Wilson Disease Watch
January-March 2012. vol 3

- New articles: Summary and comments.
- Proposition of research on Wilson Disease
- Minutes of Patient Representatives meeting 2012
- Minutes of Follow Up Meeting 2012
- Agenda

EuroWilsoN: European Wilson’s Disease Network
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
Dear readers,

We are happy to present you the latest « Wilson Disease Watch ». We would like to thank all the authors of the articles presented in this journal for having submitted abstracts and few comments on their publications. In addition, we suggest you a proposition of research made by a Serbian Physician, Dr S. Kazic, member of EuroWilson consortium. Finally, you will find the summaries of the two meetings organized at the beginning of 2012; the European patient representatives meeting and the follow up meeting about the European database.

The next edition of the Wilson Disease Watch will be published at the beginning of July 2012. Feel free to contact us if you have any new propositions and/or to submit your latest articles published.

Enjoy the reading!

Dr Jean-Marc Trocello  
EuroWilson Network Director

Emeline Ruano  
EuroWilson Communication Officer

emeline.ruano@gmail.com
Wilson disease (WD) is an autosomal recessive inherited disorder of copper metabolism. Failure to diagnose WD can be dramatic leading to irreversible damages. The molecular genetic analysis of ATP7B gene is the reference test for diagnosis but the number of reported mutations of the ATP7B gene is on the rise. The analysis is cumbersome and requires tedious work. Other clinical and biological tests are proposed but it is often difficult to interpret some patients’ results. A rapid and reliable biological test for WD diagnosis is still needed. Analytical reliability of Exchangeable copper (CuEXC) determination procedure is examined by studying the repeatability, the short term stability and stability in frozen serum. Relative exchangeable copper (REC=CuEXC/total copper%) is proposed and evaluated as a new diagnostic test and compared to classic tests used for WD diagnosis. Sixteen new Wilson disease patients were diagnosed in our institution between January 2009 and May 2011. The different biological tests used for WD diagnosis yielded lower sensitivity and specificity compared to our new biomarker, the REC. We show that REC is an excellent discriminatory tool for the diagnosis of WD offering 100% sensitivity and 100% specificity.

Comments

To determine free copper was still a goal for diagnosis or follow up. The relative exchangeable copper open a new way to evaluate « potential toxic copper ».

Take home message

REC seems to be an excellent discriminatory tool for the diagnosis of Wilson Disease.
Gender differences in Wilson’s disease.
Litwin T.*, Gromadzka G. /***, Członkowska A. /***
*2nd Department of Neurology, Institute Psychiatry and Neurology, Warsaw, Poland
**Department of Experimental and Clinical Pharmacology, Medical University, Warsaw, Poland.

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


Summary

**Background:** Wilson’s disease (WD) is a rare autosomal recessive disorder of copper metabolism. Although very well documented in many other neurological and liver disorders, gender has not been directly addressed in WD, so the aim of this study was to assess gender related differences in WD.

**Methods:** We analyzed data on 627 consecutive WD patients entered into our registry between 1958 and 2010.

**Results:** We observed a male predominance in Polish population of WD patients (327 males vs. 290 females). At disease diagnosis, 510/627 patients were symptomatic. The neuropsychiatric form occurred predominantly in men versus women (209/278 vs. 136/232), especially the rigidity-tremor (71/111 vs. 40/111), rigidity (23/33 vs. 10/33), and psychiatric forms (46/71 vs. 25/71). The hepatic form occurred more frequently in women (96/165 vs. 69/165), and women developed the neuropsychiatric form almost 2 years later than men (29.4 vs. 27.1 years).

**Conclusions:** We speculate these differences may be due to the protective effect of estrogens and are associated with iron metabolism.

Comments

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

Take home message

There are gender differences in Wilson disease presentation, especially according to clinical presentation – neuropsychiatric signs occur more frequently and earlier in men and hepatic signs occur more often in women.
Apolipoprotein E gene (APOE) genotype in Wilson’s Disease: impact on clinical presentation

Litwin T.*, Gromadzka G.**/ Członkowska A.**

* II Department of Neurology, Institute Psychiatry and Neurology, Warsaw, Poland
** Department of Experimental and Clinical Pharmacology, Medical University, Warsaw, Poland


Summary

Background: Wilson’s disease (WD), an inherited copper metabolism disorder that leads to pathological tissue copper accumulation and secondary organ damage, is caused by mutations in the ATPase 7B gene (ATP7B). The reason for the high variability in phenotypic expression of WD is still unknown. There is a documented association between the apolipoprotein E gene (APOE) ε4 allele and the risk of many neurological disorders but in WD data were conflicting so far. So the aim of this study was to evaluate the impact of APOE genotype on the variability of WD phenotypic expression.

