Wilson Disease Watch

April-June 2012. vol 4

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EuroWilsoN: **E**uropean **W**ilson's **D**isease **N**etwork
Improving information, knowledge and access to expertise and care

This publication arises from the project « APHP FY_2012 » which has received funding from the European Union in the framework of the Health Programme

Edito

Dear readers,

We are happy to present you the « Wilson Disease Watch », 4th edition.

We would like to thank again all the authors of the articles presented in this journal for having submitted abstracts and few comments on their publications.

You will find also the summaries of the two meetings where EuroWilson has attended from April to June 2012:

*The European Conference on Rare Diseases and Orphan Products

*The International Congress of Parkinson's Disease and Movement Disorders

The next edition of the Wilson Disease Watch will be published in October 2012.

Feel free to contact us if you have any new propositions and/or to submit your latest articles published.

We hope you will have the opportunity to join us for the Wilson Disease Centennial Symposium which will be held in London, October 5/6th 2012.

Enjoy the reading!

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Association of dopamine receptor gene polymorphisms with the clinical course of Wilson disease

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Article published in Journal of Inherited Metabolic Disease Reports 2012; DOI 10.1007/8904_2012_163

Summary

Background: Dopamine receptor D2 (DRD2) polymorphisms are proposed to be important factors in the presentation of neuropsychiatric symptoms in many neurodegenerative disorders including decreased striatum levels of dopamine D2 receptors in Wilson's disease.

The aim of the present work was to investigate the possible association between DRD2 gene polymorphisms and clinical manifestation of WD.

Methods: We analyzed data from 97 symptomatic WD patients, investigating the dopamine receptor D2 gene polymorphisms: rs1800497, rs1799732 and rs12364283 and their impact on WD presentation.

Results: Generally, the dopamine receptor D2 gene polymorphisms had no impact on Wilson disease presentation. However, rs1799732 deletion allele carriers with neuropsychiatric symptoms presented earlier onset of WD symptoms compared with individuals without this allele by almost 6 years (22.5 vs. 28.3 years; $p<0.05$). This unfavourable effect of the rs1799732 polymorphism was even more pronounced among adenosine triphosphatase 7B gene (ATP7B) p.H1069Q homozygous patients, in whom carriership of the deletion allele was related to earlier initial neuropsychiatric manifestation by 14 years (18.4 vs.32.2 years; $p<0.01$).

Conclusions: Genetic variation of DRD2, rs1799732 polymorphism, may produce an earlier clinical presentation of Wilson disease neuropsychiatric signs in the course of dopaminergic system impairment due to copper accumulation in the brain.

Comments

We speculate that this effect may be due to the impact of DRD2 polymorphism on dopamine receptor density in striatum.

Take home message

Changes in dopamine receptor density due to genetic variation in DRD2 gene may produce an earlier clinical presentation of neuropsychiatric WD signs in the course of dopaminergic system impairment due to copper accumulation in the brain.

This publication arises from the project « APHP FY_2012 » which has received funding from the European Union in the framework of the Health Programme

Longitudinal analysis of serum miR-122 in a rat model of Wilson's disease

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Article published in Hepatology International 2012, DOI: 10.1007/s12072-012-9348-5

Summary

Purpose

MicroRNA-122 (miR-122) has recently been shown to represent a novel biomarker of liver disease. However, the presence of serum miR-122 after liver injury was mostly studied at singular time points. The course of serum miR-122 was determined at consecutive time points during the onset of disease.

Methods

Fulminant hepatitis was induced by a high-copper diet in Long-Evans Cinnamon (LEC) rats that were used as models for Wilson's disease (WD). Levels of serum miR-122, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and liver histology were determined.

Results

Toxic copper given to isolated hepatocytes induced release of miR-122 into the tissue culture medium. Levels of serum miR-122 were highly elevated (21.9 ± 5) in LEC rats after high-copper diet in fulminant hepatitis, whereas healthy rats showed low (<0.6) baseline levels of miR-122. Levels of miR-122 in the serum of LEC rats after high-copper diet continuously increased for about 4 weeks prior to the onset of fulminant hepatitis. In most of the animals (77.8%), significantly increased levels of miR-122 were detected about 2 weeks (13.7 ± 2 days) earlier as compared to hepatitis-associated serum markers ALT, AST, and bilirubin. Analysis of miR-122 in survivors after cell-based therapy of WD demonstrated a rapid decrease of miR-122 levels following hepatocyte transplantation. miR-122 expression in the serum was normalized to baseline levels in most of the (4/5) survivors.

