A case of hereditary movement and metabolic disorder with complex clinical findings

Ettore Nicolini1, F. Pauri1, L.M. Basili1, A. Fasolino1, P. Giacomini1
1Department of Neurology and Psychiatry, Sapienza University of Rome, Italy

BACKGROUND

Juvenile Parkinsonism is very rare and it results from a variety of secondary or genetic causes; most cases with a fairly pure parkinsonian syndrome are due to typical extrapyramidal pathology. An autosomal dominant trait has been described in Wilson's disease and dopa-responsive dystonia. (Schrang A., Schott J.M. 2006)

Familial Parkinson's Disease (FPD), depending on the causal mutation, can be inherited in either an autosomal dominant or in autosomal recessive manner. Genetic diagnostic testing can be performed in some patients with FPD and those with early onset of the disease (before 50) (Oczkowska A. 2014)

Spinocerebellar ataxias are an autosomal dominant clinically and genetically heterogeneous group of disorders. The disease usually begins in adulthood and has a progressive course. Extrapyramidal symptoms are sometimes the initial manifestations of the disease (Oczkowska A. 2014)

Dentorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder characterized by myoclonus, ataxia, cerebellar ataxia, choreoathetosis, dementia and psychiatric symptoms. Neuroradiological findings are extremely specific: atrophic changes in the cerebellum and brain stem (in particular in the pontine tegmentum), diffuse high-signal-intensity lesions in the cerebral white matter, brain stem and thalami in the T2 weighted images. Marked progression of cerebral atrophy is often noted (Drubay 2007)

Dentorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder characterized by myoclonus, ataxia, cerebellar ataxia, choreoathetosis, dementia and psychiatric symptoms. Neuroradiological findings are extremely specific: atrophic changes in the cerebellum and brain stem (in particular in the pontine tegmentum), diffuse high-signal-intensity lesions in the cerebral white matter, brain stem and thalami in the T2 weighted images. Marked progression of cerebral atrophy is often noted (Drubay 2007)

Domianly inherited GTP cyclohydrolase deficiency, some compound heterozygotes for GTP cyclohydrolase deficiency, and sepapienreductase deficiency do not lead to hyperphenylalaninemia and consequently are missed on newborn screening. Phenylalanine in urine are also frequently normal, but the pterin pattern in cerebrospinal fluid (CSF), is characteristic for each disorder. (Hyland 2007)

Fatty acid hydroxylase-associated neurodegeneration (FAHN) is characterized by corticospinal tract involvement (spasticity), mixed movement disorder (ataxia/dystonia), eye findings (optic atrophy, oculomotor abnormalities), and progressive intellectual impairment and seizures in the disease course. (Kraer MC 2015)

CASE REPORT

The patient is a 25 years old Macedonian man who referred not having any disease in his clinical history. He came to our neurology department because of bilateral postural and action tremor in his limbs with prevalence in upper limbs, involuntary perioral movements, disatirha and disturbance of gait.

Family history: Similar symptoms characterized by limbs tremor, behavioral disorders and progressive paralysis led to death his mother, aunt and grandmother at the age of about 30 without any defined diagnosis. We visited the patient’s sister as well and identified the same clinical signs in a mild stage.

Neurololgical examination: disatirha, perioral spasmus, tongue tremor, vulum pendulum palat deviation, extrapiramidal limbs rigidity and a tabetacititis gait. We subitted also the patient to the III Part of UPDRS scale, in order to have a helpful datatum to underline any clinical changing, with a result of 4.5 points

General Body examination: habitus longilineus, spinal scolioisis, pes cavus, pectum excavatum, hyperhydrosis.

DIAGNOSTIC TESTS

Brain and column MRI: white matter hiperintensity, ventricular dilatation, reduced corpus callosum thickness and atrophy of the arbor cerebellum as well as a syringomyelic cavity and angiomas.

Electrophysiological tests: absence of SSEPs in lower limbs.

CSF analysis: signs of altered blood-CSF barrier.

Urinary Pterines: low Neoptiorine concentration (0.19 mmol/mol creatinina n.v. 0.30 – 4.00),

Urinary Pterines concentration: Low bioprotein concentration (1.48 mgc/L n.v. 2.40 – 7.10),

Urinary Neurotransmitters metabolites: Altered values of Urinary Neurotransmitters metabolites in particular 5-HIIA (37 mmol/L n.v. 45 – 135), HVA(25 mmol/L n.v. 98 – 450), 5-HTP (13 mmol/L n.v. <10)

Somni Y (2011)

Plasmatic Amino acids concentration: Low values of some plasmatic amino acids in particular Histidine, Tyrosine, 2-aminoacibutaric acid, valine, leucine, lysine, proline .

Other tests: McArge test and copper serum test as well. The molecular analysis of the CHD1/DYT5 gene didn’t show any pathological mutation, neither did the CHG array test. Furthermore We analyzed the chitotriosidase enzymatic function and the long chain fatty acid dosage but didn’t reach any significant result.

GTPCH genetic test: Normal

We tried as we well a therapeutical approach with L-DOPA that led to a slight improvement of the symptoms, with reduced rigidity, bradykinesia and improvement of the patient's walking that were confirmed after six months of therapy during an office visit.

DISCUSSION:

This clinical case owns several clinical features of different hereditary movement and metabolic disorder although it doesn’t figure out any typical pattern of them. There are several possible differential diagnosis for this patient. First of all it is necessary to exclude any cause of early onset parkinsonism, both the potentially treatable ones as Wilson’s disease, dopa-responsive dystonia, drug-induced parkinsonism, and structural causes and the genetic ones. Between these lasts the likelists in our case were some forms ock SCA af the DRPLA. MR imaging of our patient owns some features that match with the DRPLA specific ones1) atrophy of the cerebellum and brain stem 2) high-signal-intensity lesions in the cerebral white matter and brain stem on T2-weighted images 3) signal-intensity changes in the cerebral white matter restricted to the periventricular white matter and 4) progressive cerebral atrophy.

The second likelists diagnosis is an inherited monoaomic neurotransmitter disorder . On this hand aour work was guided by ptirines, amino acids and neurotransmitters’ metabolites values in serum, urines and CSF, that led us to look for the GTP-CH1 deficiency (L-DOPA responsive dystonia) genetic test without success. We have planned further studies for this patient and of other members of his family as a da’Scan hoping that they could lead to the diagnosis of a new hereditary neurological or oculomotoric disorder that could involve both central and peripheral nervous system.

Metabolic patterns observed in urines, plasmas, and CSF in the inherited disorders affecting dopaminergic and serotonergic metabolism

| Test | DH | BH | N | EPG | HAA | SEM
|------|----|----|---|-----|-----|----|
