Epidemiological features and socioeconomic burden of childhood Wilson Disease

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Abstract: Wilson Disease is a rare autosomal recessive disorder of copper metabolism with a disabling chronic evolution. This condition requires lifelong treatment of the patient. Positive diagnosis is hard to establish due to the fact that a single test alone does not provide certainty. After the diagnosis is established the chelating treatment must be started. Delaying the treatment can be fatal to the patient. The socioeconomic factor is very important during the diagnostic stage and monitoring of the patient. In special literature, this subject is not addressed. This factor must not be ignored, especially in Romania. The purpose of this paper is to highlight the costs generated by the diagnosis and treatment of Wilson Disease in South-Eastern Romania taking into consideration the main research results of a study elaborated in the "Grigore Alexandrescu" Emergency Hospital for Children, in Bucharest, between January 2004 and December 2014.

Keywords: children Wilson Disease, rare disease, socioeconomic, medico economic

JEL Classification: I10, I15

Introduction

Wilson disease (WD) is a rare autosomal recessive inherited disorder of copper metabolism that is characterized by excessive deposition of copper in the liver,

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brain, and other tissues. WD is a chronic and progressive condition and is often fatal if not recognized and treated when symptomatic. If untreated, Wilson disease invariably results in severe disability and death. The treatment of Wilson disease is based on the use of copper chelators to promote copper excretion from the body, or the use of zinc to reduce copper absorption. Liver transplantation is indicated for patients with liver failure that are unresponsive to medical treatment. Compliance is a very important issue for patients with this disease, because the treatment is lifelong and is burdened by severe side effects.

Wilson Disease also known as hepatolenticular disorder was first described by S.A. Kinnier Wilson in his doctoral thesis published in *Brain* magazine in 1912 (Wilson SAK, 1912). It is a severe inherited condition of copper metabolism, caused by mutations in ATP7B gene, which is located on chromosome 13 and it is expressed predominantly in the liver (Bull, P.C., 1993). More than 500 mutations have been described in pathogenesis of Wilson Disease. ATP7B is expressed in various tissues, including liver, central nervous system, kidney, mammary glands, and others (Lutsenko, S., 2007). The major role of ATP7B is in copper's metabolism homeostasis. Mutations in this gene results in low biliary excretion of copper and leads to its accumulation in the liver, brain, cornea and kidneys with consequent pathologic changes in these organs. Knowledge of the clinical presentations and treatment of WD are important both to the generalist and to specialists in gastroenterology and hepatology, neurology, psychiatry, and paediatrics.

The main purpose of this paper is to review the current evidence on the economic costs and consequences of chronic evolution of Wilson Disease in general, with a special emphasis on Romania's case study.

We try to analyze some aspects of childhood Wilson Disease including: main characteristics of patients diagnosed with WD, diagnostic tools and screening methods, and also we intend to treat some socioeconomic features of this condition. We present the results of an ongoing study which aimed to evaluate the socioeconomic features of Romanian pediatric patients with WD.

Epidemiology

The incidenece of WD is more common than previously expected and can rich 1 in 30000. The disease may be diagnosed at any age, especially in children and young adults, but may be present simptomatically at any age, although the majority of pstients are diagnosed between ages 5 and 35. It is esentialy to screen the family of WD patients beacause the chance of a sibling being a homozygote and therefore developing clinical disease is 25% (Ferenci, P., 2005).

The prevalence of WD is estimated at one in 30,000 for the major part of populations, with a carrier frequency in the general population of one in 90 (Olivarez, L., 2001). Recent studies suggest a prevalence as high as one in 10,000 (Coffey, A.J., 2013).

Patients with rare diseases generally suffer from an insufficient supply of medical care and medications, due mainly to the low prevalence and low knowledge of these diseases (Drummond, M.F., 2007).

Compared to widespread conditions affecting hundreds of millions of people, rare diseases can lack similar levels of interest amongst the general public and medical research communities. Most of these individual diseases receive little attention because they affect only thousands – or sometimes only hundreds – of patients worldwide (WHO, 2013).

Due to the relatively low prevalence of rare diseases, the private sector tends to view the development of treatment for them as economically unattractive, which msy be a cause of unequal access between patients with rare comparative to common diseases (Denis, A., 2013).This special characteristic of WD has to be assisted from public health providers.

