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Clinical and Evolutionary Specifics in Pediatric Neurowilson: About 12 Cases

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Summary

Introduction: *Wilson's disease is a genetic disorder encompassing neurowilson as a clinical form dominated by neuropsychiatric symptomatology.*
The objective of this study is to reveal the clinical and evolutionary aspects of neurowilson as a late diagnosed clinical form.
Methods: *We performed a retrospective study of 12 cases of neuroWilson disease collected in the pediatric service of the University Hospital Mohammed VI of Marrakech over a period of 11 years.*
Results: *The cases studied included five boys (42%) and seven girls (58%). The mean age of onset of symptoms was 11 years with age extremes ranging from 7 to 13 years. The average time to confirmation of diagnosis was 25 days. The clinical presentations of neurowilson included tremors and dystonia with a percentage of 50% of cases for each symptom, dysarthria was found in 33% of cases, coma in 25% of cases, and psychiatric manifestations in 58% of patients. 70% of patients with the neurological form of Wilson's disease had abnormalities on brain magnetic resonance imaging. D-penicillamine was the treatment of choice in all patients, with neurological worsening noted in only 40% of cases. Neurological symptoms of Wilson's disease were largely reversible on D-penicillamine and zinc acetate with a rate of 42%, while about 33% of patients died with an estimated mean time to death of 1.75 years.*
Conclusion: *Despite therapeutic progress in the field of Wilson's disease, the prognosis of neurowilson remains reserved. this is why other more effective therapeutic strategies should be promoted.*

Mots clés: *neurowilson, D pénicillamine, child, neurological manifestation.*

Introduction

Wilson's desease is an autosomal recessive genetic disorder characterized by a toxic accumulation of copper in the body, and this pathological entity is dominated by neuropsychiatric and hepatic symptoms.

The objective of this study is to reveal the clinical and evolutionary aspects of neurowilson as a late diagnosed clinical form.

Methods

We performed a retrospective study of 12 cases of neuroWilson disease collected in the pediatric service of the University Hospital Mohammed VI of Marrakech over a period of 11 years.

Results

The cases studied included five boys (42%) and seven girls (58%). The average age at onset of symptoms was 11 years with extremes ranging from 7 to 13 years. The average duration of diagnostic confirmation was 25 days.

The neurowilson clinical presentations included tremors and dystonia with a percentage of 50% of cases for each symptom, dysarthria was found in 33%, coma in 25% of cases, not to mention psychiatric manifestations in 58% of patients like (irritability, depression, delirium). Patients usually manifest with various combinations of these symptoms.

70% of patients with the neurological form of Wilson's disease had abnormalities in cerebral magnetic resonance imaging, while the remaining 30% could not benefit from this radiological exploration due to the associated severe liver damage creating instability hemodynamics.

D penicillamine was the treatment of choice in all patients, in 40% of the cases there was no neurological worsening at the start of treatment but our attitude consisted in maintaining this molecule due to the unavailability of trientine in our country as a therapeutic alternative.
The neurological symptoms of Wilson's disease are largely reversible under anti-copper treatment (D penicillamine and zinc acetate) with a rate of 42%, knowing that these patients retained at least residual neuropsychiatric sequelae, while approximately 33% of patients died with an average time to death estimated at 1.75 years.

Discussion

Although the diagnosis of wilson's disease is made in the first decade of the child's life neurological symptoms of the disease are mainly observed in the second decade [1] .

Usually patients with neurowilson's disease initially presented clinical signs related to liver dysfunction, but studies had reported cases that presented only neurological signs [2].

In our series, 25% of the patients presented neurological signs at the beginning of the disease, whereas 75% of the cases presented a hepatic impairment that preceded the neurological picture.

The average time to confirmation of diagnosis was 25 days compared to 2.45 years in the series by Bono.W et al [3]. The diagnosis can be delayed because of the insidious onset and variable succession of hepatic, neurological and psychiatric symptoms, especially since the disease is under-diagnosed due to its rarity and neurological heterogeneity that may evoke other pathologies such as hereditary dystonia, hereditary ataxia, etc [4].

Psychiatric disorders can sometimes inaugurate the clinical picture of neurowilson in 14 to 20% of cases. These may be personality or behavioral disorders; emotional lability, impulsivity, aggressiveness, disinhibition or mood disorders [5] [6] [7]. Indeed, the typical psychiatric manifestation (irritability, depression, delirium) was present in 58% of the patients in our series with neurowilson.

Cerebral computed tomography, and at best magnetic resonance imaging, have an important contribution in estimating the severity of central nervous system damage. The most frequent lesions are represented by hyposignals in T1 and hypersignals in T2 and Flair, most often these lesions are multiple, symmetrical and they affect the midbrain, the thalamus, the basal ganglia, and the caudate nucleus [8].

In our series, 70% of patients with the neurological form of Wilson's disease had abnormalities on brain magnetic resonance imaging, while the remaining 30% could not benefit from this radiological exploration due to the associated severe hepatic involvement creating hemodynamic instability.

