μg/l (normal, 5–30) and of coproporphyrin, 10 μg/l (normal, 5–30) were within the normal ranges. The results of CSF examination were normal. Bilateral hearing loss of the sensorineural type was revealed. Electromyogram (EMG) demonstrated myopathy.

The akinetic and mute state and myoclonus remarkably improved following the daily intravenous hyperalimentation with 200 mg of Coenzyme-Q, 100 mg of cytochrome C and various vitamins. He became well oriented for place, person and time and recovered comprehension of simple commands. Subsequent simple neuropsychological examinations revealed dyscalculia and constructional apraxia, dysgraphia without alexia. Recent memory did not seem to be disturbed although detailed assessment of W AIS was impossible to perform because of poor comprehension of commands.

H and E staining of a biopsy specimen of the left quadriceps femoris muscle showed small angulated fibres and the size of the fibres varied moderately. Modified Gomori-trichrome staining showed ragged-red fibres having red granular materials in the subsarcolemmal regions (fig 1). NADH-TR staining showed some fibres with excessive oxidative activity. It also showed disruption of the fibre structure and a clear subsarcolemmal rim. An electron microscopic examination of the muscle confirmed an enlargement of the size of mitochondria and aggregation of abnormal mitochondria having paracrystalline formations (fig 2).

The present case was finally diagnosed as mitochondrial encephalomyopathy with schizophrenia-like symptoms from the mitochondrial changes in muscle. The recurrent mental disorder was the main remarkable symptom in the present case during the earlier stage of illness. It included auditory hallucination, delusional mood, delusion of reference, psychomotor excitement and anxious or agitated mood without an obvious disturbance of consciousness. These symptoms were regarded as schizophrenia-like mental disorders before admission to Tsukuba University Hospital.

There have been few reports describing psychiatric manifestation of mitochondrial encephalomyopathy. Morgan-Hughes et al reported a patient who showed confused and agitated state, perseveration, and paranoid ideas without unconsciousness. Pavlakis et al also described acute psychotic episodes with hyperaggressive or paranoid delusion. A patient with mitochondrial encephalomyopathy reported by Hart et al showed a prolonged episode of agitated confusion in which the patient “acted like an animal” for several days. These psychiatric symptoms are generally called "confusional state", but this condition is classified as delirium in DSM-III. The condition develops rapidly and fluctuates in a course of illness to change behaviour and cause inattention, incoherent though and impairment of memory. The delusion of delirium is usually fragmentated and rarely systematized, unlike that of schizophrenia. The present patient, however, suffered from a more systematized delusion which first occurred at a younger age without showing any distinctly abnormal physical symptoms. This prominent psychiatric symptom observed as an initial sign of neuropsychiatric symptoms occurred repeatedly over a long time. He showed psychiatric symptoms similar to those of schizophrenia. It may be assumed that he had both schizophrenia and mitochondrial encephalomyopathy. It is, however, our opinion that schizophrenia-like symptoms seen in the present case were possibly those of the CNS manifestation in mitochondrial encephalomyopathy during the course of illness for the following reasons. His muscle atrophy had already occurred when these symptoms appeared and dementia developed insidiously. Moreover, flat affect and disturbance in volition were not observed in the later course of the psychiatric disturbance.

It has been reported that schizophrenia-like mental disturbances occurred in other organic brain syndromes including Huntington’s disease, Wilson’s disease, chronic encephalitis, cerebrovascular infarction and metabolic disorders. The present case clinically showed several attacks of abdominal pain and neuropsychiatric disturbances besides generalised muscle atrophy.

Fig 1 Modified Gomori-trichrome staining to illustrate ragged-red fibres in the centre of the image.

Fig 2 Electron micrograph showing subsarcolemmal accumulation of mitochondria having paracrystalline formations.
Therefore, it seems to be important to be differentiated from hepatic porphyrias and pellagra sine pella agrā. Recently, it was reported that mitochondrial encephalomyopathy was similar to pellagra neuropathologically. Severe muscle atrophy has not, however, been reported in either porphyria or pellagra. The present case did not show symptoms such as photosensitivity, dark-red urine and high values of δ-ALA and porphyrin. It was necessary to examine the muscle and to demonstrate the abnormal mitochondria in the biopsy specimen in order to confirm the diagnosis of mitochondrial encephalomyopathy. In conclusion, the present case can be suggested to be those due to mitochondrial encephalomyopathy. Mitochondrial encephalomyopathy is one of the organic brain syndromes which should be differentiated from schizophrenia.

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Accepted 6 February 1989

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Psychiatric disturbance in mitochondrial encephalomyopathy.

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*J Neurol Neurosurg Psychiatry* 1989 52: 920-922
doi: 10.1136/jnnp.52.7.920-a

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