Wilson Disease Watch

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- Latest articles : Summary and comments
- Agenda EuroWilson Network
- Agenda European Patient Organizations

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Improving information, knowledge and access to expertise and care

The effect of gender on brain MRI pathology in Wilson's disease.

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Summary

Background: Gender influence on the clinical manifestations of Wilson's Disease (WD) has been suggested; however, brain MRI pathology based on sexual dimorphism in WD has not yet been examined. Aim of our study was to evaluate and correlate it with clinical symptomatology.

Methods: We retrospectively analysed the brain MR images of 204 newly diagnosed and untreated WD patients.

Results: Overall, neuroimaging pathologies were found in 64.2% WD patients. The clinical form analysis revealed significant gender-related differences. In the neuropsychiatric form, men presented with cerebellar atrophy and cortical brain atrophy more often than women (25/58 vs. 11/47; $p<0.05$) and (23/58 vs. 12/47; $p=0.09$), respectively. In contrast, women tended to present with globus pallidus lesions more often than men (25/47 vs. 20/58; $p=0.054$). There were no gender differences observed in the hepatic form, but cortical brain atrophy presented more often in men than women (3/12 vs. 0/20; $p<0.05$) in the presymptomatic form.

Conclusions: According to our findings, there is a gender-dependent brain vulnerability to copper toxicity. We speculate that these differences are potentially related to an oestrogen protective effect and are due to differences in gender-related clinical presentation.

Comments

The gender seems to be an important factor predicting WD presentation. Further investigation according gender differences in iron metabolism and hormones are needed to better understand this effect.

Take home message

There is a gender-dependent brain vulnerability to copper toxicity.

Encopresis and epilepsy: An unusual presentation of Wilson's disease

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Published in: Epilepsy & Behaviour, August 2010, Volume 18, Issue 4, Pages 507–508

Summary

We describe an atypical neuropsychiatric presentation of Wilson's disease in a 26-years old man. He presented with affective and behavioral disorder in childhood and encopresis that extended to adulthood, followed by headache, tremor, and epilepsy as neurological symptoms that ultimately led to establishment of the diagnosis of Wilson's disease. This sequential development of clinical symptoms through life represents the natural history of unrecognized Wilson's disease in this patient. If we consider psychological manifestations and encopresis in childhood as initial atypical clinical presentations of the disease, delay in establishing the diagnosis was 21 years. Two main points of clinical importance are raised by this case. First, it is important to make a differential diagnosis in patients with nonspecific neuropsychiatric presentations, even though liver function seems to be normal. Neuropsychiatric Wilson's disease may have diverse presentations, and should be considered in children who present with behavioral disturbances and epilepsy. Second, encopresis may be the first clinical sign of Wilson's disease in childhood. It is of utmost importance to rule out an organic cause of fecal incontinence.

Comments

To our knowledge this is the first report of fecal incontinence in a patient known to have Wilson's disease and successfully treated with zinc acetate.

Take home message

The diversity of clinical manifestations of Wilson's disease makes its early diagnosis very difficult unless there is a high index of suspicion..

Identification of a novel Wilson disease gene mutation frequent in Upper Austria: a genetic and clinical study

Hofer H, Willheim-Polli C, Knoflach P, Gabriel C, Vogel W, Trauner M, Müller T, Ferenci P.
Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria.

J Hum Genet. 2012 Sep;57(9):564-7. doi: 10.1038/jhg.2012.65. Epub 2012 Jul 5.

Summary

Wilson disease (WD), a disorder of copper metabolism is caused by mutations in the ATP7B gene, a copper transporting ATPase. In the present study we describe a novel mutation in exon 9 of the ATP7B gene. The ATP7B gene was analyzed for mutations by denaturing HPLC and direct sequencing. DNA from 100 healthy blood donors from the same geographic area was examined as control. Sixteen (7.4%) out of the 216 patients diagnosed with WD in Austria carried the newly identified R816S(c.2448G>T) point mutation in exon 9 (4 male, age: 19 (6-30) years, median (range)). One patient was homozygous for R816S(c.2448G>T). Thirteen patients were compound heterozygotes (p.H1069Q(c.3207C>A)/R816S(c.2448G>T) (N=6), P539L/R816S(c.2448G>T) (N=3), each one G710S/R816S(c.2448G>T), P767P(2299insC)/R816S(c.2448G>T), W779G/R816S(c.2448G>T), T1220M/R816S(c.2448G>T)). In two patients no second mutation was identified. Interestingly, all but three of the patients originated within a distinct geographical area in Austria. Eleven patients presented with hepatic disease, 3 patients with neurological disease and 2 were asymptomatic sisters of an index case. A liver biopsy was available in 14 patients. Three patients showed advanced liver disease with liver transplantation for acute hepatic failure in two. The remaining patients had only mild histological changes, most commonly steatosis. Chronic hepatitis was described in five patients. Kayser-Fleischer ring was present in five patients. None of the 100 healthy controls carried the mutation. We describe a novel mutation in the ATP7B gene, occurring in patients originated from a distinct geographical area in Austria associated with a variable course of the disease.

Molecular analysis of Wilson patients: direct sequencing and MLPA analysis in the ATP7B gene and Atox1 and COMMD1 gene analysis.

Bost M, Piguet-Lacroix G, Parant F, Wilson CM.

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J Trace Elem Med Biol. 2012 Jun;26(2-3):97-101. doi: 10.1016/j.jtemb.2012.04.024. Epub 2012 Jun 5.

