Mitochondrial gene abnormalities as a cause of psychiatric diseases

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(Summary)
Genetic predisposition has been implicated in the pathogenesis of mental disorders including schizophrenia. Mitochondrial dysfunction has been shown to be associated with mitochondrial myopathies, type 2 diabetes. We encountered with a diabetic woman who was associated with mitochondrial myopathy and schizophrenia. To know an involvement of mitochondrial DNA abnormalities in the pathogenesis of psychiatric diseases, we screened patients with schizophrenia for mitochondrial DNA abnormalities. By screening for an A3243G mutation of the tRNA(LEU) of the mitochondrial DNA, no one carried this mutation. Other mutations were also analysed. Although some mitochondrial DNA abnormalities may be associated with schizophrenia, the A3243G mutation is unlikely to play a major role in the pathogenesis of schizophrenia in Japanese.

Schizophrenia is a heterogeneous disorder. Although a genetic predisposition has been implicated, genes involved in the pathogenesis of this disorder are generally unknown. Schizophrenia has been reported to be more frequently observed in those patients with glucose intolerance. Mitochondrial DNA (mtDNA) abnormalities are associated with type 2 diabetes mellitus and with MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes). This mutation has been shown to be associated with about 1% of type 2 diabetes mellitus (1). Mitochondria also play an important role in normal functions of the brain through generation of ATP. Mt dysfunctions may lead to development of Parkinson's disease or Alzheimer's disease (2). Schizophrenia is a common disorder, causes of which are yet to be defined. MtDNA abnormalities might also lead to mental disorders such as schizophrenia. We have encountered with a patient that suggested an involvement of mtDNA abnormalities in the pathogenesis of schizophrenia, mitochondrial myopathy, and type 2 diabetes mellitus (3). Besides
mitochondrial myopathy, she also had schizophrenia and diabetes mellitus for many years. As two of the diseases, mitochondrial myopathy and diabetes mellitus, have been shown to be associated with mtDNA abnormalities, schizophrenia may also be caused by mt dysfunctions. We hypothesised that impaired mitochondrial functions or mtDNA abnormalities may be associated with psychiatric diseases such as schizophrenia. The increased prevalence of type 2 diabetes mellitus among patients with schizophrenia might be partly due to mtDNA abnormalities.

To investigate whether mtDNA abnormalities are associated with schizophrenia, we screened patients with schizophrenia for the presence of the A3243G mutation of the mtDNA. 300 unrelated Japanese patients with schizophrenia were randomly selected for the screening. The diagnosis of schizophrenia was based on the criteria of DSM-III-R(4). The patients consisted of 125 males (mean+SD age: 42.3+-12.5 years/ age range: 18-80 years/ mean age of onset: 23.8+-7.7 years/ onset age range: 12-68 years) and 168 females (mean+-SD age: 44.8+-13.8 years/ age range: 21-75 years / mean age of onset: 25.1+-9.6 years/ onset age range: 13-68 years). The presence of the A3243G mutation of the mitochondrial DNA was confirmed by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method using Apa-1. Of the 300 patients with schizophrenia, no one turned out to carry the A3243G mutation of the mtDNA. Involvement of other abnormalities in mtDNA in the pathogenesis of schizophrenia remains unknown. Other deletions or mutations should be rigorously investigated in those patients with schizophrenia. In conclusion, although previous clinical observations including ours suggested some involvement of mitochondrial dysfunctions in the etiology of schizophrenia, the A3243G mutation of the mtDNA is not likely to be a major cause of schizophrenia in Japanese.

References