

A case report: Co-occurrence of Wilson disease and oculocutaneous albinism in a Chinese patient

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Abstract

Rationale: Both Wilson disease (WD) and Oculocutaneous Albinism (OCA) are rare autosomal recessive disorders that are caused by mutations on chromosome 13 and chromosome 11, respectively. Here, we report on a patient with coexisting WD and OCA, initially presenting episodes of tremors.

Patient concerns: WD is a disorder of copper metabolism. The main sites of copper accumulation are the liver and the brain, resulting in hepatic symptoms. OCA is a disorder of melanin biosynthesis, characterized by a generalized reduction in pigmentation of the eyes (oculo-), skin (-cutaneous), and hair.

Diagnosis: The diagnosis of WD was confirmed by neurological symptoms, metabolism tests, and MRI scans. Interestingly, the patient also had very light skin color, blond hair and eyebrows, and dark brown eyelashes and irises. Because the association of dermatologic signs in WD has rarely been reported, OCA was highly suspected based on these clinical findings. Genetic analysis was subsequently conducted, and the results revealed the p. (Arg778Leu) mutation in 1 allele and the p. (Asn1270Ser) mutation in the other allele of the ATP7B gene, confirming the diagnosis of WD; the p. (D456fs) mutation in 1 allele and the p. (R299H) mutation in the other allele of the TYR gene, confirming the diagnosis of OCA. The family history was positive for WD with a 14-year-old younger brother also being diagnosed with it. Her parents are negative for OCA and WD.

Interventions: Sodium dimercaptopropanesulfonate (DMPS) was given during hospitalization. D-penicillamine and zinc sulfate treatment was initiated after discharge for long-term control.

Outcomes: Postural and intention tremor disappeared, and other symptoms and signs markedly improved after treatment.

Lessons: In this study, we reported on the first case of a child who simultaneously presented WD and OCA, bringing up the possibility of a presumable link between these 2 rare diseases.

Abbreviations: DMPS = dimercaptopropanesulfonate, KF rings = Kayser–Fleischer rings, MRI = magnetic resonance imaging, OCA = oculocutaneous albinism, WD = Wilson disease.

Keywords: copper, melanin synthesis, oculocutaneous albinism, Wilson disease

1. Introduction

Wilson disease (WD) is a rare autosomal recessive disorder of copper metabolism, with an estimated 1 in 30,000 people

Editor: N/A.

This research was financially supported by Natural Science Foundation of Anhui province (No. 1708085QH190).

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

This case report received the institutional review board approval. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:50(e13744)

Received: 23 August 2018 / Accepted: 27 November 2018

<http://dx.doi.org/10.1097/MD.0000000000013744>

worldwide being born with it. Males and females are equally affected.^[1] A mutation in the Wilson disease protein (ATP7B) gene renders copper unable to link to ceruloplasmin and to be released into the bloodstream, causing copper accumulation in the body.^[2] The main sites of copper accumulation are the liver and the brain, resulting in hepatic symptoms including vomiting, weakness, ascites, limbs edema, itchiness, and yellowish skin. Neuropsychiatric symptoms include tremors, trouble speaking, muscle stiffness, anxiety, and personality changes.^[3,4] Kayser–Fleischer rings (KF rings) are the pathognomonic sign of WD, resulting from copper deposition in Descemet’s membrane. KF rings have been found in approximately 66% of diagnosed cases.^[4] WD can be suspected when patients present with the symptoms mentioned above. Levels of ceruloplasmin and copper in the blood and the amount of copper excreted in urine are both used to form an impression of the accumulation of copper in the body. Magnetic resonance imaging (MRI) of the brain is usually performed. In the T2 setting, images show hyperintensities in the area of the basal ganglia.^[5] There is no totally reliable test for diagnosing WD. A liver biopsy and genetic analysis can be ideal tests to confirm the diagnosis.^[6]

Oculocutaneous albinism (OCA) is a group of autosomal recessive disorders of melanin biosynthesis, characterized by a generalized reduction in the pigmentation of the eyes (oculo-), skin (-cutaneous), and hair. There are several subtypes of OCA that are caused by mutations in several genes. Overall, OCA occurs in about 1 in 20,000 people.^[7] People with OCA usually