Clinical presentation of Wilson Disease

As a multisystemic disorder, WD is characterised by a large spectrum of simptomes: hepatic (asymptomatic hepatosplenomegaly, persistently elevated serum aminotransferase activity AST and ALT, fatty liver, subacute or chronic hepatitis, cirrhosis: compensated or decompensated, acute liver failure); neurological: movement disorders (tremor, involuntary movements), drooling, dysarthria, rigid dystonia, pseudobulbar palsy, migraine headaches, insomnia, seizures; psychiatric manifestations: depression, neurotic behaviours, personality changes, psychosis. Ocular signs: Kayser-Fleischer rings, sunflower cataracts can be present. Other manifestations: cutaneous – lunulae ceruleae, renal abnormalities: aminoaciduria and nephrolithiasis, skeletal abnormalities – premature osteoporosis and arthritis, cardiomyopathy, dysrhythmias, pancreatitis, hypoparathyroidism, menstrual irregularities; infertility, repeatedmiscarriages. (Balistreli, W.F., Carey, R.G., 2011)

The diagnosis of WD is difficult to establish because there is not a single test that can rule out or confirm the diagnosis with certitude. Several tests are required including: ophthalmologic slit lamp examination for Kayser-Fleischer rings (copper rings around the eyes), neurologic examination, serum ceruloplasmin and serum copper blood tests, 24-hour urine copper test, liver biopsy for

histology and histochemistry and copper quantification, genetic testing, haplotype analysis for siblings, and mutation analysis. Failure to diagnose WD can be dramatic causing to severe complications.

A lot of factors are involved in delaying the diagnosis establishment. Among these factors, the economic aspect plays a very important role. Some investigations needed for the diagnosis are very expensive and are not being covered by the health insurance company.

The genetic analysis of ATP7B gene is the reference test for the diagnosis but is expensive and requires precise and careful work (El Balkhi S, 2011). Although this analysis is avaiable, its costs are very high in Romania. Costs for detection of the most frequent mutations are: 120-150 euro (500-700 RON) and entire gene sequencing cost is about 1500 euro (about 7500 RON) in our country. The limitation to molecular testing (aside from availability and cost) has been the ability to identify all the affected alleles in suspect individuals, and in many studies only about 65% of all affected alleles were identified in patients with an appropriate phenotype. (Davies, L.P., 2008)

Recent studies proposed two new biomarkers, both with high sensitivity and specificity: Relative exchangeable copper (El Balkhi, S., 2011) and Urinary copper/Urinary zinc ratio (Wang, J., 2010). If these biomarkers prove to be efficient they could provide a viable alternative for diagnosing and follow-up. Relative exchangeable copper and Urinary copper/Urinary zinc ratio can be powerful diagnosing tools, replacing many of the tests used today for WD. The result of implementing these biomarkers will be a reduction in both time and costs.

Early diagnosis and treatment are mandatory in order to reduce the number of complications. Furthermore, early diagnosis allows the doctor to treat the patient before the complications become disabling and affect the patient's quality of life. An important tool for early diagnosis is the screening of first degree relatives of a patient diagnosed with WD.

Literature review

Complementary to clinical or epidemiological approaches to disease assessment, the analysis of the economic impact can address a number of questions concerning the consequences of disease on long, medium an short terms.

The socio-economic status compries three major determinants of health: health care; environmental exposure; health behavior; in addition, chronic stress associated with low incomes may also increase morbidity and mortality. (Nancy, E., 2002) The socio-economic status, whether assessed by income, education, or

occupation, is linked to a wide range of health problems, including low birthweight, cardiovascular disease, hypertension, arthritis, diabetes, and cancer (Pamuk, E.,1998).

McGinnis and Foege pointed out in a study that the most fundamental causes of health disparities are socioeconomic disparities (Mc Ginnis J.M., 1993).

Lower socioeconomic status is associated with higher mortality but the mechanisms responsible for this association are not well understood. Identifying these mechanisms provides more options for policy remedies.

