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

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BACKGROUND

Juvenile Parkinsonism is very rare and it results of various secondary or genetic causes; most cases with a fairly pure parkinsonian syndrome are due to typical Lewy-body Parkinson's disease or less commonly, genetic causes. The main differential diagnoses are Wilson's disease and dopa-responsive dystonia. *(Schrang A., Schott J.M. 2006)*

Familiar 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 observed (chorea, PD) as well as abnormal eye movements, symptoms of upper motoneuron damage, demntia, and peripheral neuropathy. *(Oczkowska A. 2014)*

Dentorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder characterized by myoclonus, epilepsy, cerebellar ataxia, choreoatetosis, dementia and psychiatric symptoms. Neuroradiologic 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 thalamus in the T2 weighted images. Marked progression of cerebral atrophy is often noted. *(Sunami Y. 2011)*

Dominantly inherited GTP cyclohydrolase deficiency, some compound heterozygotes for GTP cyclohydrolase deficiency, and sepiapterin reductase deficiency do not lead to hyperphenilalaninemia and consequently are missed on newborn screening. Pterin patterns 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. *(Kruer 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, disarthria 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.

Neurological examinatiom: disarthria, perioral spasmus, tongue tremor, velum pendulum palati deviation, extrapyramidal limbs rigidity and a tabeticataxic gait. We submitted also the patient to the III Part of UPDRS scale, in order to have an helpful datum to underline any clinical changing, with a result of 42 points

General Body examination: habitus longilineus , spinal scoliosis, pes cavus, pectum excavatum, hyperhidrosis.

DIAGNOSTIC TESTS

Brain and column MRI: white matter hiperintensity, ventricular dilatation, reduced corpum 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 Neopterine concentration (0,19 mmol/mol creatinina n.v. 0,30 – 4,00),

CSF Pterines concentration: Low Biopterine concentration (1,48 mcg/L n.v. 2,40 - 7,10);

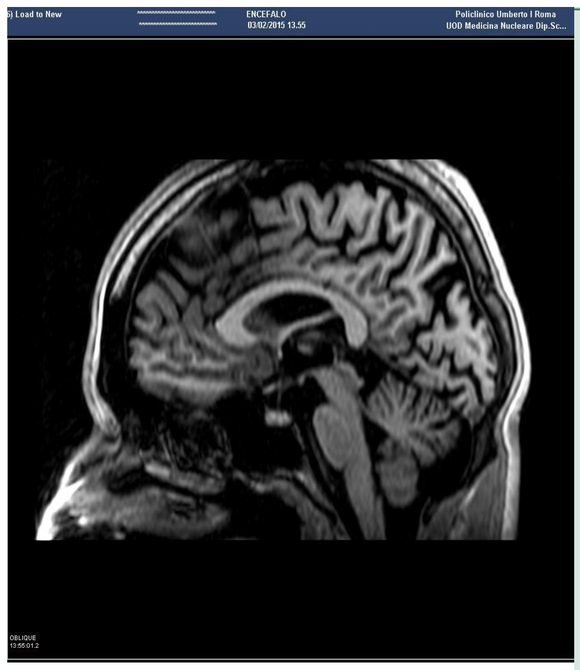
Urinary Neurotransmitters metabolites: Altered values of Urinary Neurotransmitters metabolites in particular 5-HIAA (37 mmol/L n.v. 45 – 135) , HVA(25 mmol/L n.v. 98 – 450), 5-HTP (13 mmol/L n.v. <10) HVA/5HIAA ratio 0,67 (n.v. 1,5 – 3,5);

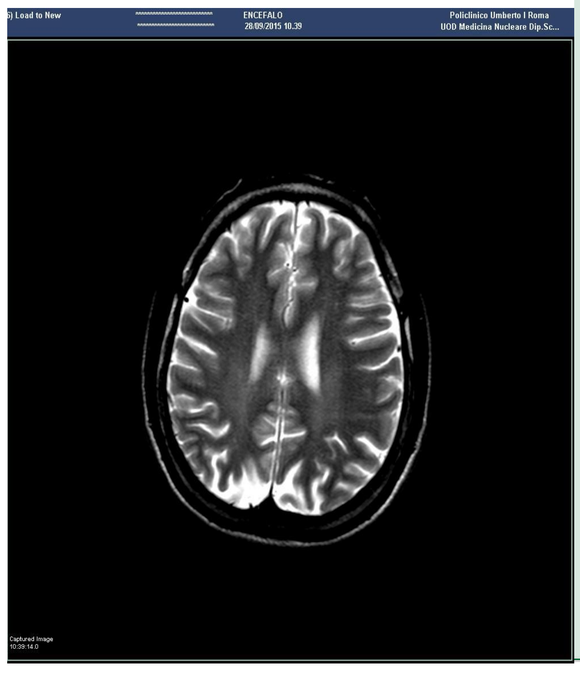
Plasmatic Amino acids concentration: Low values of some plasmatic amino acids in particular Histidine, Tyrosine, 2-aminobutyric acid, valine, leucine, lysin, proline .

Other tests: McArdle test and copper serum test as well The molecular analysis of the GCH1/DYT5 gene didn't show any pathological mutation, neither did the CGH-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 well a terapeuthical approach with L-DOPA that led to a slight improvement of the symptoms, with reduced rigidity, bradykinesia and improvement of gait disorders which were confirmed after six months of therapy during an office visit.