Figure 1. Physical examination that showed very light skin with blond hair and eyebrows, dark brown eyelashes and irises and KF rings bilaterally. KF rings = Kayser Fleischer rings.

have vision problems, such as reduced sharpness and increased sensitivity to light (photophobia). Nystagmus, which is rapid, involuntary eye movements, is sometimes noted.^[7] WD and OCA are both monogenic, autosomal recessive conditions. There has been no report in the literature about the co-existence of OCA and WD in 1 patient. Here, we are reporting on a patient with coexisting WD and OCA.

2. Case report

A 19-year-old girl was born of non-consanguineous marriage and presenting episodes of tremors since July 2013. One year later, she developed noticeably slow speech and movements. As a result, she came to a local neurological department for help. Based on a review of her chart, a neurological examination revealed marked postural and intention tremors of the hands, hypomimia, dysarthria, dysdipsia, and adiadochokinesis. Measurements of copper metabolism confirmed a diagnosis of WD:

lower levels of serum ceruloplasmin (<0.079 g/L; normal range 0.2–0.6 g/L). The diagnosis of WD was confirmed by neurological symptoms, metabolism tests, and MRI scans. D-penicillamine and zinc sulfate treatment was initiated. Postural and intention tremors disappeared, and other symptoms and signs markedly improved after treatment. However, the patient stopped the treatment after 1 year as a result of poor compliance. The neurological symptoms were all markedly aggravated. As a result, she came to our department in 2016.

On arrival to our department, a neurological examination revealed marked postural and intention tremors of the hands, hypomimia, dysarthria, dysdipsia, adiadochokinesis, and ataxic gait. She had photophobia, nystagmus, and greatly decreased visual acuity. Slit lamp examination of the eyes revealed KF rings bilaterally (Fig. 1). Measurements of copper metabolism confirmed the diagnosis of WD: lower levels of serum ceruloplasmin (47.7 mg/L, normal range 200–420 mg/L), decreased copper serum levels ($3.3 \mu\text{mol/L}$, normal range 10.5–24.4 $\mu\text{mol/L}$), and increased

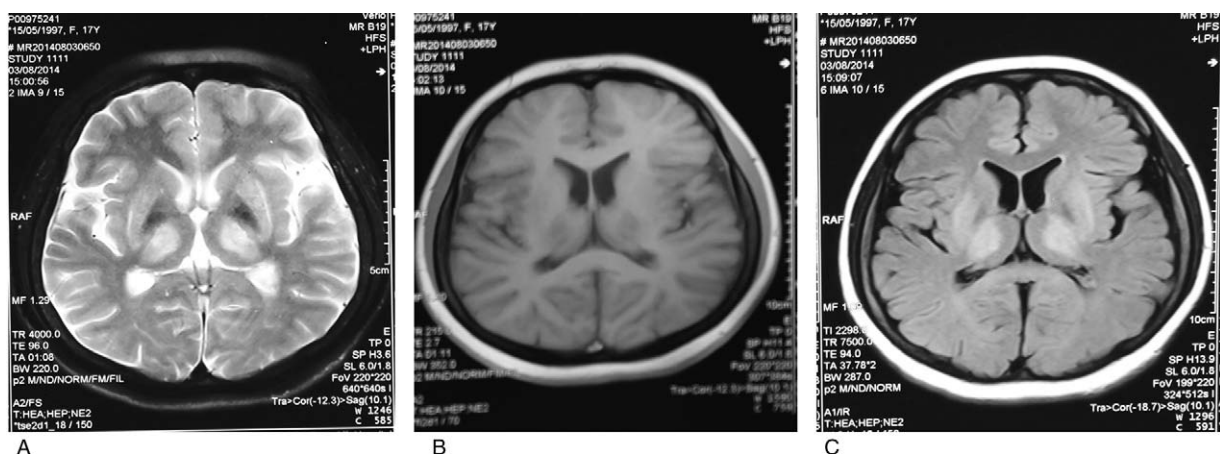


Figure 2. MRI image showing bilaterally symmetric hyperintensities involving the basal ganglia, thalami and pons in T2-weighted images (A) T1-weighted image (B) FLAIR images (C). FLAIR = fluid attenuation inversion recovery, MRI = magnetic resonance imaging.