Conclusion

Our results suggest that longitudinal analysis of miR-122 allows detection of severe liver disease at an early stage and might be excellently suited to monitor therapy, at least when severe liver disease can be restored as observed after cell-based therapy of WD.

Comments

Micro RNA miR-122 is a novel biomarker found in serum that was shown to specifically indicate liver disease. The role of miR-122 during the course of Wilson disease is not known.

Take home message

miR-122 is highly elevated during ongoing disease in the Wilson disease LEC rat model. miR-122 is an excellent marker that can detect early disease caused by high liver copper and may also serve to monitor therapy of Wilson disease patients.

This publication arises from the project « APHP FY_2012 » which has received funding from the European Union in the framework of the Health Programme

Miscellaneous non-inflammatory musculoskeletal conditions. Musculoskeletal conditions associated with Wilson's disease

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Article published in Best Pract Res Clin Rheumatol. 2011 Oct;25(5):627-36

Summary

Wilson's disease (WD) is a rare disease, defined as an autosomal recessive disorder characterised by release of free copper and dramatic accumulation of intracellular hepatic copper with subsequent hepatic and central nervous system abnormalities. Mutations of the ATP7B gene are responsible for the metabolic dysfunction. Small open studies have reported spinal radiological abnormalities including scoliosis, diffuse bone demineralisation, osteochondritis and occasionally fracture. Prevalence of osteoporosis in young adult patients is debated, ranging from 10%, with normal mean Z-score values, to 43% in adults. Past history of spinal or peripheral fractures might be present in 50% of patients. Articular disorders include arthralgias of large joints, such as knee pain, rare effusions, early onset of radiological features of osteoarthritis and associated osteochondritis of the knee joint. Radiological chondrocalcinosis, an unusual feature in young adults, has to be confirmed. Few patients may develop drug-induced lupus with arthralgias, positive anti-nuclear and anti-histone antibodies, secondary to D-penicillamine, the major copper chelator used in WD. In this orphan disease, small retrospective studies cannot allow ascertaining definite WD-related articular and bone manifestations. However, such clinical and radiological abnormalities are occasionally the first symptoms leading to diagnosis. Physicians should be aware that unexplained joint pain and effusion, or even radiological features of osteoarthritis, of the large joints in adolescents could suggest WD and lead to copper survey.

Comments

This paper is original because it underlines that articular or bone mainfestation could be sometimes the first symptoms of Wilson disease.

Take home message

Unexplained joint pain and effusion or feature of ostheoarthitis of the large joints in adolescent must lead to copper explorations to eliminate the diagnosis of Wilson disease.

This publication arises from the project « APHP FY_2012 » which has received funding from the European Union in the framework of the Health Programme

Clinical presentation and mutations in Danish patients with Wilson disease

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Article published in European Journal of Human Genetics (2011) 19, 935–941; doi:10.1038/ejhg.2011.80; published online 25 May 2011

Summary

This study describes the clinical presentation and diagnosis in all Danish patients (49, 41 unrelated) with Wilson disease (WND). On the basis of the number of diagnosed patients from 1990–2008, the prevalence was estimated to be 1:49□500. Among routinely used diagnostic tests, none were consistently indicative of WND, with the exception of the 24-h urine-Cu test, which is always outside the normal range. Mutations were identified in 100% of the screened ATP7B alleles (70 unrelated), including five novel mutations: p.1021K; p.G1158V; p.L1304F; IVS20-2A>G; Ex5_6del. In all, 70% of mutations were found in exons 8, 14, 17, 18, and 20. The most frequent mutation, p.H1069Q, comprised 18%. We propose a new and simple model that correlates genotype and age of onset. By assuming that the milder of two mutations is 'functionally dominant' and determines the age of onset, we classified 25/27 mutations as either severe (age of onset <20 years) or moderate (age of onset >20 years), and correctly predicted the age of onset in 37/39 patients. This method should be tested in other Wilson populations.

Comments

The study describes the WD mutations in a population based study. It illustrates the plurality of mutations in Western Europe. The idea that "least severe" mutation determines phenotype should be tested in other cohorts of WD patients.

Take home message

If the estimated prevalence of 1:49 500 is correct, WD has been severely underdiagnosed in Denmark in past decades.