A better identification of economic costs involving WD are especially helpful for understanding the financial consequences of chronic diseases. Such information is essential for making well grounded investment decisions for WD evaluation, prevention of disease progress, resource allocation, and disease management programs on short, medium and long terms.

The evolution of hepatic WD is to chronic liver disease and cirrhosis. So Wilson disease is one of the causes of chronic liver disease, which is relatively rare though, should not be ignored. The overall cost of cirrhosis includes direct costs (drug and hospitalization costs) and indirect costs (due to loss of work productivity and reduction in health-related quality of life).

In 2004, the direct costs of cirrhosis and chronic liver disease in the United States (excluding patients with HCV infection) were estimated to be $2.5 billion, whereas indirect costs were estimated to be $10.6 billion. (Ruhl CE, 2008) Studies showing costs of Wilson disease are very rare so that our research was confrunted with such an obstacle.

Acording to ”Rare Disease Impact Report” commissioned by Shire Human Genetic Therapies, published in april 2013, rare diseases touch more than just the patient. These conditions also impact families, friends, physicians, and society as a whole. There is an urgent need to understand the state of rare diseases and the current gaps in care and support. The overarching concerns centered on several key themes:

- There is a lack of resources and information to address these less common illnesses like WD;
- The economic impact of diagnosing and managing rare diseases is high and it is imposible to be fully covered only by the patient.
- Rare diseases create a major emotional impact on patients and caregivers.

Microeconomic analysis of the consequences of disease: an important economic consequence of disease or injury at the microeconomic level of households, firms and government is that, through its impact on functioning, individuals are unable to perform their usual day-to-day activities. Wilson disease is a degenerative, debilitating condition with significant neurological damage. Illness typically leads to increased household expenditures on health services and also reduce time spent to produce income that allows them to consume market goods. Many patients who suffer from Wilson Disease will be unable to perform usual activities due to the neurological symptoms that affects their movements. In these cases, an application for Social Security Disability benefits may help offset some of the financial stress caused by this condition.

Although insufficient as a basis for setting priorities and allocating resources in health – economic burden, studies in this domain may help to identify possible strategies for reducing the cost of disease or injury via appropriate preventive action or treatment strategies.

The second part of our paper contains preliminary data obtained from our ongoing study about epidemiological aspects of our patients diagnosed with WD and analyze the costs of diagnosis and treatment of this condition.

Presentation of our study purpose, methods and partial results

Purpose

In order to establish the mean cost of evaluation, diagnosis and treatment per pediatric patient with Wilson Disease and the epidemiological features of these disease in South-Eastern Romania, we have conducted an observational study in the Hepatology department of ”Grigore Alexandrescu” Emergency Hospital for Children in Bucharest. This study is performed with the consent of the ethics committee and patients were included after their parents signed the consent form.

Materials and Methods

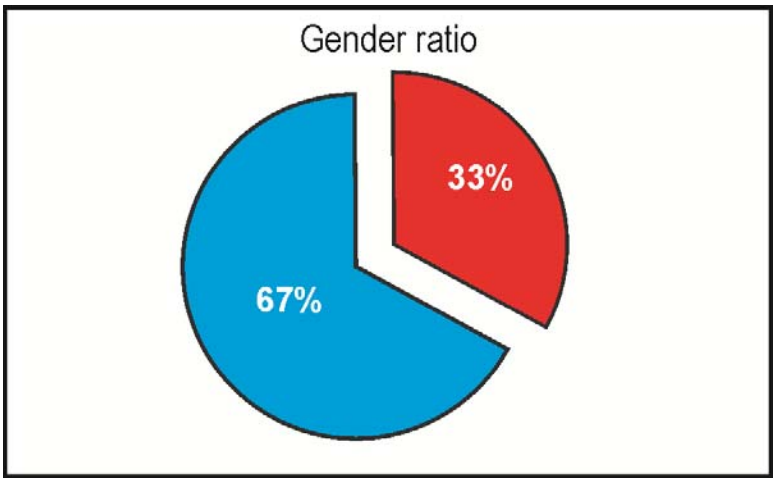
It is an observational retrospective study, which included the patients diagnosed with Wilson Disesase between January 2004 and January 2015 in the Hepatology Departament of the ”Grigore Alexandrescu” Emergency Hospital for Children. From the medical records we extracted: year of diagnosis, living area (urban or rural) and county of residence. The economic burden of the diagnosis

and evaluation of Wilson Disease was established through the costs of patient evaluation. The medical data were analized by using Microsoft Office Excel 2007.

