Challenges in the diagnosis of Wilson disease

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Abstract: The understanding and management of Wilson disease (WD) have dramatically improved since the first description of the disease by K. Wilson more than a century ago. However, the persistent long delay between the first symptoms and diagnosis emphasizes challenges in diagnosing earlier this copper overload disorder. As a treatable disease, WD should be detected early in the course of the disease by any health professionals at any care level, but the rare prevalence of the disease explains the lack of awareness of referring physicians. The most important challenge is to train physicians to recognize atypical or rare symptoms of WD that will lead to discuss the diagnosis more systematically. Atypia can come from the age of onset, the liver [non-alcoholic steatohepatitis (NASH) presentation], the central or peripheral nervous system (neuropathy, epilepsy, sleep disorders…) or may be due to lesions of other organs (renal manifestations, osteo-articular disorders or endocrine disturbances). Isolated biological anomalies, rare radiological findings or inadequate interpretation of copper test may also lead to misdiagnosis. The second challenge is to confirm the diagnosis faster and more effectively so as not to delay the initiation of treatment, and expand family screening as the genetic prevalence is higher than previously expected. Generalization of the exchangeable copper assay and the next generation sequencing (NGS) are two promising ways to overcome this ultimate challenge. By drawing attention to the earliest and rare symptoms and to new biomarkers and diagnostic tools, we hope that this article will increase diagnostic awareness and reduce delays so that patients can start their treatment earlier in the course of the illness and thus have a better disease prognosis.

Keywords: Wilson disease (WD); diagnosis; misdiagnosis; genetics; exchangeable copper; atypia

More than one century after the first description of Wilson disease (WD) by Sir K. Wilson (1,2) the understanding and management of the disease have dramatically improved but challenges in diagnosing this copper overload disorder remain as it is extremely important for physicians and health professionals at any care level to recognise and diagnose this treatable disease at an early stage.

The most important challenge is to recognise atypical or rare symptoms of WD that will lead diagnosis. The second challenge is to confirm the diagnosis faster, not to delay the initiation of treatment, and expand family screening as the genetic prevalence is higher than previously expected.

Consider WD diagnosis more often

A long delay between first symptoms and diagnosis

In theory, thinking of the diagnosis of WD is usually straightforward in a child with liver manifestation or an adolescent with changes in personality and disturbances of movement, when associated with the classical biological triad [low ceruloplasmin (Cp), low serum copper and elevated 24-h urinary copper excretion]. But data from different WD cohorts show that diagnosing this rare disease remains difficult as the mean time between the first symptoms and the diagnosis usually exceeds 2 years (3-5). In the

German cohort of 137 symptomatic WD patients diagnosed between 1957 and 2005, the mean time lag between the first symptoms and diagnosis was 25.3 months. A proportion of 60.3% were diagnosed within 1 year, 68.2% within 2 years and in 22.5% of all patients, diagnosis was established 3 years after the appearance of initial symptoms (3). In every WD cohorts, neurological presentation is associated with a significantly longer time from onset of symptoms to diagnosis than hepatic presentation, ranging from 2.5 to 6 years (3,5,6). Despite modern medical advances, improvement in time to diagnosis over the last decades appears minimal (6). Various studies showed that the absence of diagnosis and misdiagnosis explain most often this long delay (7-9). Prashanth *et al.* ascertained diagnostic errors at initial evaluation in WD patients, analysing medical records of 307 patients of WD registered over 30 years [1970–2003] and followed up at the Department of Neurology in a university hospital in south India. They looked at presenting manifestations, initial diagnostic omissions, and interval between onset of symptoms to diagnosis and treatment. Diagnostic errors by referring doctors from different specialties of health care (general practitioners, physicians, paediatricians, nephrologists, psychiatrists, and neurologists) were detected in 192 patients (62.5%). They included more than 100 different diseases that included schizophrenia, juvenile polyarthritis, rheumatic chorea, nephrotic syndrome, metachromatic leukodystrophy, congenital myopathies, subacute sclerosing panencephalitis, neurodegenerative disease among others. The mean delay was 2 years (SD 3, range, 0.08–30 years) and some patients underwent heavy interventions before establishment of the correct diagnosis (electroconvulsive therapy, thalamotomy, antipsychotics, and surgical correction for bone deformity) (7). Ten years before, Walshe and Yealland stated similar results after analysis of 136 WD patients and concluded that "no two patients are ever the same, even in a sibship and there is no such thing as typical picture of Wilson disease" (8). Of course, the rarity of the disease is the main reason for the lack of awareness of doctors, and therefore the misdiagnosis and delay in diagnosis. The clinical prevalence of WD is low, estimated to be between 1.2/100,000 and 2.0/100,000 in European countries (10). For example, in the French population of 66 million inhabitants, the total number of cases of WD is about 900 (11). Thus, a general practitioner or even a pediatrician or a neurologist may never encounter a patient with WD in his career and, therefore, may never think about it. Moreover, atypical presentations may also worsen the underestimation of the diagnosis and the lack of awareness of referring physicians.