This publication arises from the project « APHP FY_2012 » which has received funding from the European Union in the framework of the Health Programme

Re-evaluation of the diagnostic criteria for Wilson disease in children with mild liver disease

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Hepatology. 2010 Dec;52(6):1948-56. doi: 10.1002/hep.23910.Epub 2010 Oct 21.

Summary

The diagnosis of Wilson disease (WD) is challenging, especially in children. Early detection is desirable in order to avoid dramatic disease progression. The aim of our study was to re-evaluate in WD children with mild liver disease the conventional diagnostic criteria and the WD scoring system proposed by an international consensus in 2001. Forty children with WD (26 boys and 14 girls, age range = 1.1-20.9 years) and 58 age-matched and sex-matched patients with a liver disease other than WD were evaluated. Both groups were symptom-free and had elevated aminotransferases as predominant signs of liver disease. In all WD patients, the diagnosis was supported by molecular analysis, the liver copper content, or both. A receiver operating characteristic (ROC) analysis of ceruloplasmin at the cutoff value of 20 mg/dL showed a sensitivity of 95% [95% confidence interval (CI) = 83%-99.4%] and a specificity of 84.5% (95% CI = 72.6%-92.6%). The optimal basal urinary copper diagnostic cutoff value was found to be 40 μg/24 hours (sensitivity = 78.9%, 95% CI = 62.7%-90.4%; specificity = 87.9%, 95% CI = 76.7%-95%). Urinary copper values after penicillamine challenge did not significantly differ between WD patients and control subjects, and the ROC analysis showed a sensitivity of only 12%. The WD scoring system was proved to have positive and negative predictive values of 93% and 91.6%, respectively. Conclusion: Urinary copper excretion greater than 40 μg/24 hours is suggestive of WD in asymptomatic children, whereas the penicillamine challenge test does not have a diagnostic role in this subset of patients. The WD scoring system provides good diagnostic accuracy. 13

Comments

This study re-evaluates the conventional diagnostic criteria and the WD scoring system in the specific subset of WD children with mild liver disease (i.e. symptom-free; elevated aminotransferases as predominant signs of liver disease) . In this subset of "asymptomatic" patients, basal urinary copper excretion > 40 μg/24 hours is suggestive of WD , while the penicillamine challenge test does not have a diagnostic role.
The WD scoring system provides good diagnostic accuracy.

Take home message

Urinary copper values after penicillamine challenge do not significantly differ between asymptomatic WD children and age matched control subjects with a non WD hepatopathy.

This publication arises from the project « APHP FY_2012 » which has received funding from the European Union in the framework of the Health Programme

RNA analysis of consensus sequence splicing mutations: implications for the diagnosis of Wilson disease

Lovicu M, Lepori MB, Incollu S, Dessì V, Zappu A, Iorio R, D'Ambrosi M, Pellecchia MT, Barone P, Maggiore G, De Virgiliis S, Cao A, Loudianos G.
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Article published in Genet Test Mol Biomarkers. 2009 Apr;13(2):185-91.

Summary

Wilson disease (WD) is an autosomal recessive disorder caused by a defective function of the copper-transporting ATP7B protein. This results in progressive copper overload and consequent liver, brain, and kidney damage. Approximately 300 WD-causing mutations have been described to date. Missense mutations are largely prevalent, while splice-site mutations are rarer. Of these, only a minority are detected in splicing consensus sequences. Further, few splicing mutations have been studied at the RNA level. In this study we report the RNA molecular characterization of three consensus splice-site mutations identified by DNA analysis in WD patients. One of them, c.51 + 4 A --> T, resides in the consensus sequence of the donor splice site of intron 1; the second, c. 2121 + 3 A --> G, occurred in position + 3 of intron 7; and the c.2447 + 5 G --> A is localized in the consensus sequence of the donor splice site of intron 9. Analysis revealed predominantly abnormal splicing in the samples carrying mutations compared to the normal controls. These results strongly suggest that consensus sequence splice-site mutations result in disease by interfering with the production of the normal WD protein. Our data contribute to understanding the mutational spectrum that affect splicing and improve our capability in WD diagnosis.

Comments

This study identifies three rare consensus sequence splicing mutations of the ATP7B gene, probably resulting in Wilson's disease by interfering with the production of the normal copper transporting ATP7B protein.

Take home message

Missense mutations of the ATP7B gene are the prevalent WD-causing mutations, while splice-site mutations are rarely described.
This study broadens the spectrum of mutations causing WD and improve our ability to diagnose this genetic disease.