Results

Between January 2004 and January 2015, 27 patients were diagnosed with Wilson Disease in Hepatology Departament of our Hospital. The mean age at diagnosis was 11.2 years. The sex ratio male/female was 18/9 (2/1)

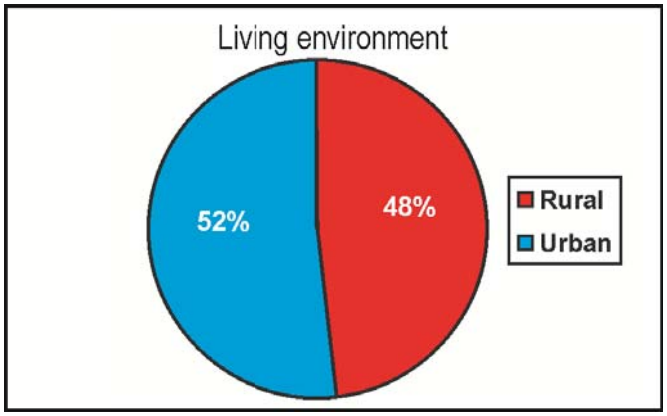
Figure 1. Gender ratio of WD study group in the period 2004-2014 in Hepatology Departament of "Grigore Alexandrescu" Emergency Hospital for Children



Source: own results of personal study research.

The rural/urban ratio of patients living in rural and urban areas was 52 percent and 48 per cent respectively (Figure 2)

Figure 2. Living areas of our patients diagnosed with WD between January 2004 and December 2014

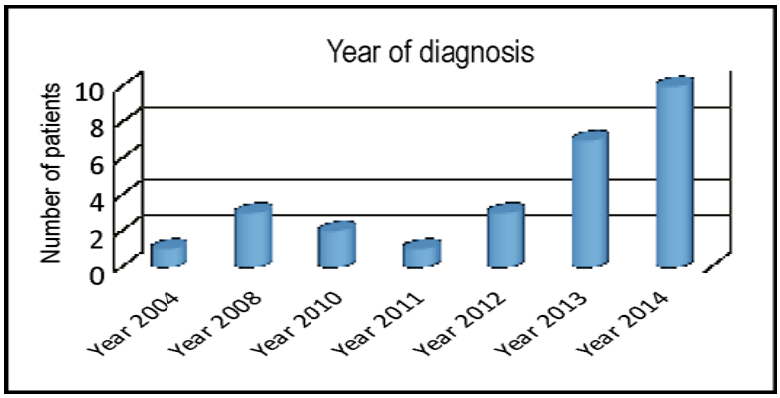


Source: own results of personal study research.

We evaluated our patients according to their age at the diagnosis moment. Most of the patients were within the 10-14 years age group.

Data regarding the year of diagnosis showed that most of our patients were diagnosed with Wilson Disease in recent years. More exactly, 21 patients were diagnosed since 2010 (84% of the patients included in the study).

Figure 3. The evaluation of the number of cases diagnosed per year



Source: own analysis based on the data from our patients diagnosed with WD between January 2004-December 2014.

The counties with the highest number of patients diagnosed with Wilson Disease were Prahova, Dambovita, Constanta, Arges and Bucharest.These counties are among the most populated in our country.

The patients were hospitalized for evaluation and diagnosed during a period of 9.2 days and the mean cost /evaluation/patient was 3311.768 RON. We analyzed the cost of evaluations, hospitalization, laboratory investigations and supportive treatment for patients included in the study. The average cost was 736 euro/patient (3311.768 RON/patient). This amount included expenses resulting from hospitalization, laboratory investigations and supportive treatment at the hospital. To this amount we added the price of investigations necessary for positive diagnosis. These investigations could not be worked of the hospital's laboratories, such as ceruloplasmin-10 euro (45 RON) , 24 hours urinarry copper-10 euro (45 RON) and genetic testing-120 euro (500 RON) for detecting the most frequent mutation – H1069Q – present in patients with Wilson disease in Europe).