Rare clinical presentations at diagnosis

A large variability in the age of onset and in the clinical presentation of WD exists and reflect our limited knowledge on the natural history of WD.

Atypical age of onset

Hepatic symptoms are the most common onset presentation in children with a mean age of 11 years (3,12,13), but some examples of liver disease due to WD in very young patients exist and include three young children aged 8, 9 and 13 months who were evaluated for transaminitis (14-16), a 3-year-old with cirrhosis (17), and acute liver failure (ALF) in a 5-year-old patient (18). Mean age at onset of neurologic symptoms range in large case series (19) from about 15–21 years of age, a decade after onset of liver disease, but a few patients have been diagnosed with an initial neurologic onset before aged 10 (20). Conversely, late onset WD over 40-year-old are also described in the literature and so far, 94 cases are reported: 20 case reports (21-33), 4 case series (28 patients) (34-37) and 1 large European study of 46 patients (38). These late forms can be limited to a strict hepatic phenotype sometimes with mild and unspecific clinical complaints (21,24,25,28,29,31,32,34,36), to an isolated Kayser-Fleischer ring (KFR) (22) or to a neurological disease with or without clinical evidence of liver involvement (23,26,27,30,33,35,36). For example, Ala *et al.* reported the diagnostic features of two septuagenarian siblings. The 72-year-old woman index case suffered progressive neurological disability, then developed sub-fulminant liver failure. Her 70-year-old brother, had a mild hand tremor since the age of 45 years and a mild depressive disorder. His liver biopsy revealed steatosis and minimal fibrosis and an elevated hepatic copper content. Both patients had compound heterozygote ATP7B mutations (E1064A and H1069Q). A dual-therapy with trientine and zinc salt followed by zinc salt maintenance therapy allowed their clinical course to improve (27). In general, it is assumed that all untreated WD patients will develop liver disease and especially cirrhosis (17,27), but Wang *et al.* have observed a case with only some fibrotic changes and fatty vacuoles in the liver in a newly diagnosed patient aged 49 (35). Thus, age of onset and phenotype in WD probably depend on the individual liver resistance to copper toxicity and on genetic factors. If considering the large European

multicenter study exploring 1,223 WD patients with 46 WD patients (3.8%) who were older than 40 at onset of symptoms, neurological presentation was the most frequent onset form. Indeed, two-thirds of patients presented with neurologic symptoms (mean age, 44.5 years; range, 40–52 years; male/female, 14/17), whereas one-third presented with liver disease (mean age, 47.1 years; range, 40–58 years; male/female, 6/9). One patient with hepatic presentation had "fulminant" WD, the remaining 14 abnormal liver function tests and/or hepatomegaly. 27/46 cases had mutations on both chromosomes (including 13 H1069Q/H1069Q), 13 on just 1 chromosome (38). So far, the oldest patient who started out with a neurological form of WD is a 77-year-old Turkish woman whose symptoms started ten years before the diagnosis with a mild head tremor and a slight forgetfulness. At the age of 75, she developed slurred speech and tremor in both hands followed by severe postural instability. Cp and serum copper were normal. However, bilateral brain MRI T2 hypersignal in basal ganglia along with high urinary copper excretion and high copper levels in the liver biopsy highly suggested WD while genetics were not available. She markedly deteriorated after initiation of D-penicillamine therapy (30). Late neurological forms of the disease may be difficult to diagnose like the 57-year-old man described by Ko *et al.* who presented with a 2-year history of a progressive gait ataxia associated with mild parkinsonism and cerebellar atrophy at brain MRI. In this case, degenerative cerebellar ataxia such as sporadic adult-onset cerebellar ataxia or multiple system atrophy is usually first considered. Worsening of symptoms with apparition of a punctiform hypersignal in the pons along with a negative genetic panel testing including spinocerebellar ataxia, led to further search and then to diagnosis of WD (33).

