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Jansky-Bielschowsky Disease in 2 Moroccan Girls. Clinical Cases

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Abstract **Case Report**

Neuronal ceroid lipofuscinoses (NLCs) belong to the group of lysosomal diseases. Their transmission is autosomal recessive. They are characterized by progressive degenerative neurological damage of variable clinical expressions, and by ophthalmic damage. Jansky-Bieloschowsky disease is the classic late infantile form of CLNs or classic CLN2. The EEG tracing is characteristic. Visual and somaesthetic cortical evoked potentials are abnormal. Cerebral MRI shows cerebellar and then cerebral cortical atrophy associated with T2 hypersignal of the periventricular white matter. The diagnosis was confirmed by biochemical, histological, and molecular tests. Patient n°1 is 7 years old. She is bedridden and visually impaired. She was presented with psychomotor regression at the age of 3 and epilepsy 6 months later. Brain imaging and EEG were typical. TPP1 (*tripeptidyl-peptidase1*) enzyme activity was significantly reduced. Patient 2 is a 5-year-old girl who is also bedridden and visually impaired. She presented with psychomotor regression at the age of 3 years and 2 months, and epilepsy 11 months later. Brain imaging and EEG were typical, and TPP1 enzyme activity had collapsed. These two observations illustrate the diagnostic particularities of this very rare disease and current therapeutic perspectives.

Keywords: neuronal ceroid lipofuscinosis, Jansky-Bielschowsky disease, diagnosis - treatment.

INTRODUCTION

Jansky-Bieloschowsky disease is the classic late infantile form of CLNs or classic CLN2. It is characterized by a progressive degenerative neurological disorder of variable clinical expression, and by ophthalmic involvement. The EEG shows a slowing of background activity, and a highly specific response to intermittent light stimulation. Visual evoked potentials are large, and the amplitude of cortical somaesthetic evoked potentials is greatly increased. Cerebral MRI shows cerebellar and then cerebral atrophy, with T2 hypersignal of the periventricular white matter. Diagnosis is confirmed by enzyme activity, molecular biology and electron microscopy of curvilinear granular inclusions in the skin, peripheral nerve or rectal mucosa. These two observations illustrate the diagnostic features of this very rare disease and discuss new therapeutic perspectives.

PATIENTS AND OBSERVATION

Our patient N°1 is a 7-year-old girl, the eldest of 2 siblings from 1er degree consanguineous parents. Her pregnancy was carried to term, with no evidence of neonatal distress. Psychomotor development was delayed, with walking acquired at 2? Years and poorly structured language at 3 years. From the age of 3, she presented a psychomotor regression with frequent falls, then a walking disorder which became uncertain, and a regression of speech. After six months of evolution, the family reported the appearance of generalized abnormal movements with loss of consciousness lasting 5 to 10 minutes, associated with a total loss of walking and speech. Repeated startle attacks and suspensions of contact with movements of the eyelids and corners of the mouth were also reported. Clinical examination on admission to our department revealed a bedridden child whose weight, height and head circumference were normal for her age. She reacted with head and hand movements to tactile and auditory stimuli, and did not follow with her gaze. She showed an overall decrease in muscle strength, predominantly in the upper limbs, and spasticity predominantly in the lower limbs. Osteotendinous reflexes were sharp and symmetrical. Sensitivity was preserved. Ophthalmological examination revealed cortical blindness, alternating divergent strabismus and poorly reactive semi-mydriasis. The rest of the physical examination was unremarkable. The electroencephalogram showed several myoclonic episodes punctuated by intermittent light stimulation (ILS) over a slowed background. There was also phototic entrainment to low-frequency (1 HZ)

SLI, with a fairly wide spike or wave spike pattern at the same frequency as the SLI and stopping with it [fig.2]. Cerebral CT showed diffuse cortical and subcortical cerebral atrophy [fig.1]. Visual evoked potentials were hypovolemic with profound gangliono-cortical conduction disorder. CSF, blood and urine amino and organic acid profiles were unremarkable. Lactatemia was normal. In view of this array of symptoms, the classic late infantile form of NLC was evoked, specifically NLC2 or Jansky-Bielschowsky disease. TPP1enzymatic activity, which was very low at 3 mmol/h/mg protein (normal lab range 30-50 mmol/h/mg protein), supported the diagnosis. A molecular study of the CLN2/TPP2 gene was not performed. The patient benefited from nursing, antiepileptic treatment, and muscle relaxant therapy. At the age of 7, the patient was bedridden. She underwent gastrostomy for enteral feeding. Seizures are partially controlled by sodium Valproate, Levetiracetam and Clonazepam.

