

## Newsletter

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### Wilson's disease: Creating a European clinical database and designing randomized controlled clinical trials

(December 2008)

The current phase of the EuroWilson project, supported by the European Union FP6 funding, was completed on 31 August 2008, and we have submitted a report to the Commission (see summary below).

The database is continuing. It has some interim funding, and we will be applying for a further substantial grant in 2009. The original reason for setting up the database was to assess the feasibility of clinical trials. That has been achieved, and as you will see from the summary, Prof Roderick Houwen and colleagues are making progress in planning two trials. The database is a very valuable resource not only for these trials, but also in generating a lot of information about the epidemiology of Wilson's disease in Europe, the treatments which are being used, and outcomes. Several publications are in progress:

- The challenges of developing a European database
- Wilson Disease: the European experience
- Systematic review of the treatment of Wilson's disease
- Pseudoautosomal dominant inheritance in patients with Wilson's disease

In May or June of 2009, EuroWilson will be organizing their third SCC meeting. The emphasis of this meeting will be on outcomes on the progress of the cohort of patients which we have documented.

Summary of the EuroWilson project:

1. A database has been established to record details of patients with Wilson Disease (WD) presenting in Europe since January 1st 2005. It may also be used by individual clinicians or centres, or national bodies such as GeneMove or the Centre National de Reference Bernard Pepin pour la Maladie de Wilson, to record their own cases, including those diagnosed before January 1st 2005 ("retrospective cases"). The primary objective is to assess the feasibility of clinical trials in WD.
2. 86 Specialist Country Coordinators (SCCs) in 20 countries have been appointed.
3. SCCs use a web-based protocol using secure CPS cards and card readers to enter data. Clinicians may send patient details on a paper form to SCCs or to the EuroWilson office. Information sheets for patients and families and consent forms are available on line in many languages.
4. A neurological clinical rating score was validated and published. A training DVD on this scoring system has been produced.
5. The Genetics workpackage leader collaborated with the European Molecular Quality Network in an audit of laboratories undertaking molecular diagnosis of WD. The second round of audit in 2007 showed an improvement from 2006.
6. A Best Practice in molecular diagnosis meeting held in Paris, June 2007 was an opportunity to discuss techniques, nomenclature and distinguishing between DNA sequence changes which are disease-causing from those which are benign polymorphisms. Best practice guidelines are being submitted for publication.
7. There were 523 family pedigrees recorded by October 2008. The number of patients satisfying our diagnostic criteria and diagnosed after 1st of January 2005 was 347.
8. The database is yielding information on epidemiology, spectrum of disease, current treatment choices, and frequency of mutations which for the first time gives all-age data for a large population.
9. The apparent incidence is higher in central than in western European countries. This is partly due to the higher prevalence of the most common WD mutation, H1069Q, in Eastern Europe. However even allowing for this genetic difference the incidence is higher in the east.
10. The mean age of presentation was 20.7 years but cases presented as early 0.2 years and as late as 57.5 years. Those patients homozygous for H1069Q were significantly older than the remainder. Those with neurological features were significantly older at presentation (mean age 26.7 years) than those without (mean 17.6 years). There was no relationship between the age of presentation and the severity of neurological abnormality, or between the age of presentation and the severity of hepatic abnormality.
11. Penicillamine was the commonest initial treatment. Discussion with country coordinators showed that this was due to its availability and relative low cost rather than this being an evidence based clinical decision. In 23 patients a change of drug was documented. The doses used varied widely, being in many cases above or below those recommended.
12. We are learning about early cases of symptomatic Wilson's which has implications concerning treatment in those diagnosed through early screening of established mutations.
13. The RCT group has repeated its literature survey and confirmed that trials remain not only feasible but necessary and justifiable. Two trials are proposed; an RCT of penicillamine versus trientine in patients with neurological disease and an RCT of zinc versus penicillamin in patients with mild hepatic disease. A study of amitriptyline in patients with severe liver disease is under consideration.
14. There has been considerable interest in EuroWilson from outside Europe, resulting in active participation from Croatia, Turkey and India. India and Turkey are entering mostly paediatric cases due to the strong links within paediatrics, and these two countries may be partners in the paediatric trial.

Newsletter

News

15. EuroWilson is managed from an office in Sheffield UK, with a Programme Manager based in Paris. There are 5 salaried part-time staff; the Coordinator, consortium members, and SCCs are honorary. An Oversight Committee with strong patient representation oversees the work of the consortium, and has stimulated patient involvement and interaction with other European clinical databases.
16. Communications are maintained by: a monthly Newsflash to SCCs and a quarterly Newsletter to contacts; the website; availability of a Project Officer to answer queries; weekly Skype conferences of the management team; many emails.
17. The public website receives many hits and generates enquiries from patients and clinicians, many of which demonstrate the continuing need for expertise and information about WD.
18. The effort which has been spent in establishing the EuroWilson database, and the data which are now accruing from it, are powerful reasons for continuing the database beyond October 2008. Follow-up data on this well documented cohort will be invaluable.