RESIDENT & FELLOW SECTION

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Clinical Reasoning: A young woman with rapid mental deterioration and leukoencephalopathy

A treatable cause

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SECTION 1

A 21-year-old woman was admitted due to rapid worsening of mental deterioration, which led to her becoming bedridden for over 3 months. She was born to consanguineous parents and had mild mental retardation and spastic paraparesis that impaired running. She became pregnant 4 months before admission. During the first weeks of pregnancy she developed deep vein thrombosis, which was treated with anticoagulant therapy. A medical abortion using misoprostol and mifepristone was performed. Since this event, mental changes progressed rapidly. She had a brain MRI showing multifocal T2 white matter signal changes (figure, A and B). A diagnosis of psychosis was considered.

At admission 3 months later, she was bedridden, confused, uncooperative, and aggressive. She complained of visual trouble. Neurologic examination found a marked flaccid paraparesis with urinary and fecal incontinence. Reflexes were all abolished, in contrast to the presence of a bilateral Babinski sign. Funduscopy was normal. The rest of the examination was normal.

A new brain MRI was performed, revealing a symmetric, confluent, supratentorial leukoencephalopathy (figure, C). Lesions were not enhanced by gadolinium injection. Caudate nuclei appeared hyperintense in diffusion-weighted images (figure, D) associated with a decreased diffusion on the apparent diffusion coefficient map (not shown). Compared to the previous MRI, white matter high intensities had increased.

Question for consideration:

1. What do you think about this clinical and radiologic presentation? How would you investigate it?

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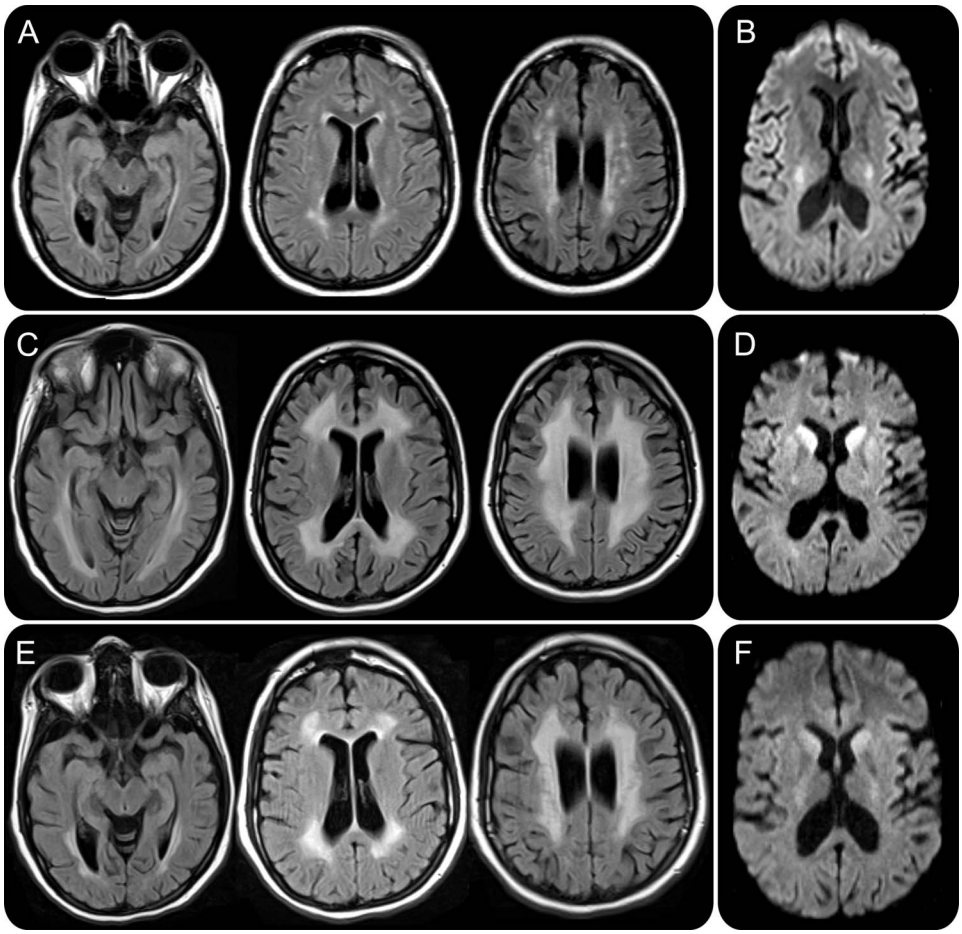
Figure Brain MRI



Fluid-attenuated inversion recovery and diffusion-weighted images: 3 months before admission (A, B), at admission (C, D), and 3 months after treatment onset (E, F).

