

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/331739177>

Mutation of the MMADHC gene in adult-onset cobalamin D deficiency: a report of 2 potentially treatable cases

Article · March 2019

DOI: 10.1016/j.nrleng.2019.02.007

CITATIONS

0

READS

18

5 authors, including:



Bartomeu Oliver

Reference Laboratory Genetics

2 PUBLICATIONS 0 CITATIONS

SEE PROFILE

dehydrocholesterol resulting in a cytotoxic effect that leads to anomalies, intellectual disability, and neurological alterations.^{10,11}

In conclusion, we underscore the importance of clinical suspicion of influenza A (H1N1) virus as the aetiology of neurological symptoms coexisting with influenza-like or respiratory infection symptoms, once other diagnostic possibilities have been ruled out. In our case, we assume that the progression of influenza A, affecting multiple lower cranial nerves, may have been promoted by the Smith-Lemli-Opitz syndrome due to its interference in myelin metabolism. This may have increased susceptibility to neurological damage and inhibited myelin repair.

References

- Cárdenas G, Soto-Hernández JL, Díaz-Alba A, Ugalde Y, Mérida-Puga J, Rosetti M, et al. Neurological events related to influenza A (H1N1) pdm09. *Influenza Other Respir Viruses*. 2014;8:339–46.
- Asadi-Pooya AA, Yaghoubi E, Nikseresht A, Moghadami M, Honarvar B. The neurological manifestations of H1N1 influenza infection; diagnostic challenges and recommendations. *Iran J Med Sci*. 2011;36:36–9.
- Davis LE, Koster F, Cawthon A. Neurologic aspects of influenza viruses. *Handb Clin Neurol*. 2014;123:619–45.
- Nakamura Y, Ikeda K, Yoshii Y, Ito H, Hirayama T, Kawabe K, et al. Influenza-associated monophasic neuromyelitis optica. *Intern Med*. 2011;50:1605–9.
- Morita A, Ishihara M, Kamei S, Ishikawa H. Opsoclonus-myoclonus syndrome following influenza a infection. *Intern Med*. 2012;51:2429–31.
- Hara M, Morita A, Ichihara K, Kashima Y, Kamei S, Kuwahara M, et al. Miller Fisher syndrome associated with influenza A infection. *Intern Med*. 2012;51:2621–3.
- Bartual-Pastor J. Vestibular neuritis: etiopathogenesis. *Rev Laryngol Otol Rhinol*. 2005;126:279–81.
- Gutiérrez Ríos R, Castrillo Sanz A, Gil Polo C, Zamora García MI, Morollón Sánchez-Mateos N, Mendoza Rodríguez A. Síndrome de Collet-Sicard. *Neurología*. 2015;30:130–2.
- Sibai TA, Ben-Galim PJ, Eicher SA, Reitman CA. Infectious Collet-Sicard syndrome in the differential diagnosis of cerebrovascular accident: a case of head-to-neck dissociation with skull-based osteomyelitis. *Spine J*. 2009;9:e6–10.
- Jira P. Cholesterol metabolism deficiency. *Handb Clin Neurol*. 2013;113:1845–50.
- Svoboda MD, Christie JM, Eroglu Y, Freeman KA, Steiner RD. Treatment of Smith-Lemli-Opitz syndrome and other sterol disorders. *Am J Med Genet C Semin Med Genet*. 2012;160C:285–94.

F.J. Zamudio Moya^{a,*}, D. Sagarra Mur^b,
M. Pereira de Vicente^a

^a *Servicio de Medicina Interna, Hospital Santa Bárbara, Soria, Spain*

^b *Servicio de Neurología, Hospital Santa Bárbara, Soria, Spain*

*Corresponding author.

E-mail address: fzamudiomoya@hotmail.com

(F.J. Zamudio Moya).