Our patient N°2 is a 4-and-a-half-year-old girl. She was first seen in consultation at the age of 3 years and 2 months for psychomotor regression following delayed psychomotor acquisition, tremor when grasping objects and abnormal movements that had appeared 1 year earlier. Seven months later, she presented with a loss of walking and language. On neurological examination, standing was still possible for a few seconds, the upper and lower limbs were hypertonic, osteotendinous reflexes in the lower limbs were brisk, and cutaneous-plantar reflexes were flexed. Muscle strength and sensitivity were preserved. Examination of the cranial pairs revealed no abnormalities. Hair appearance was normal. There was no hepatomegaly or splenomegaly. The rest of the clinical workup was unremarkable. Ophthalmological examination revealed good visual behavior. The child followed light and caught objects. Ocular motility was normal. The anterior segment and fundus were normal. Brain MRI revealed cortical atrophy with widening of the cortical sulci and subcortical atrophy with widening of the ventricular structures and basal cisterns. There were no signal abnormalities in the brainstem, cerebellum or cerebral parenchyma.

The first sleep EEG was indicated by the appearance of repeated abnormal movements of the right lower limb. It showed an overall slowing of background activity and epileptic abnormalities in the form of symmetrical and synchronous diffuse wave spikes. Intermittent light stimulation (ILS) had no effect. The patient was put on sodium Valproate without any real control of the abnormal movements. The rest of the work-up included blood and urine toxicity tests, lactatemia and pyruvatemia, cerebrospinal fluid chemistry, blood count, blood ionogram, hemostasis, protidemia, renal function, blood glucose, creatinine phosphokinase, lipid profile, ammonia, thyroid profile, Acyl-carnitine profile, amino acid and fatty acid chromatography, very long-chain fatty acid profile and organic acid profile, all of which were abnormal. The patient was seen again at the age of 3 years and 10 months. Another cerebral MRI was performed in view of the persistent psychomotor regression. It also showed signs of vermian and hemispheric cerebellar atrophy with a mega-cisternary appearance and a T2 hypersignal in the periventricular white matter [Fig.3]. At the age of 4 years and 1 month, the patient presented with repeated generalized tonic-clonic seizures. A 2ème EEG was performed. It showed a significant slowing of the background trace (fast-paced notched delta activity) on all leads [Fig.4]. There was also phototic entrainment (SLI at 1-2Hz) in the form of spikes followed by waves mainly in the occipital region [Fig.5]. Further ophthalmological examination revealed retinal and optic atrophy. Jansky-Bielschowsky disease was suggested. TPP1 enzymatic activity, which was low at 8 mmol/h/mg protein (normal lab values between 30 and 50 mmol/h/mg protein), supported the diagnosis. A molecular study of the CLN2/TPP2 gene was not possible due to lack of funds. Currently aged 5, our patient is bedridden. Tonic-clonic and myoclonic epilepsies are partially controlled by sodium Valproate, Clonazepam and Levetiracetam. She is on Baclofen for spasticity and enteral feeding via a gastric tube.