Methods: We analyzed data on 383 WD consecutive patients in the WD registry. The APOE genotypes (APOE ε3/ε3 (wild-type), APOE ε2-positive, and APOE ε4-positive) and their impact on the phenotypic WD presentation was assessed in all symptomatic WD patients, as well as in patient subgroups divided according to sex and ATP7B genotype.

Results: APOE genotype had no impact on WD presentation in the general population of Polish symptomatic WD patients. However, APOE ε4-positive women tended to present WD symptoms earlier than women possessing the wild-type APOE ε3/ε3 genotype (24.2 vs. 27.9 years). The effect of the APOE ε4-positive genotype was more pronounced in ATP7B p.H1069Q homozygous women, in whom disease symptoms started almost 6 years earlier (23.6 vs. 29.9 years) than in APOE ε3/ε3 women.

Conclusions: In women, APOE ε4-positive genotype is associated with earlier onset of WD symptoms, particularly among ATP7B p.H1069Q homozygous patients.

Comments

Because of conflicting data, the present study was performed to verify the APOE impact on Wilson disease presentation.

Take home message

APOE ε4-positive genotype seems to be another important factor which has impact on WD presentation but this effect is restricted only for women.


Source
Department of Internal Medicine, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium.

Summary

BACKGROUND AND STUDY AIMS:
Detailed data on long-term effectiveness of various drug therapies in Wilson's disease (WD) are lacking. Therefore, we retrospectively reviewed our patient cohort treated with D-penicillamine.

PATIENTS AND METHODS:
This study reports on the clinical presentation, the diagnostic evaluation, and the disease course in 24 WD patients treated long-term (15+/-12 years, between 1969 and 2009) with D-penicillamine.

RESULTS:
The overall survival in our cohort was 91.6%. Twenty-two of 24 patients had liver disease at presentation, 17 of 24 patients (71%) had cirrhosis, 11 of whom had complications of cirrhosis. Six of 11 of these patients showed hepatological improvement (five of six) or stabilization (one of six), three of 11 were transplanted, one of 11 died, one of 11 discontinued follow-up. In the six of 17 cirrhotic patients without complications, improvement (four of six) or stabilization (two of six) occurred. Of all other patients (seven of 24), five of seven showed improvement (three of five) or stabilization (two of five), hepatological deterioration occurred only in one patient due to poor therapy compliance and one of seven discontinued follow-up. Neuropsychiatric symptoms were present in 13 of 24 at presentation and resolved in one of 13, decreased in seven of 13, stabilized in four of 13 and worsened in one of 13 patients (due to poor compliance). In general, we observed a favorable hepatological and neurological evolution with D-penicillamine.

CONCLUSION:
Despite the presence of liver disease or neuropsychiatric symptoms at baseline in all but one of the patients, we report beneficial results on liver and neurological disease after very long-term treatment with D-penicillamine, thereby adding to its reputation as 'first-line' therapy in WD.

Comments

In this retrospective single centre analysis of long-term data on D-penicillamine treated patients, we demonstrate that the liver damage in Wilson’s disease stabilises or even regresses under D-penicillamine treatment, while treatment failure, adverse events and neurological progression do not appear a major impediment to long-term D-penicillamine treatment.

Take home message

D-penicillamine is a reasonably safe, well tolerated and effective treatment for a very large majority of Wilson’s disease patients, in our hands.
Iron metabolism and the role of HFE gene polymorphisms in Wilson disease

Jan Pfeiffenberger¹, Daniel N. Gotthardt¹, Thomas Herrmann¹,², Jessica Seeßle¹, Uta Merle¹, Peter Schirmacher³, Wolfgang Stremmel¹ and Karl Heinz Weiss¹

¹ Department of Gastroenterology, University Hospital Heidelberg, Heidelberg, Germany
² Klinikum Idar-Oberstein GmbH, Idar-Oberstein, Germany
³ Department of Pathology, University Hospital Heidelberg, Heidelberg, Germany

Summary

Wilson disease (WD) is a rare inherited disorder of copper metabolism, which can lead to severe liver failure and to a variety of neuropsychiatric symptoms. Previous animal studies and case reports suggest that hepatic iron overload and alterations in iron processing are associated with WD. The aim of this study was the assessment of iron metabolism and of the frequency of the most common HFE gene polymorphisms in WD patients.