Advanced age and different clinical presentations of subjects with identical ATP7B mutations like in Ala paper, raises the question of the degree of penetrance for these and other ATP7B mutations (27). Environmental and extragenic factors are pivotal determinants of disease phenotype. So WD must be considered at all ages in patients with hepatic disease, neurological disease, or psychiatric symptoms.

Atypical liver features at diagnosis

Hepatic manifestations of WD at presentation can be extremely variable, and range from asymptomatic hepatomegaly, isolated splenomegaly, persistent or intermittent elevation of serum aminotransferases, jaundice, fatty liver or pseudo-autoimmune hepatitis, acute hepatitis,

compensated or decompensated cirrhosis to ALF (13). Some presentations of liver disease can be misleading, especially those mimicking non-alcoholic steatohepatitis (NASH) in obese patients (31,39) or in the situation of ALF. The diagnosis of WD in the setting of ALF remains challenging because the serum Cp level may be normal in ALF secondary to WD, and 24-hour urine copper is usually high in all ALF patients regardless of the etiology. Hemolytic anemia should be a red flag as it is common in ALF due to WD. This leads to disproportionate elevation of AST compared with ALT, since AST is present in red blood cells, and a ratio AST/ALT >2.2 provides a sensitivity of 94% and a specificity of 86% for the diagnosis of WD (40,41). Moreover, additional testing should include Coombs testing (typically negative in WD) and examination of the peripheral smear to exclude other etiologies, since such conditions as thrombotic thrombocytopenic purpura may present with multiorgan failure as well (42). So, all patients with chronic or acute hepatitis or cirrhosis of unknown etiology should be screened for the possibility of WD.

Eye and brain presentations at diagnosis

The two most frequent extrahepatic presentations are the KFR and the cerebral involvement. They may be the only manifestations of the disease.

KFR can be detected by chance during a routine ophthalmologic examination and should be considered as indicative of WD until proven otherwise. Rings are rarely observed in other conditions like obstructive liver diseases, monoclonal gammopathies, multiple myeloma, arci senilis, and pulmonary carcinoma (22,43). As KFR is not so easy to diagnose without experience, Danish colleagues suggest that anterior segment Scheimpflug imaging (Pentacam, Oculus) could be an interesting tool to diagnose or confirm KFR by ophthalmologists with little experience in patients with WD (44). When neurological symptoms are present, KFR is present in almost all WD patients at disease diagnosis (20). Some retrospective studies have reported that only 72–85.2% of neurologic WD patients show a KFR (45-48) but these discrepancies could be due to the lack of experience in detecting KFR, even with a slit lamp, as the rings or crescents can easily be missed by an inexperienced ophthalmologist particularly if the iris is brown. Otherwise, KFR is initially present in almost 50% of patients with a hepatic presentation, and in 20–30% of presymptomatic patients (20,49,50).

Concerning neurological symptoms, they are reported

in approximately 18–68% of patients (19) and are mostly due to basal ganglia or brainstem lesions. Dysarthria is the most frequent neurologic feature reported in large cohorts (19,20,45,51) (from 57.6% to 79.7%) and is followed by dystonia (42.4–58.7%), tremor (36.2–50.1%), abnormal gait (37.8%), parkinsonism (30.4%) and chorea (12.7–15.3%). Dysarthria, dystonia, tremor, and parkinsonism can be sole initial disease manifestations (52,53) but since other rarer neurologic conditions may also develop initially, neurologists must be cautious about any manifestation related to central or peripheral nervous system involvement. A few case reports have documented polyneuropathy or autonomic dysfunction (sympathetic, parasympathetic fibres) as an initial manifestation of WD (54-56). For example, Jung *et al.* published the case of a 17-year-old man who developed intermittent paresthesias and weakness in both hands and feet at least 6 months prior to developing more typical symptoms of WD. Electrophysiological and pathological studies suggested a neuropathy of mixed type. Treatment for WD resulted in clinical and electrophysiological improvement (55). Seizures can also be the only presenting symptom of WD (57-62), up to 5.5% according to a retrospective study of 490 WD patients by Prashanth *et al.* (60). The most common type of seizures is of generalized seizures followed by partial simple or complex seizures. Status epilepticus is also described as first presenting manifestation of WD but is rarer (58,59). Inhibition of membrane ATPase by the toxic free copper is a hypothesis to explain the occurrence of seizures in early phases (63).