FIGURES

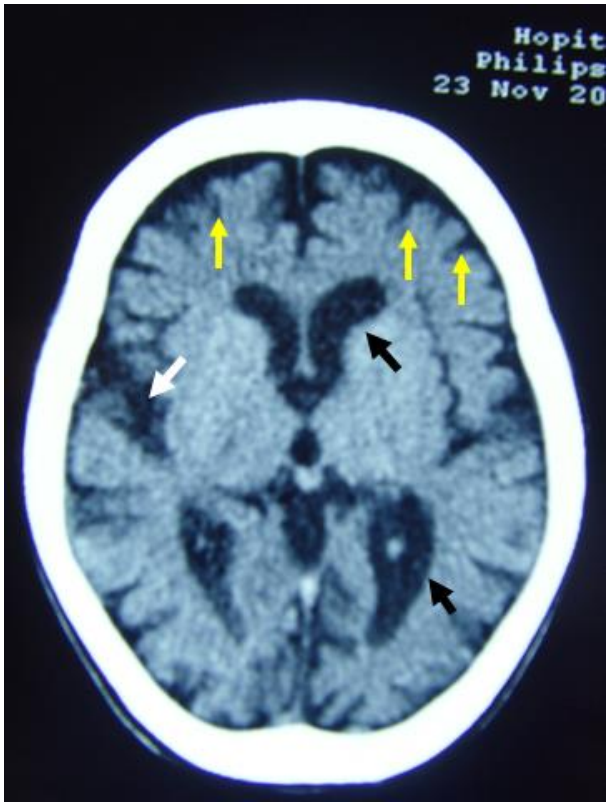

Figure 1: Cerebral CT in axial section showing widening of sylvian valleys (white arrow) and cortical sulci (yellow arrows) indicative of cortical atrophy, and ventricular widening indicative of subcortical atrophy (black arrows).