2173-5808/

© 2016 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Mutation of the *MMADHC* gene in adult-onset cobalamin D deficiency: a report of 2 potentially treatable cases[☆]

Mutación del gen *MMADHC* de la cobalamina D con comienzo en el adulto: a propósito de 2 casos potencialmente tratables

Dear Editor:

Methylmalonic acidemia with homocystinuria is an infrequent inborn error of vitamin B₁₂ (cobalamin) metabolism. It is caused by defects in the synthesis of the coenzymes adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl), leading to decreased activity of the corre-

sponding enzymes methylmalonyl-CoA mutase (MUT;609058) and 5-methyltetrahydrofolate-homocysteine methyltransferase, also known as methionine synthase (MTR;156570). Four complementation classes of cobalamin defects (cblC, cblD, cblF, and cblJ, caused by mutations in the corresponding genes) are responsible for methylmalonic acidemia with homocystinuria. Methylmalonic acidemia with homocystinuria type cblD is caused by mutations in the *MMADHC* gene (2q23.2), following an autosomal recessive inheritance pattern. We present 2 cases.

Patient 1 is an 18-year-old woman of Roma origin. The patient had no relevant medical history and did not follow a specific diet, and was admitted due to fever of 38.5 °C, sudden-onset confusional symptoms, disorientation in time and space, incoherent but non-dysarthric speech, and psychomotor delay. She displayed a good level of consciousness; she was alert, disoriented, anxious, and irritable but not aggressive. The patient presented no headache or meningeal signs. A blood test, biochemical test, total protein test, immunoglobulins, autoimmunity study, serological test, and tests for thyroid hormone levels, ferritin, vitamin B₁₂, and folic acid all yielded normal results. Results of a head CT scan and lumbar puncture were normal (negative microbiological study).

The internal medicine department prescribed empirical treatment with aciclovir, which achieved favourable

[☆] Please cite this article as: Cancho García E, Geán E, Oliver Tormo B, Torrents A, Esteban Durán E. Mutación del gen *MMADHC* de la cobalamina D con comienzo en el adulto: a propósito de 2 casos potencialmente tratables. *Neurología*. 2019;34:419–421.

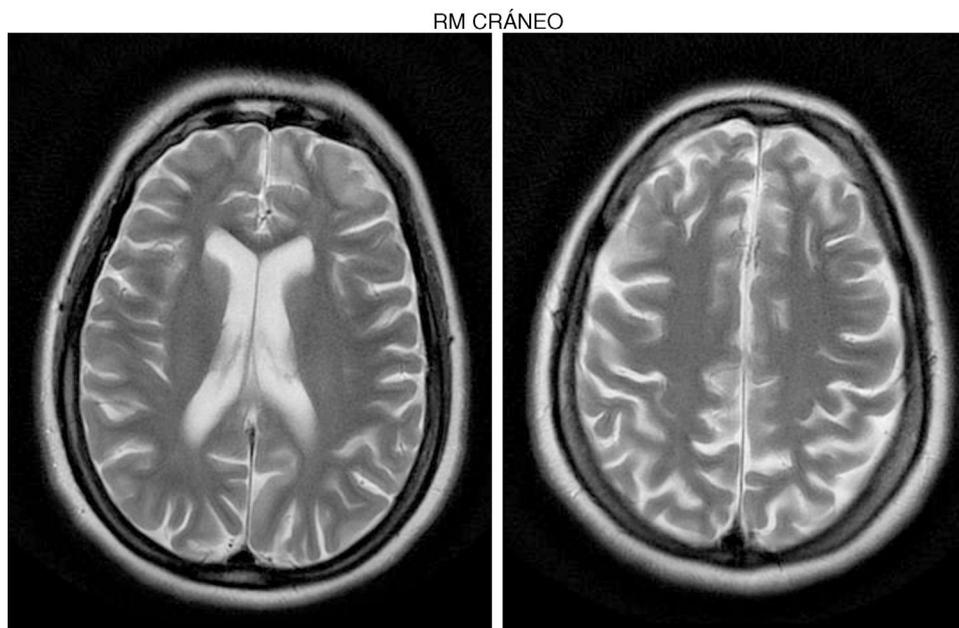


Figure 1 Patient 1. Axial T2-weighted TSE sequence showing cortical retraction with slight dilation of the subarachnoid spaces of the convexity, and discrete enlargement of the supratentorial ventricular system.