All textbooks and courses on WD emphasize the classic psychiatric presentations of the disease and every physician has learned that WD should be suspected in any young patient with psychiatric features. Studies confirmed that up to 64.8% of patients reported psychiatric symptoms (with or without hepatic or neurologic findings) at their initial presentation and up to 20% of patients had seen a psychiatrist prior to the diagnosis of WD (64). Despite these high figures, the diagnosis of a purely psychiatric form of WD remains extremely sophisticated and is responsible for a long diagnostic delay (average of 2.4 years, as reported by the meta-analysis of Zimbrean and Schilsky) (65). Acute or chronic psychosis (66-68), mania (69), obsessive-compulsive disorder, depressive disorder with or without suicidal ideation (70,71), catatonia, behavioural changes are the main presenting syndromes reported in the literature (64). This wide and non-specific clinical spectrum with symptoms usually worsened by

antipsychotics drugs explain the difficulty of diagnosis and should encourage physicians to look more often to the copper triad (Cp, serum copper and 24-hour urinary copper excretion). MRI should also be more frequently performed although brain imaging is usually normal in pure psychiatric presentations of WD (67). However, there are no studies looking at correlations between MRI studies and specific psychiatric presentations in WD.

Sleep disorders confirmed by sleep recordings are other common features of WD, combining insomnia, daytime sleepiness, restless legs syndrome (RLS), cataplexy-like episodes, and REM sleep behaviour disorder (RBD) (72), some of which being the first presenting symptom of WD. Insomnia, usually related to depression or anxiety, and conversely hypersomnia have been described as the sole presenting symptoms of WD (73,74). For instance, Firneisz *et al.* described a 21-year-old male patient who developed throughout 3 months an excessive daytime sleepiness with an increased total sleep time. He had no other symptoms except fatigue and decreased level of attention. Brain MRI was normal. Only a moderate elevation of liver enzymes was present lead finally to the diagnosis of WD. A 24-h sleep recording confirmed the increase in total sleep time (the patient was sleeping for more than 16 h) and the presence of many sleep-onset REM periods and an increase REM sleep percentage on the 24-h recording as it is seen in narcolepsy. Symptoms and sleep recording abnormalities disappeared after 14 months of D-penicillamine treatment (74). Another rare and atypical presenting symptom is RBD which may start early in the life with a poor quality of sleep and acted out dreams, and may persist despite the treatment of WD (75).

Other rare extra-hepatic presentations at diagnosis
To improve our diagnostic performance, we need to understand that WD can be a multisystemic disease right from the beginning, not only limited to liver or brain damage. As with the liver and brain, copper accumulates in different organs and may impair their function (76). Thus, other early extra-hepatic features include renal manifestations, osteo-articular disorders and endocrine disturbances.

Renal impairment is often missed because of its subtle manifestations that include proteinuria, glucosuria, phosphaturia, uricosuria, generalized aminoaciduria, microscopic haematuria and decreased glomerular filtration rate (76). In a retrospective analysis of 276 patients with WD, Saito *et al.* reported that 7.6% of WD patients had a past medical history of renal disturbances such as

nephritis, glomerulonephritis, or nephrotic syndrome, before the setting of the copper disease (77). Hypercalciuria, nephrolithiasis, and episodes of renal colic were also described by other authors as common signs preceding the diagnosis of WD (78-82). Concomitance of an immunoglobulin M nephropathy was once reported by Ul Abideen *et al.* in an adolescent who presented with nausea, vomiting, diarrhea, and worsening anasarca. He was found to have nephrotic-range proteinuria that did not respond to conventional corticosteroid treatment. A renal biopsy revealed a diagnosis of immunoglobulin M nephropathy. As his liver function tests were slightly abnormal and abdominal ultrasound scan revealed a coarse irregular liver, another diagnosis was looked at. Workup revealed elevated urine copper excretion and a low Cp level compatible with WD. D-penicillamine and cyclophosphamide for the corticosteroid-resistant nephrotic syndrome allowed a full remission of symptoms (81).