The monthly average wage in Romania is 1552 RON (the equivalent of 350 Euro) and it is not sufficient to cover the key diagnostic investigations (urinary cooper, serum ceruloplasmim, serum copper and genetic test) free of charge and medical assistance is not availalble for pediatric Romanian patients.

Two of the patients included in the study were diagnosed at a late stage of the disease. They were hospitaliyed on average 45 days, and costs of hospitalization, clinical and laboratory evaluations were 17,346.575 RON.

In the study group, six patients were diagnosed in presimptomatic stage, starting from an index case (a first degree relative diagnosed with Wilson disease). In the case of these patients, the cost for diagnostic evaluation was 876.7 RON/patient plus the following determinations: ceruloplasmin-10 euro (45 RON); cuprurie-24 hours-10 euro (45RON); genetic testing-120 euro (500 RON for detecting the most frequent mutations present in patients with Wilson's disease in Europe). Even in this case, the average monthly wage could not cover the expenses.

The determination of these costs, which vary according to the stage of disease at diagnosis, highlights the importance of early diagnosis, even in presymptomatic stage, reducing costs. In this stage, patients will receive the treatment with zinc salts and will be monitored every 6 months and then every 1 year, under the circumstances of gradual reducing costs.

Conclusions

A. Methodological and theoretical conclusions

The Wilson Disease is a severe autosomal recessive disorder that can be fatal if missdiagnosed. In recent years Wilson Disease was diagnosed more frequently. Every patient with suggestive symptoms has to be tested for Wilson Disease.

Early diagnosis is mandatory for this condition, greatly reducing the incidents of severe complications, considerable social damage and the economic costs, and could be established by family screening. Disease evolution is slower if a rigorous treatment is used. Modern medicine is based mainly on prevention. In order to reduce the number of fatal complications it is essential to introduce accurate screening and diagnosing methods. First-degree relatives of any patient diagnosed with WD must be screened for WD. Early diagnosis leads to chelation therapy initiation which prevents the disease evolution.

New biomarkers have proved highly efficient in the diagnosis of Wilson disease in some studies, but more studies are needed to evaluate the efficacy.

The best therapeutic approach remains controversial and there is no universally accepted regime. There are two aspects of optimizing clinical outcome — first, proper monitoring of patients and second, support to ensure compliance with whichever regimen is used.

Genetic therapy and hepatocyte transplantation represent future curative treatments for Wilson disease, along with currently available liver transplantation. Gene therapy trials and continuing research will hopefully achieve the safety and the effectiveness of the gene transfer, and overcome obstacles to permit efficient transduction of large genes, such as ATP7B.

B. Practical conclusions

In Romania, the incidence of WD is not known, but our study showed positive diagnosis rate increasing in recent years. Most of our cases came from rural areas, probably due to a higher incidence of consanguinity.There is a severe lack of information regarding prevalence of WD among children in our country. Few studies are performed in our country. According to our study WD has a different prevalence function of specificity in each county or area.

We mention that only a few European countries have a National Register which include:patient's data; the disease stage at diagnosis; treatment; evolution; complications; socioeconomic informations, improving statistical records of such

cases. In our opinion, a National Register has to be implemented in Romania in order to get an improvement in patient identification and treatment in due time and with a higher efficiency. Besides this registration in a special national document, a significant contribution is given by each patient improving his medical care.

When a patient is diagnosed with a rare disease like WD, his active participation is absolutely essential. WD patients require the attention of an entire team formed of gastroentherologyst, neurologist, ophthalmologist, paediatrician, psychiatrist. We need in Romania an association and support group for WD.

In our study, the medium cost of evaluation per patient is twice the monthly average level of income per employee. Patients with medium incomes can't handle the treatment and evaluations by their own financial means.

Taking into consideration the financial inafordability of WD patients it is necessary to create special health insurance founds at least at the national if not even at regional level.

The other conclusion of practical significance refers to the necessity of improvement of statistics in this domain both in pre and post treatment periods. We consider the creation of a National Center for WD study. The main objective will be state-of-the-art scientific reseach in cooperation with other centers from EU countries.

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