PATIENTS AND METHODS:
Data from 143 patients with WD were analysed. Clinical presentation, liver function and iron metabolism parameters were recorded. Blood samples of the patients were analysed for HFE gene alterations (H63D; C282Y). Twenty-seven liver biopsies of these patients were studied with regard to iron content and fibrosis score.

RESULTS:
Contrary to previous reports of HFE gene polymorphisms in WD patients, in our cohort the allele frequencies (C282Y: 2.1%; H63D: 7.3%) were in line with frequencies obtained for general population. Male WD patients with decreased serum ceruloplasmin (Cp), showed increased serum ferritin levels. Hepatic iron content was normal in most cases.

DISCUSSION:
Male patients with very low Cp serum concentrations showed slightly elevated median serum ferritin concentrations, probably related to lack of ferroxidase activity. However, in consideration of absolute numbers of ferritin concentrations, these changes seem to be of minor clinical relevance.

Comments

The role of iron in the pathogenesis of Wilson disease is still not finally elucidated. Like other recent studies from the Członkowska group our result show gender specific differences in clinical presentation.

Take home message

Changes in parameters of iron metabolism are a new finding especially in male patients. However, so far no relevant hepatic iron overload has been reported.
Musculoskeletal conditions associated with Wilson’s disease

Anne-Sophie Quemeneur a,1, Jean-Marc Trocillon c, Hang-Korng Ea a,b,d, France Woimant c, Frédéric Liotta c,a,b,d,2

a AP-HP, Service de Rhumatologie, pôle appareil locomoteur, Hôpital Lariboisière (Assistance Publique-Hôpitaux de Paris), F-75010 Paris, France
b Uln, Paris Ouest, Seine-Saint-Denis, France
c AP-HP, Centre Hospitalier Universitaire, Hôpital Lariboisière, F-75010 Paris, France
d Inserm, UMR-S 606, Hôpital Lariboisière, F-75010 Paris, France

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

Only small open studies have been focussed on musculoskeletal abnormalities in Wilson disease.

This review realizes a state of the art of this subject.

Take home message

Unexplained joint pain of osteoarthritis of the large joints in adolescents should lead to copper survey.
Repeated Transplantation of Hepatocytes Prevents Fulminant Hepatitis in a Rat Model of Wilson’s Disease

Vanessa Bauer,1 Ramsi Siaj,1 Sandra Stüppeler,2 Ralf Bahde,2 Hans-Ulrich Spiegel,2 Gabriele Köhler,3 Andree Zibert,1 and Hartmut H.-J. Schmidt1
1Clinic for Transplantation Medicine, 2Department of Surgical Research, Clinic for General and Visceral Surgery, and 3Gerhard Domagk Institute for Pathology, Münster University Clinic, Münster, Germany

Summary

The outcome of consecutive hepatocyte transplants was explored in a rat model of Wilson's disease before the onset of fulminant hepatitis without preconditioning regimens. Rats received a high-copper diet in order to induce a rapid induction of liver failure. Sham-operated rats (15/15) developed jaundice and fulminant hepatitis, and they died within 4 weeks of first transplantation. Despite the continuation of a high dietary copper challenge, long-term survival was observed for a notable proportion of the transplanted animals (7/18). All survivors displayed normalized levels of hepatitis-associated serum markers and ceruloplasmin oxidase activity by posttransplant days 50 and 98, respectively. The liver copper concentrations, the liver histology, and the expression of marker genes were significantly restored within 4 months of transplantation in comparison with the control group. The high expression of a copper transporter gene (ATPase Cu++ transporting beta polypeptide) in the livers of the survivors indicated a high rate of repopulation by donor hepatocytes. Our data suggest that repeated cell transplantation can overcome the limitations of a single therapy session in rats with severe hepatic disease by functionally restoring the host liver without preconditioning.

Comments

Establishment of an animal model to investigate the full impact of cell based therapy is an important issue of the current research in the area of Wilson disease. Such work is the basis to explore the therapeutic efficacy of hepatocytes and/or stem cells for future management of patients.

Take home message

Repeated hepatocyte transplantation can prevent fulminant hepatitis in a novel dietary-copper induced rat model of Wilson disease even when potential harmful preconditioning is not involved.