progression until all symptoms disappeared. She did not attend the follow-up appointments scheduled at discharge, and consulted 10 months later due to gradual, progressive gait disorder (weakness in the lower limbs), frequent falls, and loss of strength in the upper limbs. During the examination, she was alert and presented mild dysarthria, pronounced bradypsychia, and difficulty maintaining attention. The patient displayed frontal release signs. Pupils were isocoric and reactive. Examination revealed muscle strength of 3/5 in the psoas, 3/5 in the quadriceps, 4/5 in the gluteus medius, 3/5 in the gluteus maximus, 2/5 in the tibialis anterior, 1/5 in the extensor digitorum muscle, 3/5 in the hamstring, and 1/5 in the ankle dorsiflexor. We identified patellar tendon hyporeflexia (2/4) and bilateral ankle clonus. In the upper limbs, reflexes were 3/4 and strength 4/5. Deep sensibility was affected in distal areas; hypoaesthesia was also observed. We also observed ataxic gait, grade I spasticity, and bilateral Babinski sign. A brain MRI scan (Fig. 1) showed cortical retraction, slight dilation of the subarachnoid spaces of the convexity, and discrete enlargement of the supratentorial ventricular system with thinning of the corpus callosum. An EEG revealed slow background activity with no epileptiform abnormalities. A motor nerve conduction study showed a discrete sensorimotor axonal polyneuropathy predominantly affecting the lower limbs. The differential diagnosis included the study of hereditary spastic paraparesis, which yielded negative results. Furthermore, autoimmune and paraneoplastic disease screening also detected no abnormalities. We then decided to study late-onset inborn errors of metabolism and requested blood homocysteine and blood and 24-h urine amino acid and organic acid levels; results showed increased methylmalonic acid (258 nmol/mol of creatinine, normal: <0.56) and methylcitric acid and slightly elevated ketones (3-hydroxybutyric acid) in the urine, as well as increased blood homocysteine (339.2 $\mu\text{mol/L}$, normal: <10). During

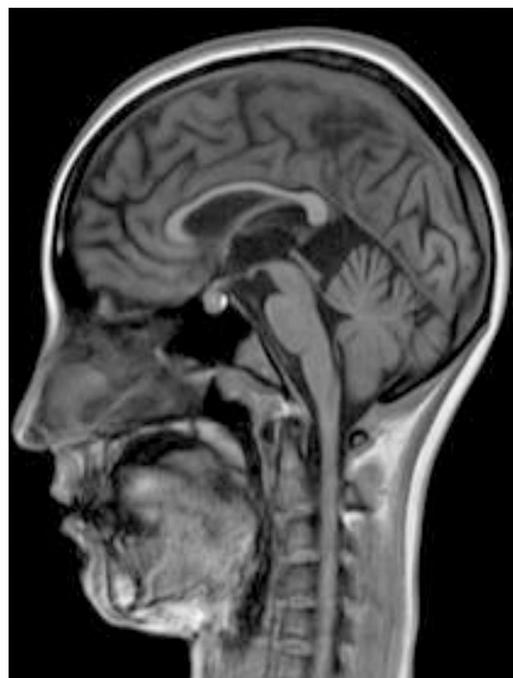


Figure 2 Patient 2. T1-weighted TSE sequence revealing slight thinning of the corpus callosum.

the study, the patient presented popliteal vein thrombosis with massive bilateral pulmonary thromboembolism, which led to the patient's death.

Patient 2 is an 15-year-old woman of Roma origin, sister of patient 1 (3 years younger).