SECTION 2

This patient presented with rapid deterioration of mental state that could be consistent with a psychiatric origin. Symptoms occurred after a peripartum deep vein thrombosis leading to an abortion. Three features were contrary to a psychiatric disease. (1) Neurologic evaluation was abnormal, showing a simultaneous bilateral Babinski sign and loss of deep tendon reflexes. (2) Brain MRI demonstrated an obvious progression of the white matter lesions, from patchy T2 white matter hyperintensities to a confluent and symmetric supratentorial leukoencephalopathy. (3) The patient was born to consanguineous parents and displayed mental retardation and difficulty walking since infancy. This last finding suggested an underlying inborn disorder.

Acquired or inherited causes of leukoencephalopathies have to be considered.

In this context, investigations have to eliminate toxic, metabolic, autoimmune, vascular, and infectious causes of leukoencephalopathy. An inherited cause had to be kept in mind, notably a possible treatable disease.

Biological testing for acquired leukoencephalopathy included blood count, sedimentation rate, C-reactive protein and fibrinogen, antinuclear antibodies, anti–extractable nuclear antigens, anti-double-stranded DNA, antineutrophil cytoplasmic antibody, antiphospholipids, antiB2GP1, antineuron (with GAD65), intrinsic factor antibody, vitamins B_1, B_6, B_{12}, folic acid, and biotin, lactate, ammonia, copper, thyroid-stimulating hormone, T3, T4, antithyroglobulin, and antithyroperoxidase. Blood tests for Lyme disease, viral hepatitis, HIV, human T-cell lymphotropic virus, syphilis, and toxoplasmosis were verified. All were within normal values or negative. CSF analysis was unremarkable; oligoclonal bands were absent.

To identify rare inherited diseases, clinicians had to perform meticulous investigations. Occurrence of neurocutaneous symptoms, visual symptoms, polyneuropathy, or acute clinical manifestations (stroke-like, coma, psychiatric symptoms, and seizures), ataxia, and paraparesis had to be searched. Visual symptoms should be assessed by the ophthalmologist to detect in particular early cataract, retinopathy,

optic atrophy, or corneal deposits. Peripheral neuropathy or myopathy had to be studied by a complete EMG examination. EMG revealed, in our case, a severe 4-limb axonal sensorimotor neuropathy. Ophthalmologic examination was not contributive and the impaired vision was related to a central origin.

Analysis of the magnetic resonance features had to be meticulous, including symmetrical aspect, location of high intensity, selective involvement of the pyramidal pathways, profound gray matter, or U fibers. The presence of cystic lesions, microbleeds, or diffusion-weighted signal abnormalities had to be examined. Brain MRI is displayed in the figure, C and D. Spinal cord MRI was normal.

Inherited causes of leukoencephalopathy had to be systematically screened. They include aminoacidopathies, organic aciduria, and disorders of homocysteine metabolism. Plasma and urine amino acids (AA) quantitative analysis, urinary organic acid chromatography, and total plasma homocysteine (tHcy) had to be measured. Depending on clinical features and MRI abnormalities, arylsulfatase A deficiency (metachromatic leukodystrophy), α-galactosidase deficiency (Fabry disease), X-linked adrenoleukodystrophy, mitochondrial diseases, and peroxisomal diseases can be considered.[1] In our patient, tHcy was elevated and plasma AA revealed high level of homocysteine and cysteine/homocysteine disulfide with a decrease of cysteine and methionine (table).