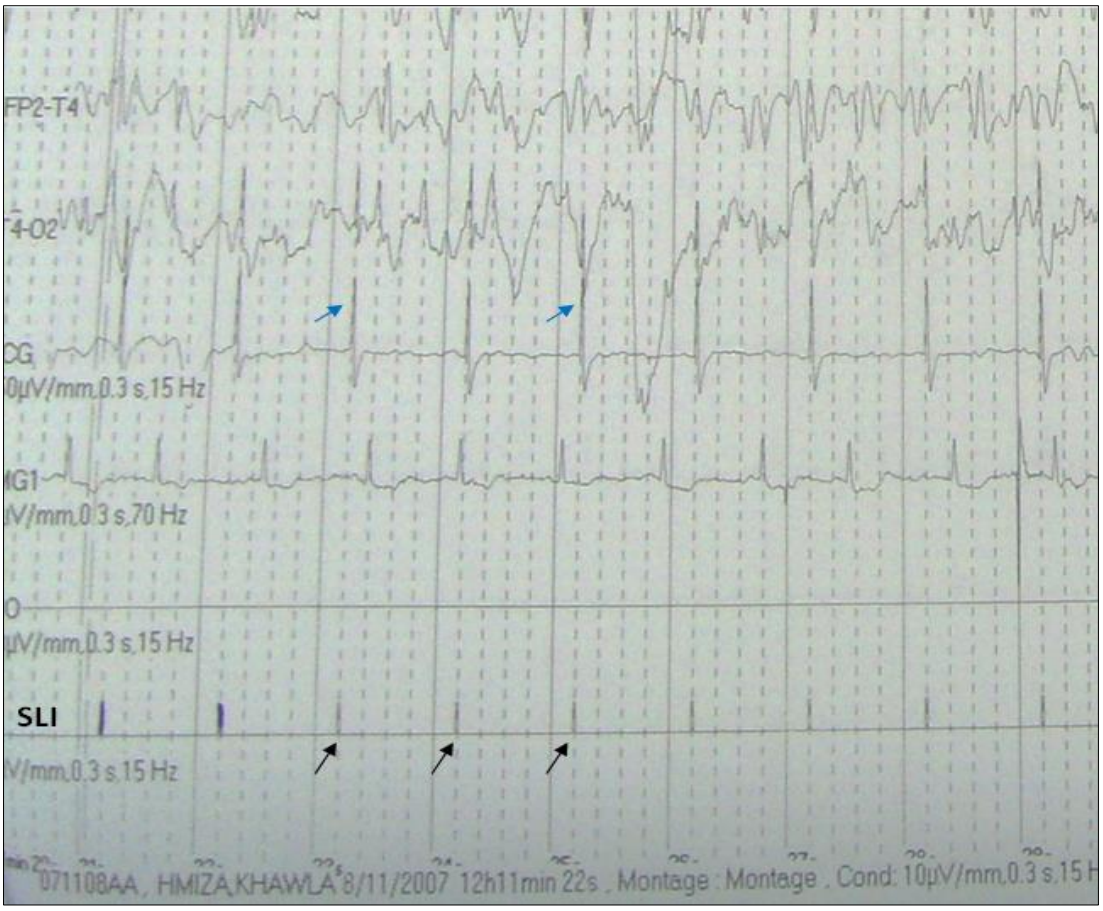

Figure 2: Electroencephalogram showed grapho-elements with fairly ample spikes or peak-waves (blue arrows) having the frequency of the SLI (1Hz) and stopping with the end of it (black arrows).

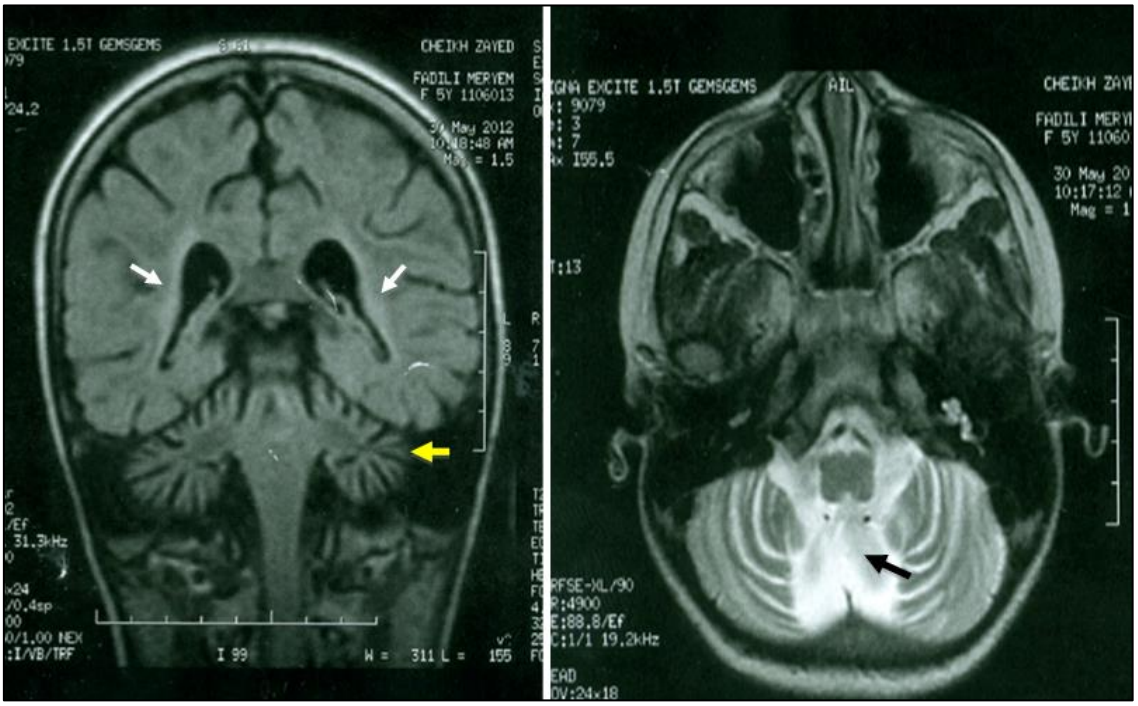

Figure 3: Cerebral MRI in coronal section shows signs of hemispheric cortical atrophy with widening of the cortical sulci, vermian and hemispheric cerebellar atrophy (yellow arrow) with mega-large cistern appearance (black arrow) and T2 hypersignal of the periventricular white matter (white arrows).