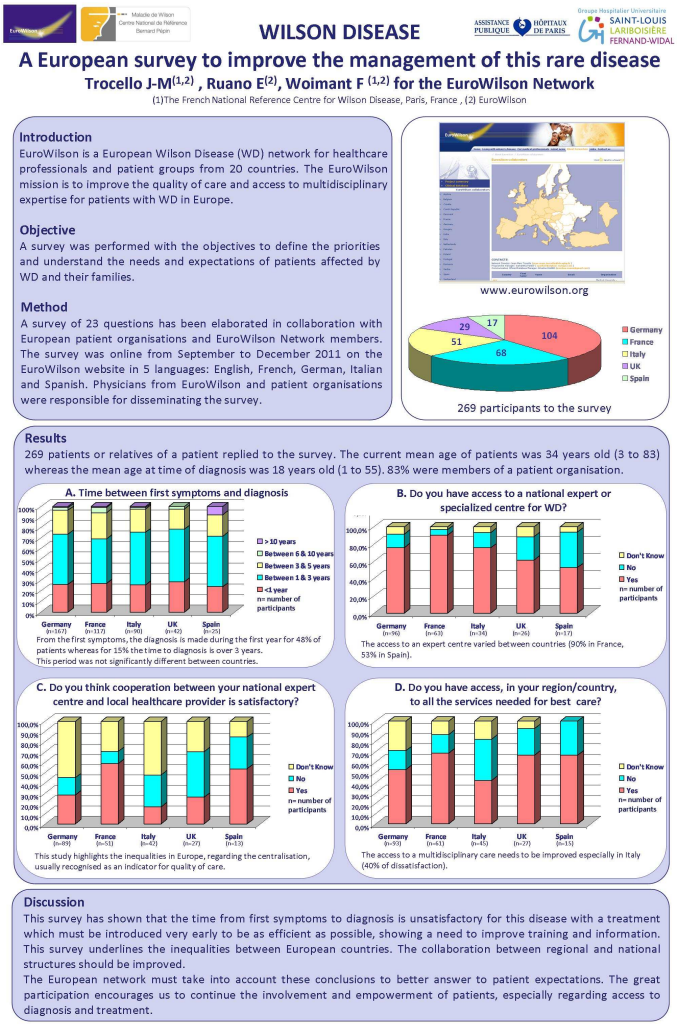
This publication arises from the project « APHP FY_2012 » which has received funding from the European Union in the framework of the Health Programme

The European Conference on Rare Diseases and Orphan Products

May 24/25th, 2012
Brussels, Belgium

The European Conference on Rare Diseases & Orphan Products is the unique platform/forum across all rare diseases, across all European countries, bringing together all stakeholders - academics, health care professionals, industry, policy makers, patients' representatives.
It is a biennial event, providing the state-of-the-art of the rare disease environment, monitoring and benchmarking initiatives.
It covers research, development of new treatments, health care, social care, information, public health and support at European, national and regional levels.
It is synergistic with national and regional conferences, enhancing efforts of all stakeholders. There is no competition with them, but efforts are complementary, fully respecting initiatives of all.
The objectives of the European Conference on Rare Diseases & Orphan Products are:
*To disseminate the most up-to-date health information related to the rare disease environment to all relevant stakeholders (patients and patients' representatives, academics, health care professionals, industry and policy makers);
*To demonstrate the importance of EU actions in the field of rare diseases and review progress made to date;
*To elaborate strategies and mechanisms for developing further exchange of information between stakeholders: people living with rare diseases, volunteers, health professionals, policy makers, researchers and industry at national and EU levels;
*To exchange knowledge and best practices on all relevant health issues related to the rare disease environment;
*To sustain efforts for rare disease policies at both the European and the national level;
*To stimulate dialogue on policies for rare diseases in some of the Member States having recently joined the EU;
*To present specific, achievable objectives at both European and national levels in order to reduce health inequalities for rare disease patients.

EuroWilson presented a poster communication about the 2011 Patient Survey.



