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Pregnancy outcome after chelation therapy in Wilson disease. Evaluation of the German Embryotox Database

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ABSTRACT

Continuation of treatment is recommended for pregnant women with Wilson disease. Therapy options include the copper chelating agents D-penicillamine and trientine. However, there are still uncertainties concerning a possible teratogenic risk. In this case series, we report on the outcome of 20 pregnancies with maternal chelator exposure at least during the first trimester. Of these 20 pregnancies documented by the German Embryotox Project, 14 were prospectively ascertained and 6 were retrospective. No major birth defects were observed. Three of the 14 prospective cases resulted in a spontaneous abortion, and one pregnancy was electively terminated. Our results do not support the hypothesis of teratogenicity based on earlier case reports of congenital anomalies. Therefore our study may contribute to reassure women needing chelation therapy during pregnancy. However, it must be taken into account that the sample size of this case series is too limited to make final conclusions on teratogenic effects.

1. Introduction

Wilson disease (OMIM#277900) is a rare genetic disorder following an autosomal recessive inheritance. Mutations in *ATP7B* are the underlying cause for this disorder resulting in a disturbed function of the copper-transporting P-type ATPase leading to an overload and accumulation of copper in different tissues. The clinical symptoms are variable and are dependent on the excess of copper accumulation in the affected organs. Whereas the clinical manifestations at an early stage are often unspecific, at a later stage the typical features include severe liver disease with or without cirrhosis and various neurologic and psychiatric symptoms. Ophthalmic features such as the Kaiser-Fleischer-ring of the cornea often occur, especially in patients with primary neuropsychiatric signs. Besides a clinical examination, biochemical and histological diagnostics, radiologic imaging as well as genetic diagnostics are often helpful to confirm the diagnosis of this disease.

The average age of onset in Wilson disease is in the first or second decade but the time of diagnosis varies depending on the severity of the organ affection. When Wilson disease is diagnosed, treatment should be started immediately and has to be life-long. This also applies to pregnant women, who need therapy to be continued in pregnancy. Depending on the copper status and the clinical symptoms, therapy regimes include copper-chelating agents, such as D-penicillamine or triethylenetetramine (trientine), or the administration of zinc, which blocks the gastrointestinal absorption of copper. The effect of zinc alone is often insufficient in symptomatic patients. Due to the different action mode, a combination therapy of zinc salts with chelators may be prescribed, but the clinical benefit is still unclear [1]. In addition, meso-2,3-dimercaptosuccinic acid (DMSA) was shown to be effective as a decoppering agent in Wilson disease with low side effects [2,3]. However, DMSA as well as other chelating agents used in heavy metal intoxication, e.g. the formerly used British anti-Lewisite molecule (BAL) or 2,3-dimercapto-1-propanesulfonic acid (DMPS) have no great importance for the treatment of Wilson disease today and are not recommended therapy options in clinical guidelines [1,4,5]. Other substances like ammonium tetrathiomolybdate or antioxidants (e.g. vitamin E) are currently not considered standard treatments [1,5,6].

Women with Wilson disease should have an optimized copper status when a pregnancy is planned. However, the best possible treatment during pregnancy is still debated. Chelator therapy has

Abbreviations: ATP, adenosin triphoshat; ATP7B, ATPase, Cu(2+)-transporting, beta polypeptide; BAL, British anti-Lewisite molecule; bpm, Beats per minute; C-section, Cesarean section; CTG, Cardiotocography; DMPS, 2,3-dimercapto-1-propanesulfonic acid; DMSA, meso-2,3-dimercaptosuccinic acid; ETOP, elective termination of pregnancy; GW, gestational week; HCP, health care provider; LMP, last menstrual period; n/a, not applicable/available; No., number; OMIM, Online Mendelian Inheritance in Man®; P, cases exposed with penicillamine; T, cases exposed with trientine; Trientine, triethylenetetramine.

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been considered teratogenic based on earlier case reports and case series on maternal penicillamine treatment associated with congenital anomalies such as cutis laxa, congenital inguinal hernia and cleft lip/palate [7–13].

Since copper is an essential trace element needed for the proper function in many enzymes, a balanced copper level is needed for undisturbed physiological signalling processes. It is required e.g. for enzymes that are involved in oxygen transport, in the scarvenge of free radicals, erythropoiesis, catecholamine biosynthesis, formation of connective tissue and myelin, melanin pigmentation and others [14]. Thus, it is not surprising that a disturbed copper homeostasis can lead to serious negative effects in humans [15]. While an overload of copper is the underlying cause of tissue damage in Wilson disease, copper deficiency can lead to severe disorders as well. Genetic copper transport disorders in humans resulting in a severely decreased intestinal copper absorption and low levels of serum copper and ceruloplasmin are known to cause serious illnesses like Menkes disease (OMIM#309400) or Occipital Horn Syndrome (OMIM#304150) [16,17]. The concerns of using chelating agents in pregnancy are based on the possibility of insufficient supply of copper and other heavy metals to the embryo and fetus resulting in disturbed development. Penicillamine, for example, carries a sulfur containing amino acid and has the ability to chelate lead and mercury in addition to copper [18]. It is conceivable that a long-term treatment could alter the homeostasis of other metals and related functions. Alterations of vital signalling pathways or the disturbance of enzyme activity by a deficient bioavailability of necessary required elements possibly result in developmental disorders. This mechanism e.g. was hypothesized for a diminished activity of the copper dependent lysyl oxidase by copper deficiency leading to connective tissue disorders [19]. In addition, a teratogenic potential of chelators on their own due to their molecular structure is possible. Toxic effects of chelators are well known and serious side effects after treatment with chelating agents in the affected persons as hepatotoxicity and nephrotoxicity are not unusual [1,18]. However, fears on teratogenic effects, e.g. for penicillamine, are based on a few case reports on congenital anomalies. Clinical data are insufficient yet to confirm or refute the hypothesis.