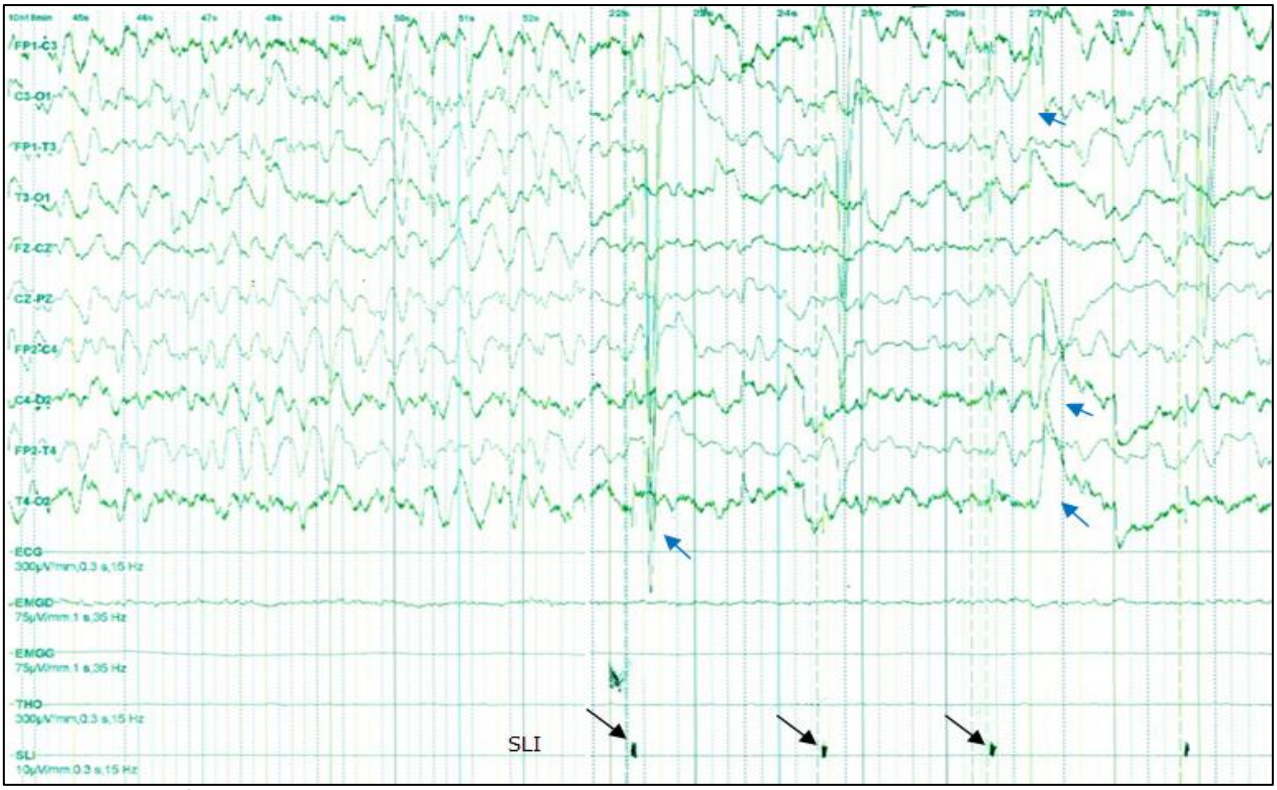

Fig. 4: On the 1ère sequence, the EEG showed a significant slowing of the background trace (fast-paced notched delta activity) on all leads. Phototic SLI training (black arrows) with spikes followed by waves mainly in the occipital region (blue arrows).