This publication arises from the project « APHP FY_2012 » which has received funding from the European Union in the framework of the Health Programme.
INTRODUCTION:
Wilson disease (WD) is an inherited disorder of human copper metabolism, characterised by accumulation of copper predominantly in the liver and brain, leading to severe hepatic and neurological disease. Interesting findings in animal models of WD (Atp7b-/- and LEC rats) showed altered lipid metabolism with a decrease in the amount of triglycerides and cholesterol in the serum. However, serum lipid profile has not been investigated in large human WD patient cohorts to date.

PATIENTS AND METHODS:
This cohort study involved 251 patients examined at the Heidelberg and Dresden (Germany) University Hospitals. Patients were analysed on routine follow-up examinations for serum lipid profile, including triglycerides, cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL). Data on these parameters at time of diagnosis were retrieved by chart review where available. For statistical testing, patients were subgrouped by sex, manifestation (hepatic, neurological, mixed and asymptomatic) and treatment (D-penicillamine, trientine, zinc or combination).

RESULTS:
A significant difference in total serum cholesterol was found in patients with hepatic symptoms, which diminished under therapy. No alterations were observed for HDL, LDL and triglycerides.

CONCLUSION:
Contradictory to previous reports using WD animal models (Atp7b-/- and LEC rats), the most obvious alteration in our cohort was a lower serum cholesterol level in hepatic-affected patients, which might be related to liver injury. Our data suggested unimpaired cholesterol metabolism in Wilson disease under therapy, independent of the applied medical treatment.

Summary

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

An 11-year-old boy was treated since 6-years-old with methylphenidate for combined attention deficit and hyperactivity disorder. At age nine his behaviour had worsened and he started to have phobias. One year later persistent hypertransaminasemia was found. Physical examination showed a dysdiadochokinesia. Laboratory investigation revealed a low caeruloplasmin and augmented basak urinary copper with a positive postpenicillamine test. Liver biopsy showed high liver copper (853 µg/g) and brain MRI was normal. D-penicillamine and zinc acetate were started without side effetc. ATP7B gene mutation was confirmed after treatment initiation.

Comments

Abnormal transaminases in a boy receiving chronic medication for hyperactivity disorder could suggest toxic hepatitis. However, children and adolescents are increasingly using methylphenidate and reports on toxicity are scarce. Drug discontinuation also didn’t improve LFT’s. Phobia and movement disorder were described in less than 7% of children with Wilson disease, as a presenting symptom. The association with persistent hepatitis lead us to exclude Wilson disease.

Take home message

Wilson disease should be screened and ruled out by appropriate score in children and adolescents with psychiatric manifestations, with or without associated attention deficit disorder.
In patients who suffer from Wilson’s disease abnormalities in structure of hepatic mitochondria consisting of alteration in mitochondrial shape and content as well as appearance of giant mitochondria, which decrease or disappear with initiation of decoppering therapy were noted a long time ago (Sternlieb et al., Gastroenterology 1976;71(3):457-61). Our study pointed that in patients with Wilson's disease same morphological abnormalities of mitochondria do exist in skeletal muscles (Kazic S et al., Journal of Hepatology 1997;vol 26/suppl 1:309).

Presence of these specific abnormalities of mitochondrial structure in skeletal muscle cells and hepatocytes in patients with Wilson’s disease forces us to consider two possibilities. One is that in basal ganglia neurons, which are commonly affected in Wilson’s disease, such morphological changes might also exist. The second is that such morphological abnormalities might have an effect on mitochondrial function, particularly on the activity of respiratory chain complexes which provide energy for cell function. One recent study in animal model of Wilson’s disease has confirmed that severe dysfunction of respiratory chain and cholesterol metabolism exists in this model (Sauer SW et al., Biochim Biophys Acta 2011;1812(12):1607-15). However, neither studies of mitochondrial morphology in basal ganglia cells nor studies of mitochondrial function of any sort of cells in humans with Wilson’s disease have been performed yet.

One of major problems in the treatment of patients with Wilson’s disease is the fact that decoppering therapy results in normalization of neurological function only in a minority of patients, but in majority of patients, despite achieved improvement, some form of neurological deficit, most commonly in the form of dysarthria, still exists. If mitochondrial abnormalities are the cause of mitochondrial dysfunction and low activity of respiratory chain in mitochondria, there is a possibility that persistence of neurological deficit in such patients reflects not only neuron loss, but and low mitochondrial energy production in neurons and possibly skeletal muscles as well. In this case, activity of respiratory chain complexes II,III and IV and mitochondrial energy production might be stimulated with supplementation of ubi quinone (coenzyme Q10) which plays a role in mitochondrial respiratory chain. In other words, if our hypothesis is correct, ubiquinone supplementation might increase cellular energy production and decrease neurological deficit.