urinary excretion of copper (109 µg/24h). The results of MRI showed bilaterally symmetric hyperintensities involving the basal ganglia, thalami, and pons (Fig. 2). Interestingly, the patient also had very light skin color, blond hair and eyebrows, and dark brown eyelashes and irises. Because the association of dermatologic signs in WD has rarely been reported, OCA was highly suspected based on the clinical findings. As a result, we performed a genetic analysis for her and her family. The genetic study revealed the p. (Arg778Leu) mutation in 1 allele and the p. (Asn1270Ser) mutation in the other allele of the ATP7B gene, confirming the diagnosis of WD; the p. (D456fs) mutation in 1 allele and the p. (R299H) mutation in the other allele of the TYR gene, confirming the diagnosis of OCA.^[8] During hospitalization, sodium dimercaptopropanesulfonate (DMPS) therapy was given intravenously. D-penicillamine and zinc sulfate treatment were maintained after discharge for long-term control of the disease. Her postural and intention tremor disappeared, and her other symptoms and signs markedly improved.

The family history was positive for WD with a 14-year-old younger brother also being diagnosed with it. Genetic analysis revealed the p. (Arg778Leu) mutation in 1 allele and the p. (Asn1270Ser) mutation in the other allele of ATP7B. He has normal yellow skin, black hair and eyes, and the genetic analysis also confirmed he was negative for OCA. Her parents were negative for both OCA and WD.

3. Discussion

This is the first case report in the literature concerning 1 patient who had WD and OCA coexisting. Based on her neuropsychiatric symptoms, KF rings, metabolism tests, and MRI scans, WD was impressed. However, her light skin color, dark brown eyelashes, blond hair and eyebrows were not compatible with the clinical features of WD. The association of dermatologic signs with WD has rarely been reported in the literature. Copper accumulation in the liver might result in the itchiness and yellowish skin. Other skin changes in WD are minor, and cutaneous findings in WD include generalized hyperpigmentation, blue lunulae of the nails, anetoderma, xerosis, acatnosis nigricans, pyoderma gangrenosum, and rippled hyperpigmentation.^[5] As a result, genetic analysis was subsequently conducted.

As a WD-causative gene, ATP7B encodes copper-transporting P-type ATPase. Most of ATP7B mutations are missense mutations, small deletions or insertions in the coding region, or splice junction mutations. The point mutation 2333G→T leading to Arg778Leu substitution in exon 8 was the most common ATP7B mutation with an allele frequency of 14 to 49% in patients from eastern Asia (China, South Korea, and Japan).^[1,3,8] Her genetic study revealed that the p. (Arg778Leu) mutation in 1 allele and the p. (Asn1270Ser) mutation in the other allele of the ATP7B gene, and this confirmed the diagnosis of WD.

According to her clinical findings, which included very light skin, blond hair and eyebrows, and dark brown eyelashes and irises, OCA1 was highly suspected. OCA is a disorder caused by lack of melanin biosynthesis resulting in hypopigmentation of the hair, skin, and eyes. Several subtypes of OCA were defined by their causative mutation(s), and clinical presentation can vary widely.^[7] OCA type 1 (OCA1) is caused by mutations in the TYR gene on chromosome 11, which encodes tyrosinase. The gene consists of 5 exons spanning approximately 65 kb of genomic DNA and encodes a protein of 529 amino acids.^[9] The diagnosis of OCA1 for the patient in this study was the p. (D456fs) mutation in 1 allele and the p. (R299H) mutation in the other allele of the TYR gene.^[8]

The color of mammalian skin and hair is determined by a number of factors. The most important factor is the degree and distribution of melanin pigmentation. Melanin is formed in specialized pigment-producing cells known as melanocytes. The major cause of OCA lies in the fact that melanin biosynthesis dysfunction. The most important enzyme in melanogenesis is tyrosinase which is expressed in epidermis, follicle and oocytes, catalyzing the first 2 rate-limiting steps of melanin biosynthesis.^[10] Interestingly enough, it is generally known that tyrosinase is a multifunctional copper-containing glycoenzyme.^[11] WD patients exhibit excessive copper accumulation in most organs but especially the liver and brain, but in this environment of excessive copper, tyrosinase can't finish melanin biosynthesis as normal.^[1] The results of our study show that the spatial distribution of 299 amino acids changed obviously, and the Cu-binding of the tyrosinase domain disappeared.