Summary

ATP7B mutations result in Cu storage in the liver and brain in Wilson disease (WD). Atox1 and COMMD1 were found to interact with ATP7B and involved in copper transport in the hepatocyte. To understand the molecular etiology of WD, we analyzed ATP7B, Atox1 and COMMD1 genes. Direct sequencing of (i) ATP7B gene was performed in 112 WD patients to identify the spectrum of disease-causing mutations in the French population, (ii) Atox1 gene was performed to study the known polymorphism 5'UTR-99T>C in 78 WD patients with two ATP7B mutations and (iii) COMMD1 gene was performed to detect the nucleotide change c.492GAT>GAC. MLPA (Multiplex Ligation-dependent Probe Amplification) analysis was performed in WD patients presenting only one ATP7B mutation. Among our 112 WD unrelated patients, 83 different ATP7B gene mutations were identified, 27 of which were novel. Two ATP7B mutations were identified in 98 WD cases, and one mutation was identified in 14 cases. In two of these 14 WD patients, we identified the deletion of exon 4 of the ATP7B gene by MLPA technique. In 78 selected patients of the cohort with two mutations in ATP7B, we have examined genotype-phenotype correlation between the detected changes in Atox1 and COMMD1 genes, and the presentation of the WD patients. Based on the data of this study, no major role can be attributed to Atox1 and COMMD in the pathophysiology or clinical variation of WD.

Comments

The first objective of this present study was to identify the spectrum of *ATP7B* gene mutations in French Wilson patients by direct sequencing and to determine whether testing for large gene rearrangements by MLPA analysis could improve the mutation detection rate. The second aim was to analyse the *Atox1* and *COMMD1* genes in WD patients with two ATP7B mutations, to identify whether any clinical and/or biochemical change in WD correlates with any change in these two metallochaperone genes.

Take home message

Direct sequencing for ATP7B mutation analysis in our French WD patients leads to the detection of about 90-95% of the mutated chromosomes. The MLPA assay for detection of large gene rearrangements may be valuable in patients with clinical WD diagnosis where one or no mutations have been identified by sequencing.

No major role can be attributed to Atox1 in the clinical variation of WD. Concerning COMMD1, we need more patients studied to see if COMMD1 variants have any major contribution towards phenotypic heterogeneity observed in WD.

Neurological Wilson's Disease Lethal For the Son, Asymptomatic in the Father.

Denoyer Y, Woimant F, Bost M, Edan G, Drapier S.
Service de Neurologie, CHU Pontchaillou, Rennes, France.

Mov Disord. 2013 Feb 6. doi: 10.1002/mds.25290

Summary

Because of its transmission mode, Wilson Disease (WD) often occurs in siblings more than in consecutive generations, reported solely in offspring. We describe a case of asymptomatic WD diagnosed in an individual several years after disease onset in an offspring. The son, born in 1992, presented with WD in 2009, with progressive neurological symptoms. In 2011 he had severe extensive neurological impairment, bilateral Kayser-Fleischer ring and asymptomatic cirrhosis. He died probably due to dysautonomic cardiac failure. The father (43 years) was unexpectedly found to have asymptomatic WD. His physical examination, hepatic workup and brain MRI were all normal. The patient was a compound heterozygote with an unclassified nonsens variant. In our report, the neurological impairment, consistent with the son's massive brain abnormalities, contrasted with the father's entirely normal clinical examination and brain MRI. The urinary copper hardly reached the pathological range in the father, whereas it was extremely high in the son, which could reflect a more severe alteration in copper excretion and partly account for the difference in the clinical presentation. The father and son had one mutation in common. Additional data is needed to clarify the role of the p.Glu127LysfsX26 (exon 2) variant. As a nonsense mutation, it is likely to have a major clinical impact.

Comments

To our knowledge, this is the first case of asymptomatic WD diagnosed in an individual several years after disease onset in an offspring.

Take home message

Familial screening is necessary not just for the sibship but also for the parents, even if they are asymptomatic.

Agenda 2013
EuroWilson Network

February

February 28th, *Rare Disease Day

April

April 3rd-5th, *1rst Francophone Spring Academies by the Francophone Society for the WD study
Paris – France
TO BE CONFIRMED

April 8-9th, *Wilson Disease Association meeting
Baltimore - USA

May

May 22nd-24th, *5th International FESTEM congress
Avignon - France

Agenda 2013
European Patient Organizations

March

March 9th, *SWITZERLAND

Morbus Wilson annual meeting

For more information please contact:
Mrs Bonny *(bonny.mouchie@bluewin.ch)*

March 23rd, *FRANCE

Bernard Pépin Patient Organization for WD annual meeting

For more information please contact:
Mr Renaud *(srenaud.abpmwilson@orange.fr)*

April

April 13th, *DENMARK

Wilson Patient Foreningen arrangement for young people "The right diet for WD patients"

For more information please contact:
Mrs Nina Tuxen *(nina@tuxen-johansen.dk)*

Agenda 2013
European Patient Organizations

June

June 8th, *GERMANY

Morbus Wilson annual symposium

For more information please contact:
Mrs Kitir *(eva.kitir@morbus-wilson.de)*

July

July 21st, *UK

Wilson's Disease Support Group annual gathering and 3rd AGM

For more information please contact:
Mrs Wheater *(val@wilsonsdisease.org.uk)*

September

September 21st-22nd, *DENMARK

Wilson Patient Foreningen annual meeting

For more information please contact:
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