Question for consideration:

1. What do you think about homocysteine level and AA abnormalities? What would you do next?

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Table Biochemical findings

	Admission	Day 5	Day 15	Day 30	Day 55	Day 80
Total plasma homocysteine (<15 μmol/L)	162	177	52	26	20	26
Homocysteine in urine (<1 mmol/mol creatinine)		39			1	1
MMA in plasma (<0.5 μmol/L)	24.9		19.3	3.5		1.5
MMA in urine (<5 mmol/mol creatinine)		2154	327.2		7.8	19.5
Homocystine (<1 μmol/L)[a]	12	9	<1	<1	<1	<1
Cysteine/homocysteine disulfide (<1 μmol/L)[a]	67	51	22	15	14	19
Cysteine (23–42 μmol/L)[a]	10	20	28	54	43	22
Methionine (21–39 μmol/L)[a]	14	20	26	24	25	29
	Total plasma homocysteine/ homocysteine in urine	**Macrocytosis**	**Folic acid**	**B_{12}**	**Methionine[a]**	**Plasma/urine MMA**
Folic acid deficiency	↑	+	↓		Normal or ↓	
B_{12} deficiency	↑	+		↓	Normal or ↓	↑
Cystathionine β-synthase	↑				↑	
Methylene-tetra hydrofolate-reductase	↑		↓		↓	
CblC, D, F, J	↑	+[b]			Normal or ↓	↑
CblE, G	↑	+			Normal or ↓	
Transcobalamin II deficiency	↑	+			↓	↑
Imerslund-Gräsbeck	↑	+			↓	↑

Abbreviation: MMA = methylmalonic acid.
Evolution of biochemical findings under treatment (upper part). Main causes of homocysteinemia: laboratory findings (lower part).
[a] Plasma amino acids quantitative analysis.
[b] Possibly absent in adults.

The high level of tHcy in this patient is highly significant. Several acquired or inherited disorders can cause hyperhomocysteinemia. They include transulfuration disorders (classical homcystinuria due to cystathionine β-synthase deficiency), remethylation disorders (MTHFR), B_{12} and folic acid absorption, and transportation and intracellular metabolism disorders. Renal insufficiency or drug toxicity (methotrexate, nitrous oxide/oxygen mixture) should systematically be ruled out. To better determine the patient's dysfunction, biochemical tests of urine and blood are needed[2] (table).

The clinical presentation, the medical history, the rapid apparition of white matter changes in association with elevated homocysteine level in blood and urine, normal folic acid and B_{12} vitamin levels, high methylmalonic acid in blood and urine, and hypomethioninemia on AA (table) indicate a disorder of early steps in intracellular cobalamin metabolism. This clinical and biochemical combination suggests cobalamin deficiency with homocystinuria type C, D, F, or J, justifying their genetic molecular screening.

Supplementation with intramuscular hydroxycobalamin (Dodecavit) was started in association with per os betaine (Cystadane), folinate, and carnitine (Levocarnil).

Three months later, symptoms improved. Cognitive function was restored except for the persistence of a disinhibited frontal syndrome. Visual symptoms disappeared; urinary incontinence only remained at night. The patient became able to stand and walk a few steps with assistance. Biochemical findings greatly improved (table) and white matter changes dramatically decreased (figure, D and E).

DISCUSSION Several weeks after admission, cobalamin deficiency, type D was genetically confirmed (homozygous mutation [c.748C > T (p.Arg250Ter)[2,3]] in *MMADHC* gene, OMIM:277410).

In this patient, occurrence of hyperhomocysteinemia, associated with an increase of methylmalonic acid and normal B_{12} level, led to the suspicion of a specific disorder of early steps in intracellular cobalamin metabolism. This allowed early treatment leading to significant clinical, biochemical, and radiologic improvement.

The transmission of cobalamin deficiency type C, D, F, or J is autosomal recessive.[2] Type CblC is the most frequent and could occur in 1:200,000 births, whereas only a few cases of adult-onset CblD are known.[2] The normal B_{12} level excluded vitamin B_{12} deficiency and Imerslund-Gräsbeck syndrome. Absence of megaloblastic anemia ruled out transcobalamin II deficiency.[2]