Menkes syndrome could have been an important differential diagnosis for this patient. Menkes syndrome is an X-linked recessive disorder caused by mutations in genes coding for the copper-transport protein ATP7A (located on chromosome Xq21.1), leading to copper deficiency.^[2] Clinical findings of Menkes syndrome include nervous system deterioration, kinky hair, and developmental delay, which were not compatible for the patient.

Treatments for WD involve diet control with low copper-containing foods and chelation therapy (D-penicillamine and zinc sulfate).^[6] These treatments were effective for the patient in this study according to her history. If left untreated, WD tends to become progressively worse and is eventually fatal. Most patients can live relatively normal lives with early detection and treatment.^[6] Treatments for OCA include strict sun protection from infancy, a comprehensive eye examination early in life, and treatment of refraction error with glasses or contact lenses.^[7] Life expectancy is not reduced in nonsyndromic OCA, although mortality from skin cancer can be increased in certain populations. Patients with OCA should have skin examinations at 6- to 12-month intervals starting in adolescence because of the increased risk of skin cancer.^[12]

Both WD and OCA are rare autosomal recessive disorder caused by mutations on chromosome 13 and chromosome 11, respectively. We have herein reported on the first case of a patient who simultaneously presented WD and OCA, bringing up the possibility of a presumable link between these 2 rare diseases.

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References

- Bandmann O, Weiss KH, Kaler SG. Wilson disease and other neurological copper disorders. *Lancet Neurol* 2015;14:103–13.
- de Bie P, Muller PA, Wijmenga C, et al. Molecular pathogenesis of Wilson and Menkes disease: correlation of mutations with molecular defects and disease phenotypes. *J Med Genet* 2007;44:673–88.
- Dziężyc K, Litwin T, Członkowska A. Other organ involvement and clinical aspects of Wilson disease. *Handb Clin Neurol* 2017;142:157–69.

- [4] Merle U, Schaefer M, Ferenci P, et al. Clinical presentation, diagnosis and long-term outcome of Wilson disease: a cohort study. *Gut* 2007;56:115–20.
- [5] Roberts EA, Schilsky ML. A practice guideline on Wilson disease. *Hepatology* 2003;37:1475–92.
- [6] Ala A, Walker AP, Ashkan K, et al. Wilson disease. *Lancet* 2007;369:397–408.
- [7] Grønskov K, Ek J, Brøndum-Nielsen K. Oculocutaneous albinism. *Orphanet J Rare Dis* 2007;2:43.
- [8] Tripathi RK, Strunk KM, Giebel LB, et al. Tyrosinase gene mutations in type I (tyrosinase-deficient) oculocutaneous albinism define two clusters of missense substitutions. *Am J Med Genet* 1992;43:865–71.
- [9] Blaszczyk WM, Arning L, Hoffmann KP, et al. A Tyrosinase missense mutation causes albinism in the Wistar rat. *Pigment Cell Res* 2005;18:144–5.
- [10] Ray K, Chaki M, Sengupta M. Tyrosinase and ocular diseases: some novel thoughts on the molecular basis of oculocutaneous albinism type 1. *Prog Retin Eye Res* 2007;26:323–58.
- [11] Riyaz A. Wilson disease. *Pediatric Gastroenterology and Hepatology Hyderabad*. 2008;Paras Medical Publisher, New Delhi:551-568.
- [12] Fogel AL, Sarin KY, Teng JMC. Genetic diseases associated with an increased risk of skin cancer development in childhood. *Curr Opin Pediatr* 2017;29:426–33.