We invite all our colleagues at EuroWilson to join us and create detailed plans of a study of respiratory chain activity in skeletal muscle cells in patients with Wilson’s disease as well as clinical trial with coenzyme Q10 supplementation in those patients with Wilson’s disease who, despite being successfully treated with decoppering therapy still have some form of neurological deficit left. We can as a group apply for EU funding for financing this project.

Yours very truly
Slobodan Kazic
kazic@scnet.rs
Jelena Popovic

This publication arises from the project « APHP FY_2012 » which has received funding from the European Union in the framework of the Health Programme
This year, the patient representatives meeting took place in Munich (Germany), on Thursday March 8th 2012. We would like to thank Eva Kitir from “Morbus Wilson” organization who welcomed us in Munich and helped us to organize the meeting there.

PARTICIPANTS

Mrs Helga BONNY – Switzerland
Mr Salvatore DILORENZO – Italy
Mr Claude GAY – France
Mrs Eva KITIR – Germany
Mr Rupert PURCHASE – UK
Mr Serge RENAUD – France
Mrs Emeline RUANO – France
Mrs Anne-Marie STYLES – UK
Dr Jean-Marc TROCELLO – France
Mr Jerry TUCKER – UK

Apologised participants:
Mrs Regine BIELECKI – Germany
Mrs Amparo MAUDOS - Spain

MINUTES OF THE MEETING

Dr Jean-Marc Trocello wanted to introduce the meeting with a tribute to Torben Gronnebaek who died on Saturday 18 February at the age of 58. He was member of the EURORDIS’ Board of Directors since 2003, representing Rare Disorders Denmark. He was also part of the executive board of EuroWilson.

1/Presentation of the patient survey 2011 results

We can consider the survey has been a success with a great participation (269 participants) from 5 European countries.
The survey shows the real inequalities between European countries in terms of health care.
The results can be considered as a work basis for EuroWilson to set up objectives and help European countries to improve themselves according to their own difficulties. It allows us to define better patient priorities.
The results are online on www.eurowilson.org.

2/Presentation of the objectives of the patient survey 2012

*To begin earlier the realization of the survey
*To empower patients since the beginning of the project
*To focus questions about specific subjects
3/Presentation of each patient organization’s suggestions about the new patient survey
Each patient organization proposed themes/topics which can be developed in the 2nd patient survey. The main topics which have been discussed were:
* The disease at time of diagnosis
* The treatments in Wilson Disease
* Quality of life of the patient – Socio-professional aspects
* Women and Wilson Disease
* Information about Wilson Disease

4/Elaboration of the patient survey 2012
After a great discussion, it has been decided that 2 main topics will be developed this year: The disease at time of diagnosis and the treatments in Wilson Disease. We hope we will have funds in 2013 in order to set up a new questionnaire with the other topics.
The set up of the questionnaire is in progress.

MILESTONES
BACKGROUND OF THE MEETING
The meeting has been organized in Lariboisière Hospital in Paris (France), by Dr Jean-Marc Trocello, network director of EuroWilson.
The EuroWilson members who wanted to participate to a Wilson Disease patient follow up needed to meet together in order to decide what sort of documents could be proposed to the European physicians to obtain follow up data of their patients.

PROPOSITIONS
It has been decided to complete initial data and to send a new document to collect up to date data for patients newly diagnosed from 2005 to 2009.
Dr Carla Lloyd, Hepato-pediatrician from Birmingham Children Hospital (UK) has chaired the working session and proposed the following agenda:

*End of March/Early April: Dr Carla Lloyd submits to the other participants a first version of the follow up documents. The participants are free to discuss about the different selected items by email.
*April 15th: Validation of the follow up documents and beginning of the sending out of the forms to all the centers concerned.
*June 15th: End of data collection. Start of data analysis.
Agenda 2012

February
February 28th, Rare disease day

March
March 8th, Patient Representatives Meeting
March 27th, Follow Up Meeting

April
April 3-6th, Journées de Neurologie de Langue Française
Club des Mouvements Anormaux

May
May 24-25th, Poster communication in ECRD Congress

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

July
July 5-6th, Summer School of Movement Disorder Society
Presentation and case report of 2 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