Symptoms related to CblD disorder overlap those due to CblC with a diagnosis made, in most cases, during neonatal screening or in the first years of life.[2,4] During this period, without treatment a lethal outcome is possible due to acute metabolic decompensation, multiorgan involvement, cardiomyopathy, or neurologic and developmental complications. In adult patients (up to the 5th decade), clinical manifestations can include isolated progressive cognitive inflection to subacute or acute decompensation of neuropsychiatric disorders, neurologic symptoms (peripheral neuropathy, combined spinal cord degeneration), and thromboembolic events (deep vein thrombosis).[4] Megaloblastic anemia is frequently missing in adults.[4,5] Brain MRI abnormalities are frequent and various, from white matter periventricular nonspecific T2 high signal to diffuse leukoencephalopathy.[2,4,6,7] Diffusion-weighted imaging hyperintensities involving the heads of caudate nuclei are unusual in our patient and could be related to cytotoxic and myelin edema induced by the underlying metabolic dysfunction. This aspect is not pathognomonic and has been observed in other inborn errors of metabolism, such as Alexander, Krabbe, or Canavan diseases and glutaric aciduria type 1. These differential diagnoses do not match the rest of the radiologic abnormalities or clinical manifestations observed in our patient.

Disorders of cobalamin metabolism should be systematically suspected in patients under age 50 years with combined manifestations of peripheral and central nervous systems. Psychiatric symptoms and possible recessive inheritance reinforces this suspicion.[4] Asymptomatic adult subjects have been diagnosed among siblings of symptomatic patients.

In our patient, the first symptoms occurred just after the beginning of pregnancy, which can be explained by an induction of oxidative and metabolism stress and hypercatabolism. Normal pregnancies and deliveries have yet to be reported, and genetic counseling should be advised.[2,8] Similar situations can be observed after surgery, prolonged fasting, nitrous oxide use, or any event generating acute metabolism stress.[2,4] Close management of at-risk periods is necessary (optimization of treatments, biochemical monitoring).

Lifelong treatment is needed with intramuscular high doses (5–10 mg/week) of hydroxycobalamin (not cyanocobalamin), per os betaine 150 mg/kg/day (to improve the conversion of homocysteine to methionine), folate 15 mg/day (to improve remethylation), and carnitine 50–100 mg/kg/day (partial depletion due to methylmalonic aciduria).[2,4]

In this case, acquired causes were first ruled out. The second step focused on inherited causes. A systematic screening for treatable disorders, which should always include total blood homocysteine levels and AA quantitative analysis, revealed obvious abnormalities. Additional biochemical tests were performed to

explore the hyperhomocysteinemia. Inherited intracellular cobalamin metabolism disorders type CblC, D, F, or J were quickly considered. Genetic molecular testing confirmed cobalamin deficiency, type CblD.

AUTHOR CONTRIBUTIONS

D. Biotti: first author, corresponding author, principal investigator. M. Esteban, C. Tilikete, E. Diot, and A. Vighetto: neurologic management. P. Labauge: genetic and neurologic advisor. C. Acquaviva, N. Guffon: biochemical investigations and therapeutics. J.-F. Benoist: genetic testing.

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DISCLOSURE

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REFERENCES

1. Saudubray JM, Sedel F. Inborn errors of metabolism in adults [in French]. Ann Endocrinol 2009;70:14–24.
2. Carrillo-Carrasco N, Adams D, Venditti CP. Disorders of intracellular cobalamin metabolism. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews®. Seattle: University of Washington; 1993.
3. Coelho D, Suormala T, Stucki M, et al. Gene identification for the cblD defect of vitamin B12 metabolism. N Engl J Med 2008;358:1454–1464.
4. Thauvin-Robinet C, Roze E. Cobalamin metabolism disorders in adult patients [in French]. Rev Neurol 2007;163:911–918.
5. Roze E, Gervais D, Demeret S, et al. Neuropsychiatric disturbances in presumed late-onset cobalamin C disease. Arch Neurol 2003;60:1457–1462.
6. Longo D, Fariello G, Dionisi-Vici C, et al. MRI and ^{1}H-MRS findings in early-onset cobalamin C/D defect. Neuropediatrics 2005;36:366–372.
7. Rossi A, Cerone R, Biancheri R, et al. Early-onset combined methylmalonic aciduria and homocystinuria: neuroradiologic findings. AJNR Am J Neuroradiol 2001;22:554–563.
8. Brunel-Guitton C, Costa T, Mitchell GA, Lambert M. Treatment of cobalamin C (cblC) deficiency during pregnancy. J Inherit Metab Dis 2010;33(suppl 3):S409–S412.