Rheumatoid problems are another classic early manifestation of WD characterized by joint or osseous pain as well as demineralisation leading to unusual bone fractures (7,83-85). Misra *et al.* reported a 30-year-old patient with slowly progressive pain in the small and large joints for 14 years (85). Prashanth described a girl who developed pain resistant to analgesic drugs in both lower limbs when she was seven. Deformity of the lower limbs followed and a corrective surgery for genu valgum was done at the age of 10 years without significant functional improvement. At 11.5 years of age, she broke her leg and then developed hand dystonia, a neurological symptom that lead rapidly to WD diagnosis (7).

The endocrine manifestations of WD classically include disorders of growth, hypothyroidism, hypoparathyroidism, hypoglycaemia, galactorrhoea, abnormal menstruation and infertility (76). Recurrent abortions are common especially in women with untreated WD (86). Endocrinological symptoms have rarely been reported as the initial presentation of WD (87) but amenorrhea can occur very early in the course of WD. It may be the first sign of the disease and may exist before hepatic cirrhosis. The menstrual period reappears after a few months of treatment. The pathological mechanisms of this amenorrhea remain to be studied but it may be a consequence of hypothalamic, pituitary, or ovarian disturbances (88).

Isolated biological findings at presentation

In some cases, the disease may only begin by isolated blood count anomalies like thrombocytopenia (due to hypersplenism and portal hypertension) or hemolytic anemia (42,89,90). We have the experience of a teenager who had isolated thrombocytopenia for two years during which complete hematologic investigations were negative and a diagnosis of idiopathic thrombocytopenia was settled. The diagnosis of WD was made later on, when he developed a slight hand tremor. Prella *et al.* reported a 19-year-old woman with a 2-week history of weakness, menometrorrhagia and dark urine who had hemolytic anemia and thrombocytopenia as the initial manifestation of WD. The first mentioned diagnosis was an autoimmune thrombotic thrombocytopenic purpura and initial therapy included intensive plasmapheresis that improved hemolysis. WD diagnosis was made three months later as she had an attack of biliary colic during which a cholestatic hepatitis was discovered (42).

False interpretation of copper tests

Misdiagnosis of WD may be due to inadequate interpretation of copper balance. The classical triad usually associated with a diagnosis of WD (low serum copper, low Cp and high urinary copper levels) may be absent in some cases. Indeed, the triad is incomplete or absent in 3% of patients with WD confirmed by genetic testing, and present in 16% of healthy heterozygous carriers. Cp for instance is increased by estrogen, pregnancy, and contraceptive pill. Being an acute-phase response protein, it also increases during inflammation, infections, and rheumatoid arthritis and in patients with myocardial complications or cancer. Immunologic assay also overestimates it. Conversely, low concentrations may be detected in case of acute viral hepatitis, drug-induced liver disease, alcoholic-induced liver disease, acquired copper deficiency, Menkes' disease, malabsorption, malnutrition, cachexia, marked renal protein loss, liver failure, or aceruloplasminemia (91). Interpreting the 24-h urinary copper excretion may be difficult as it may be below the conventional level taken as diagnostic of untreated WD (100 μg/24 h or <1.6 μmol/24 h) at presentation in 16–23% of patients, especially in children and asymptomatic siblings (92). Moreover, high urinary copper values could be seen in other types of liver disease (e.g., autoimmune hepatitis, chronic active liver disease, or cholestasis and in particular during acute hepatic failure of any origin). Heterozygotes may also have intermediate levels.

Atypical radiological findings

The classical lesions present in patients with neurological WD are symmetrical and localized in the basal ganglia (lenticular nucleus, caudate nucleus, thalamus) and the brainstem (midbrain, pons) in association with cerebral atrophy (93,94). However, to avoid diagnostic errors, neurologists and radiologists should be aware of atypical brain images like T2/flair hypersignal in the posterior part of the corpus callosum (95), in the medulla oblongata (96), in the cortex, or asymmetrical white-matter changes in the cerebral hemispheres with a predilection for the frontal lobes (97,98). Moreover, neurologists shall remember that a normal liver ultrasound (and even normal liver enzymes) in neurological patient does not rule out a liver disease, and especially WD. Conversely, exploring the brain in a patient with hepatic symptoms may help diagnosing WD as brain MRI may detect a decrease in the apparent diffusion coefficient of the putamen (99).