Development was normal. Several months before her sister's death, she presented insidious symptoms of difficulty walking, loss of appetite, and inappropriate laughter. Examination revealed bradypsychia and difficulty

maintaining attention, ataxic gait with generalised spasticity (grade I), impaired hip adduction, mild genu recurvatum, muscle strength of 4/5 in the psoas, 3/5 in the quadriceps, 1/5 on dorsiflexion, sustained soleus clonus when seated (nonsustained when standing), and mild ataxia of the left arm. We observed symmetrically increased deep tendon reflexes in the lower limbs and bilateral Babinski sign. Muscle strength was 4/5 proximal and 5/5 distal in the upper limbs. Eye fundus and MRI findings were similar to those observed in her sister (Fig. 2). An EEG revealed slow background activity. She presented 2 generalised tonic-clonic seizures with no apparent trigger, which required antiepileptic treatment.

The determination of amino acid and organic acid levels showed increased blood homocysteine (169.9 $\mu\text{mol/L}$, normal: <10) and urine methylmalonic acid (15.40 nmol/mol of creatinine, normal: <0.56). The study of genes involved in methylmalonic acidemia with homocystinuria detected a homozygous mutation (c.748C>T) in the *MMADHC* gene (found in the DNA of both sisters), which generates a stop codon that results in a truncated protein, provoking the disease.^{1–3} The patient is currently receiving treatment, and presents significant improvement and neurological stability.

Conclusion

Definitive diagnosis of these patients enables the early introduction of a specific treatment, as well as genetic counselling and, where necessary, prenatal diagnosis.

In patients presenting symptoms of paraparesis, axonal and demyelinating polyneuropathies, cognitive impairment of unknown cause, and deep venous thrombosis, we should analyse homocysteine and vitamin B₁₂ metabolism.^{4,5}

Informed consent

This article was submitted for publication with the written consent of the patients' parents.

Authors' contributions

Dr E. Cancho García established clinical diagnosis and treatment. Dr E. Geán and Dr T. Oliver Tormo performed the genetic/metabolic study. Dr Torrents performed the

metabolic study. Dr E. Esteban Durán was responsible for the radiology studies.

References

1. Yamada K, Gherasim C, Banerjee R, Koutmos M. Structure of human B12 trafficking protein CblD reveals molecular mimicry and identifies a new subfamily of nitro-FMN reductases. *J Biol Chem.* 2015;290:29155–66.
2. Gherasim C, Hannibal L, Rajagopalan D, Jacobsen DW, Banerjee R. The C-terminal domain of CblD interacts with CblC and influences intracellular cobalamin partitioning. *Biochimie.* 2013;95:1023–33.
3. Atkinson C, Miousse IR, Watkins D, Rosenblatt DS, Raiman JAJ. Clinical, biochemical, and molecular presentation in a patient with the cblD-homocystinuria inborn error of cobalamin metabolism. *JIMD Rep.* 2014;17:77–81.
4. Huemer M, Kožich V, Rinaldo P, Baumgartner MR, Merinero B, Pasquini E, et al. Newborn screening for homocystinurias and methylation disorders: systematic review and proposed guidelines. *J Inherit Metab Dis.* 2015;38:1007–19.
5. Parini R, Furlan F, Brambilla A, Codazzi D, Vedovati S, Corbetta C, et al. Severe neonatal metabolic decompensation in methylmalonic acidemia caused by CblD defect. *JIMD Rep.* 2013;11:133–7.

E. Cancho García^{a,*}, E. Geán^b, B. Oliver Tormo^c,
A. Torrents^d, E. Esteban Durán^e

^a Neurologist, Hospital Don Benito-Villanueva de la Serena, Don Benito, Badajoz, Spain

^b Clinical Genetics Specialist Consultant, Reference Laboratory Genetics, L' Hospitalet de Llobregat, Barcelona, Spain

^c Pharmacist, Reference Laboratory Genetics, L' Hospitalet de Llobregat, Barcelona, Spain

^d Metabolic Diseases Specialist, Reference Laboratory Genetics, L' Hospitalet de Llobregat, Spain

^e Radiologist, Complejo Hospitalario Infanta Cristina, Badajoz, Spain

*Corresponding author.

E-mail address: dresthercg@hotmail.com

(E. Cancho García).

2173-5808/

© 2017 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).