Due to limited observations of the treatment of Wilson disease during pregnancy, we decided to evaluate our pregnancy outcome data after first trimester exposure to chelators.

2. Methods

The German Embryotox institute offers risk assessment on drug use in pregnancy to health care professionals of all specialties as well as pregnant women. On behalf of the German Federal Institute for Drugs and Medical Devices, more than 4000 pregnancies per year with drug exposure are documented as to their outcome. Usually, data are ascertained prospectively, i.e., neither the outcome of pregnancy nor the results of prenatal diagnostics are known at first contact for risk consultation. In retrospectively reported cases, the outcome of pregnancy is primarily known and is often a trigger to contact our institute. Due to this potential reporting bias, retrospective cases will be described separately.

Our case series includes all requests for penicillamine and trientine exposure to our Institute from 1996 until October 2015. According to the inclusion criteria, the indication for treatment was Wilson disease in all evaluated cases. Since the vulnerable phase for birth defects induced by teratogens is the first trimester, only pregnancies exposed at least between the first day of the last menstrual period (LMP) and gestational week (GW) 12 + 6 days were included in the analysis. Cases were included independent of the duration of treatment within the first trimester. Exposure to chelation therapy may have been terminated within the first trimester or may have lasted longer than the first trimester. All relevant data with respect to drugs, exposure to other agents, maternal characteristics, as well as obstetric and family history, were documented with the permission of the patient, using a structured questionnaire during a phone interview. Approximately 8 weeks after the expected date of delivery, follow-up was conducted either by a questionnaire mailed to the woman or her physician or by telephone interview. A follow-up was only initiated with the consent of the patient and if an informative response could be expected. The latter was not the case when we were approached by a pharmacy or other health care provider (HCP) not directly responsible for the patient. Follow up includes information on maternal complications during pregnancy, delivery and neonatal outcome such as gestational age at birth, sex, birth weight, length, head circumference, pH, Apgar scores, and, if applicable, details of congenital anomalies and postnatal disorders during neonatal period. Classification of birth defects in major and minor were based on Eurocat guidelines (http://www.eurocat-network.eu). Weeks of gestation were calculated either based on ultrasound measures during the first trimester or, if not available, using the first day of the LMP. Spontaneous abortion is defined as spontaneous pregnancy loss of an embryo or fetus of <500 g or <23 completed pregnancy weeks if the weight is not known. Preterm delivery is defined as <37 completed pregnancy weeks. For further details on the methodology see Schaefer et al., 2008 [20].

3. Results

Our case series includes 17 pregnancies with penicillamine and 3 pregnancies with trientine exposure in the first trimester (Figs. 1 and 2). The dosage of penicillamine ranged from 300 mg to 1500 mg per day. For trientine, the daily dose was available in 2 of 3 cases (900 and 1500 mg). A combination therapy with zinc salts was reported in 5 pregnant women on penicillamine and in one on trientine. There was no teratogenic or fetotoxic co-medication in any patient. Maternal age ranged from 19 to 40 years. For details see also Tables 1 and 2.

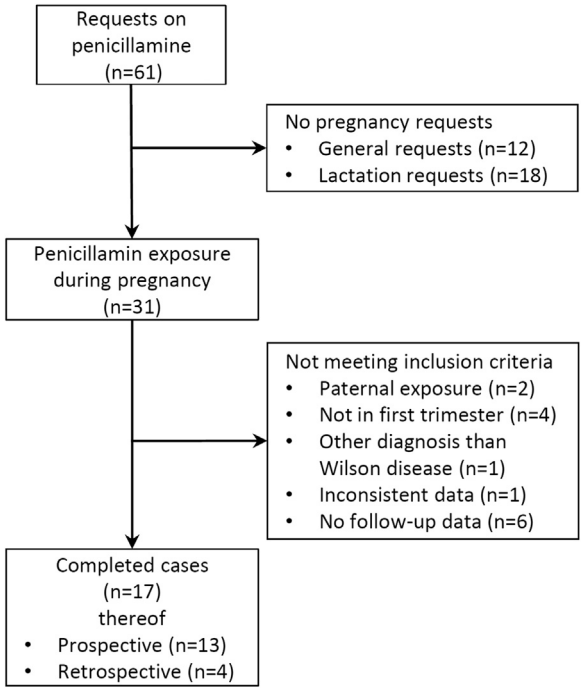

Fig. 1. Flow chart of requests to Embryotox for information on penicillamine from January 1996 until October 2015.