This publication arises from the project « APHP FY_2012 » which has received funding from the European Union in the framework of the Health Programme

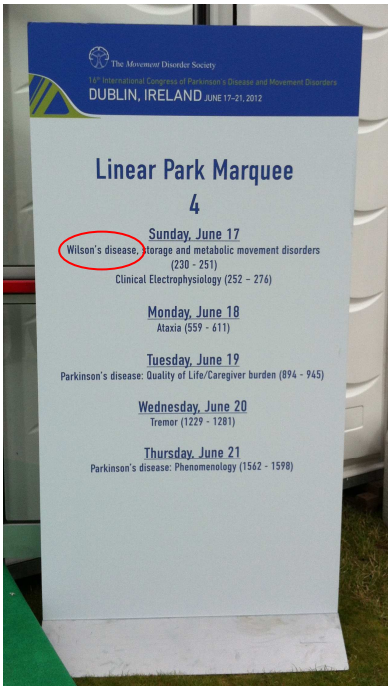
International Congress of Parkinson's Disease and Movement Disorders

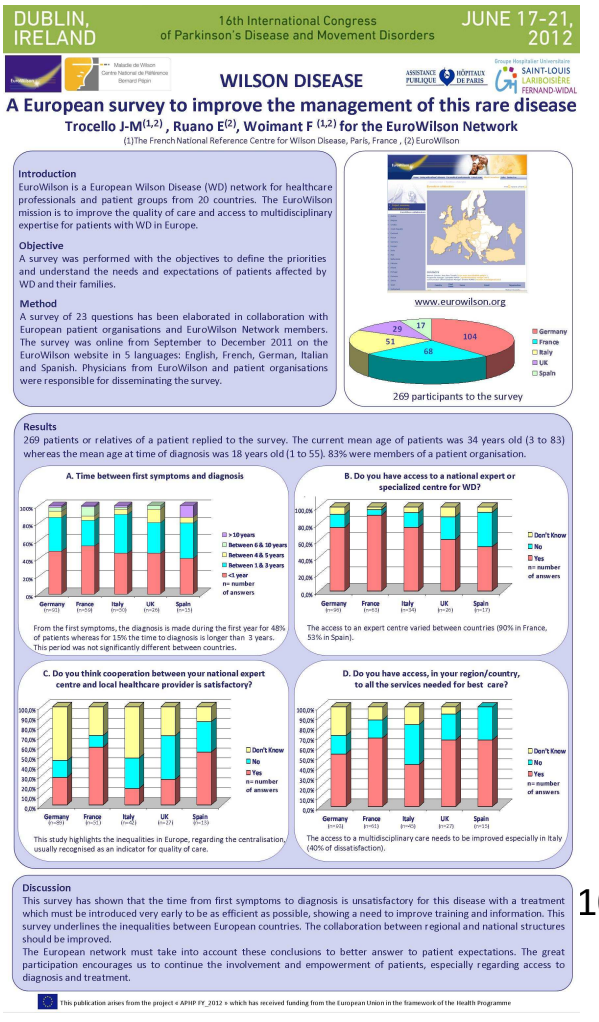
June 17-21th, 2012
Dublin, Ireland

The *Movement* Disorder Society (MDS) was founded in 1985. It is an international, professional society of clinicians, scientists, and other healthcare professionals who are interested in Parkinson's disease, related neurodegenerative and neurodevelopmental disorders, hyperkinetic movement disorders, and abnormalities in muscle tone and motor control. The spectrum of clinical disorders represented by the Society includes, but is not limited to: Ataxia, Blepharospasm, Dysphonia, Dystonic disorders, Gait disorders, Huntington's disease, Myoclonus, Parkinson's disease, Restless legs syndrome, Spasticity, Tardive dyskinesia, Tics and Tourette syndrome, Tremor.

EuroWilson presented a poster communication about the 2011 Patient Survey.

A poster session was dedicated to Wilson disease with more than 10 posters presented.





Agenda 2012

May

May 5th, *Participation to Wilson Disease Congress Valencia, Spain

May 24-25th, *Poster communication in ECRD Congress **Brussels, Belgium**

June

June 17th, *Poster communication in the Movement Disorder Society International Congress **Dublin, Ireland**

July

July 7th, *Participation to the Annual Movement Disorder Society- European Section Summer School for young neurologists
*Presentation and case report of 2 Wilson Disease patients
Paris, France

September

September 5th, *Poster communication in SSIEM Congress **Birmingham, UK**

October

October 5/6th, *Wilson's Disease Centennial Symposium **London, UK**

October 8/9th, *Oral presentation to the International Workshop Rare Diseases and Orphan drug registries **Rome, Italy**

November

November 8/9th, *Oral communication in ICNE Congress **Nice, France**

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