DISCUSSION

CLNs are inherited neurodegenerative diseases with autosomal recessive transmission. They are classified as lysosomal diseases. They are characterized by the deposition of autofluorescent lipopigments in the central nervous system and other organs. This deposition is secondary to an enzyme deficiency. The old classification, based mainly on the age of onset of the first symptoms, defined 4 main groups: early infantile forms (CLN1), late infantile forms (Jansky-Bielschowsky disease or CLN2), juvenile forms and adult forms [1]. Current classification is based on clinical and genetic features, and currently limits CLNs to 14 groups [2]. The late infantile forms of CLNs include not only Jansky- Bielschowsky disease, but also variant forms depending on the defective gene [3]. Jansky-Bielschowsky disease, or the classic or late infantile form of CLN2, corresponds to a mutation in the CLN2 gene located on chromosome 11p15, responsible for a deficiency in the activity of the lysosomal enzyme TTP1, *leading to an* accumulation of substrates normally metabolized by this enzyme in neurons, the retina and glial cells. This leads to progressive cerebral and retinal degeneration. The age of onset and speed of progression vary according to the underlying genetic abnormality. The order in which symptoms occur is variable and depends on age of onset and genetic form. The 1st symptoms appear between the ages of 2 and 4, with a delay then regression in psychomotor acquisition, followed by motor impairment (pyramidal and extrapyramidal impairment, ataxia, language impairment), severe multiform epilepsy (generalized tonic-clonic, myoclonic or atypical absence) and loss of vision due to retinal degeneration [5]. The disease progresses to almost complete psychomotor deterioration before school age. In the early stages of the disease, visual impairment often goes unnoticed. Vision loss is rapid and complete, with thinning of the retinal vessels and pallor of the macula associated with optic nerve atrophy by the age of 4 to 5. The average age of death is between 8 and 12 years, with major polyhandicap. Accurate diagnosis is essential for genetic counseling, sharing information about prognosis and future course of the disease, and for optimal symptom care [4]. The EEG shows a slowing of background activity, and a very particular response to low-frequency SLI (1-2Hz) with polyphasic complexes consisting of a spike followed by a slow wave, of maximum amplitude over the posterior regions, synchronous with light flashes [6]. Visual evoked potentials are enlarged. The amplitude of cortical somatosensory evoked potentials is also greatly increased [7]. MRI shows cerebellar atrophy as early as 4 years of age, earlier than cerebral atrophy. There is a T2 hypersignal of the periventricular white matter [8]. In 2015 13 international laboratories and experts developed an algorithm for making an early and accurate diagnosis of CLN2 that is based on the degree of clinical suspicion [9]. According to this algorithm, classic CLN2 is strongly suspected clinically by the appearance of unexplained epilepsy and/or ataxia preceded by early language delay and/or abnormal

psychomotor development (retardation or stagnation), and electrically on a slowed EEG trace and a phototic reaction at 1-2Hz. The diagnosis of classic CLN2 is based on the presence of impaired TPP1 activity in leukocytes and identification of the mutation in the CLN2/TPP1 gene (11p15). The 2 most frequently found mutations are c.509-1G>C and c.622C>T [10].

There is no curative treatment. Management consists of symptomatic and palliative care, with the aim of maintaining functional capacity and quality of life. It is based on nursing, anticonvulsants, treatment of spasticity with muscle relaxants, and gastrostomy feeding in the advanced stages of the disease. Epilepsy is often drug-resistant. Progressive cerebral degeneration reduces the efficacy of antiepileptic drugs and increases their toxicity. Consequently, the aim of antiepileptic treatment should not be the disappearance of epilepsy or the normalization of the EEG trace. Therapeutic adjustment should be based on clinical response. In late infantile forms, it is recommended not to use more than 2 antiepileptic drugs, to use mainly sodium Valproate, Lamotrigine or benzodiazepines for grand mal epilepsy, and to avoid Carbamazepine, Phenytoin and Vigabatrin [11]. Myoclonus is best controlled by Levetiracetam and Piracetam. On the other hand, they are aggravated by Carbamazepine, Gabapentin and Lamotrigine. Treatment of spasticity is based on Baclofen in 1ère intention, and Tizanidine in 2ème intention. Botulinum toxin can also be injected locally into the muscle. Gene therapy has been used without significant progress [12]. Enzyme replacement therapy with Cerliponase alpha Brineura® (recombinant TPP1) was granted marketing authorization in France in July 2017. It is administered by intracerebroventricular infusion at doses of 100, 150, 200 and 300 mg every other week, respectively before 3 months, before 1 year, before 2 years and beyond 2 years. It is not yet available in Morocco. This enzymotherapy stabilizes the disease, provided it is introduced early in the course of the disease [13].

CONCLUSION

Jansky-Bielschowsky disease has a characteristic clinical, radiological and encephalo-electrical presentation. Diagnosis is based on biochemistry, molecular biology and histology, and must be made early. The prognosis is poor. The disease progresses rapidly, and patients are usually confined to bed by the age of 5. Death occurs between 10 and 15 years of age. In our context, in the absence of enzyme therapy, prenatal diagnosis and genetic counseling are of great value.

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