Make the diagnosis more rapidly and acutely

Open up to other diagnostic tests

Once the diagnosis is highly suspected, another challenge is to confirm the diagnosis rapidly and accurately in order to start the treatment without delay. Confirmation of the disease comes from the molecular analysis of the ATP7B with the presence of one mutation in each allele but direct genetic analysis is expensive, difficult and takes time due to more than 600 possible mutations. Not all countries have easy access to it. In daily practice, symptoms of liver, brain or other organs lesions associated with the copper triad (low Cp, low serum copper and high 24-h urinary copper excretion) or the combination of KFRs and a low serum Cp give usually enough arguments for the diagnosis and allow to start chelators or zinc salts pending genetic confirmation (49,100). But sometimes it is not enough. An interesting new approach to accelerate the diagnosis without error, is the direct determination of labile copper (non-Cp-bound copper), called exchangeable copper (CuEXC). It allows to calculate the "relative exchangeable copper" (REC) which refers to the ratio of CuEXC to total copper. REC was evaluated as a relevant diagnostic tool for WD with a high sensitivity and specificity. Demonstrations of the value of this new biomarker have been done in different situations like familial screening, different liver diseases, distinction between healthy heterozygous carriers, normal and WD patients, etc. It helps to avoid

liver biopsy to estimate the intrahepatic copper and speed up the diagnosis (101-108). The challenge is to develop around the world this rapid and reliable biological test already practiced routinely in a dozen hospitals in France. It is easy to implement and inexpensive (109). Another help for diagnosing WD could come from a more reliable measurement of Cp. As it measures both apoCp and holoCp, immunological assay overestimates the holoCp activity as apoCp has no activity. The future research needs to develop more techniques of enzymatic assay of Cp to be more accurate in diagnosing WD.

Take advantage of advances in genetics methods

Next generation sequencing (NGS) appeared a few years ago and revolutionized the genetic approach. As the great number of disease-causing ATP7B gene mutations may cause a real diagnostic challenge, NGS is rapidly providing a time-saving, cost-effective method for full sequencing of the whole ATP7B gene compared to the traditional Sanger sequencing (110). Russian authors estimated the price for comprehensive analysis of 1,000 samples for middle-sized gene (3,155 bp of coding sequence) as 6.2 US dollars per sample (111). The current challenge is to make NGS accessible widely around the world. It will then probably allow to diagnose more asymptomatic patients because genetic prevalence of the disease appears higher than the clinical prevalence. Indeed, early studies found the clinical prevalence of WD as being around 30 per one million (10), and based on the Hardy-Weinberg equilibrium, a heterozygous carrier frequency of about 1:90. However, three recent British, Korean and French NGS-based genetic studies produced heterozygous carrier frequencies of 1:25, 1:53 and 1:31, respectively (112-114). The discrepancy between the high heterozygous carrier frequency and the low clinical prevalence of WD may be explained by the clinical variability, the incomplete penetrance and the existence of modifiers genes.

Familial screening will have to be rethought and expanded because phenotypic expression is highly variable, even within the same family. Guidelines on familial screening will also need to be updated. Currently, first-degree relatives of any patient newly diagnosed with WD must be screened for WD because the chance of a sibling being a homozygote or compound heterozygote is 25%. Amongst off-spring, the risk is low (0.5%) but analysis of the ATP7B gene for mutations in the children of an index patient is also justified given the potential devastating

course of WD (49,100). Future guidelines will probably recommend to screen also parents—as 'pseudo-dominant' inheritance has been reported (115-117), along with uncles, aunts and nephews (102). Another future questioning challenge is the use of NGS for prenatal testing and newborn screening (118). Furthermore, NGS will allow to explore other modulators or environmental genes or to find genetic variants.

In conclusion, the varied clinical manifestations of WD due to pathological copper accumulation in different organs, even in the early course of the disease, often pose a diagnostic challenge. The variability in clinical and laboratory findings may be due to the multiple mutations of the WD gene associated with different degree of functional impairment of ATP7B. By drawing attention to the earliest symptoms and to new biomarkers and diagnostic tools, we hope that this article will increase diagnostic awareness and reduce delays so that patients can start their treatment earlier in the course of the illness and thus have a better disease prognosis.

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Footnote

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