	Investigations
Important, potentially treatable causes	
Wilson's disease	Copper, caeruloplasmin in serum, 24-h copper excretion, Kayser-Fleischer rings, liver biopsy
Dopa-responsive dystonia-parkinsonism	Phenylalanine loading test, dopamine transporter single-photon emission CT, fluorodopa PET
Drug-induced parkinsonism	History of neuroleptic medication, antiemetics, calcium-channel blockers, and others; dopamine transporter single-photon emission CT
Structural lesions (stroke, space-occupying lesions, central extrapontine myelinolysis)	Brain MRI of basal ganglia, supratentorium, and posterior fossa
Hydrocephalus	Brain CT/MRI
Genetic causes	
PARK1, 2, 6, 7, 8	Genetic testing currently only in research setting
Huntington's disease (Westphal variant)	Genetic testing widely available
Spinocerebellar ataxia (especially spinocerebellar ataxia types 2 and 3)	Genetic testing available in selected laboratories
Neuroacanthocytosis	Acanthocytes on wet blood films
Rapid onset dystonia-parkinsonism	Genetic testing currently only in research setting; autosomal dominant
X-linked dystonia-parkinsonism (Lubag)	Genetic testing currently only in research setting; disease restricted to Filipinos
Leigh's and other mitochondrial diseases	MRI: symmetrically increased signal in basal ganglia, elevated serum and/or cerebrospinal-fluid lactate
Niemann Pick type C	Sea-blue histiocytes on bone marrow biopsy; reduced cholesterol esterification and accumulation of unesterified cholesterol in cultured skin fibroblasts
Juvenile neuronal ceroid lipofuscinosis	Rectal, muscle, skin, conjunctival, or brain biopsy: fingerprint cytosomes; genetic testing in research setting
Gaucher's disease	Reduce white-cell beta-glucosidase activity
Hallervorden-Spatz syndrome/pantothenate kinase-associated neurodegeneration and HARP (hypoprebetalipoproteinaemia, acanthocytosis, retinitis pigmentosa, pallidal degeneration)	MRI: eye of the tiger sign in globus pallidus; genetic testing for mutations in *PANK2* in research setting
Neuroferritinopathy	Genetic testing currently only in research setting
Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP17)	Genetic testing currently only in research setting
Cerebrotendinous xanthomatosis	Raised plasma cholestanol; genetic testing currently only in research setting
Other	
Carbon monoxide poisoning and other toxins	History and MRI changes in basal ganglia
Systemic lupus erythematosus	Erythrocyte sedimentation rate, anti-nuclear antibodies, anti-dsDNA, cerebrospinal fluid anaylsis
Fahr's syndrome	CT brain: basal ganglia califications, parathormone, serum calcium and phosphorus; may be autosomal dominant
Infectious/postinfectious causes	Cerebrospinal fluid: viral titres/polymerase chain reaction, mycoplasma pneumonia antibodies, oligoclonal bands; MRI; electroencephalogram; HIV test; antibasal ganglia antibodies; antistreptolysin O titres; polymerase chain reaction and small bowel biopsy for Whipple's disease
Primary neurodegenerative	
Idiopathic Parkinson's disease	Clinical diagnosis
Multiple system atrophy	Clinical diagnosis; MRI; sphincter electromyogram; autonomic function test; clonidine-test

Table: Important causes of early-onset parkinsonism and relevant investigations

Schrag, A. et al.;. 2006.

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 likeliests in our case were some forms ok 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 likeliest diagnosis is an inherited monoamine neurotransmitter disorder . On this hand aour work was guided by pterines, amino acids and neurotrasmitters' 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 daTscan hoping that they could lead to the diagnosis of a new hereditary neurological or multisystemic disorder that could involve both central and peripheral nervous system.

Metabolite patterns observed in urine, plasma, and CSF in the inherited disorders affecting dopamine and serotonin metabolism

	Phe	BH4	BH2	Neop	Sep	Prim	HVA	5HIAA	3OMD
GTPCH (Recessive)	↑ (P)	↓ (U, CSF)	N	↓ (U, CSF)	N	N	↓ (CSF)	↓ (CSF)	N
GTPCH (Dominant)	N	↓ (CSF)	N	↓ (CSF)	N	N	↓ (CSF)	±↓ (CSF)	N
6PTPS	↑ (P)	↓ (U, CSF)	N	↑ (U, CSF)	N	N	↓ (CSF)	↓ (CSF)	N
6PTPS (Mild)	↑ (P)	↓ (U)	N	↑ (U)	N	N	N	N	N
SR	N	↓ (CSF)	↑(CSF)	N	↑ (CSF)	N	↓ (CSF)	↓ (CSF)	N
PCD	↑ (P)	↓ (U)	N	N	N	↑ (U)	N	N	N
DHPR	↑ (P)	↓ (U) ±↓ (CSF)	↑(U,CSF)	N	N	N	↓ (CSF)	↓ (CSF)	N
TH	N	N	N	N	N	N	↓ (CSF)	N	N
AADC	N	N	N	N	N	N	↓ (CSF)	↓ (CSF)	↑ (P, CSF,U)

GTPCH, GTP cyclohydrolase; 6PTPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase; PCD, pterin α-carbinolamine dehydratase; DHPR, dihydropteridine reductase; TH, tyrosine hydroxylase; Phe, phenylalanine; BH2, 7, 8-dihydrobiopterin; neop, neopterin; SEP, sepiapterin; Prim, primapterin; 3OMD, 3-*O*-methyldopa; N, normal; ↓, decreased; ↑, elevated; P, plasma; U, urine.

Hyland K.; 2007

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