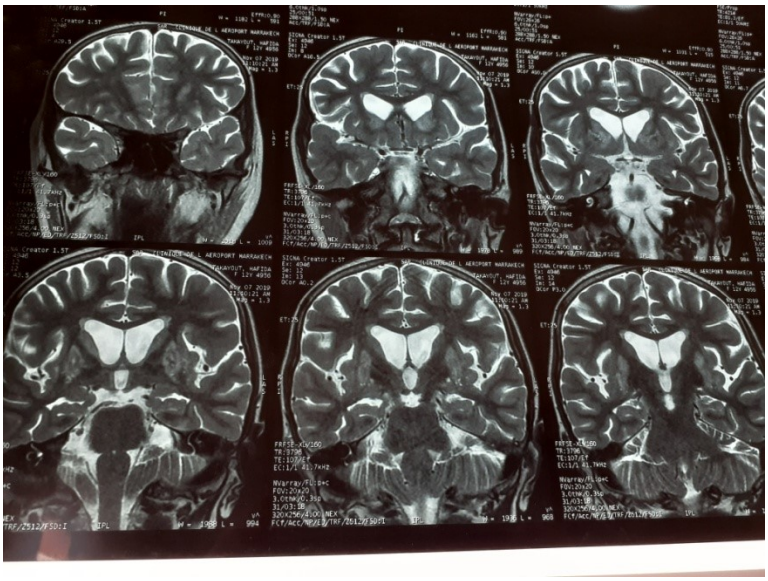

Figure 1: Coronal section of a brain MRI showing a T2 hypersignal of the caudate and lenticular nuclei bilaterally and symmetrically with secondary hemorrhagic infarction, in a child with dystonia: image in favour of a neurowilson.

Therapeutic management is based on copper chelators, zinc salts and liver transplantation [9]. However, in general, D-Penicillamine remains the gold standard of treatment for Wilson's disease. Wilson's disease, the majority of patients improve first biologically and then clinically 3 to 6 months after the start of treatment, despite the side effects that it may cause, in particular the worsening of the neurological picture at the start of treatment, which would be explained by too rapid a mobilization of copper into the plasma and its preferential redistribution to the brain [10]. This is in perfect agreement with the results of our study, which showed that the neurological symptoms of Wilson's disease are largely reversible under D-penicillamine with a rate of 42%, knowing that a neurological worsening was noted in 40% of these cases at the beginning of the treatment, but our attitude consisted in maintaining this molecule, given the non-availability of trientine in our country as a therapeutic alternative.

Tableau II. Traitements pharmacologiques spécifiques.

	Indications	Posologie	Suivi cuprique	Effets secondaires[a]
Chélateurs du cuivre				
D-Pénicillamine (DP) (Trolovol®)	Traitement de référence	Adulte : 1500 à 1800 mg/j Enfant : 750 à 900 mg/j	↑↑ cuprurie des 24 h	À court terme troubles digestifs, réactions allergiques, leucopénie, thrombopénie À moyen terme : glomérulopathies, affections auto-immunes (lupus induit) À long terme : lésions cutanées bénignes, lésions muqueuses
Triéthylènetétramine (Trientine®)	ATU[b]	Adulte : 1500 mg/j Enfant : 750 à 900 mg/j	↑ cuprurie des 24 h (plus modeste que sous DP)	Plus rares et moins bien documentés qu'avec la DP : anémie sidéroblastique, voire lupus induit
Sels de zinc				
Acétate de zinc (Wilzin®)	Formes présymptomatiques ou paucisymptomatiques	Adulte : 150 mg/j Enfant < 6 ans : 75 mg/j	↓ cuprurie des 24 h	Gastro-intestinaux (nausées en début de traitement) Pancréatite biologique

[a] Autres que l'installation ou l'aggravation des troubles neurologiques et/ou hépatiques, observés à l'instauration du traitement avec la D-Pénicillamine, le TETA ou le zinc. Cette aggravation peut, en partie, être prévenue par une augmentation très progressive des doses.
[b] Autorisation temporaire d'utilisation limitée au cas d'échec, d'intolérance ou de contre-indication à la D-Pénicillamine.

Figure 2: Summary table of specific pharmacological treatments in Wilson's disease.

The improvement of our patients was well marked, both clinically and biologically, but this did not prevent the patients from keeping at least one of the residual neuropsychiatric sequelae. The studies showed that tremor, hypertonia of the limbs, akinesia, and psychotic episodes often respond better to treatment, whereas axial dystonia, dysarthria, and behavioral disorders remain more difficult to control [4].

Two case series reported in the literature [4] show that treatment with D-Penicillamine results in a survival time close to that of the general population. However, in our study the mortality rate is still high, in fact 33% of our patients died with a mean time to death of 1.75 years.

In the context of other therapeutic alternatives, liver transplantation is indicated in the case of severe liver damage and/or in the case of severe neurological or neuropsychiatric signs that escape medical treatment [9]. However, some authors consider neurological damage as a poor prognostic factor for post-transplant survival [9].

ZINC seems to be the least toxic treatment, and has proven its efficacy, but it has a slower onset of action, which is why it is chosen as a maintenance treatment [11].

But in general the clinical and evolutionary profile of neurowilson's disease in children is marked by a very important variability that some authors had attributed to an etiopathogenicity resulting from the various mutations of the gene (ATP7B) [12].

Limitation

our work is limited by :- the insufficient number of samples even if it is explained by the rarity of the disease. the difficulty for the close clinical follow-up of patients given the easy inaccessibility to the university hospital center.

Conclusion

Despite therapeutic progress in the field of Wilson's disease, the prognosis of neurowilson remains reserved. this is why other more effective therapeutic strategies should be promoted.

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