Role of optic microscopy for early diagnosis of Menkes disease

DANA CRAIU1,2), STEPHEN KALER3), MIHAI CRAIU4,5)

1)Discipline of Pediatric Neurology, Department of Neurology, Pediatric Neurology, Psychiatry, Neurosurgery, Psychiatry for Children and Adolescents, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
2)Clinic of Pediatric Neurology, “Alexandru Obregia” Clinical Psychiatric Hospital, Bucharest, Romania
3)Section on Translational Neuroscience, Molecular Medicine Program, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA
4)Discipline of Pediatrics, Department of Pediatrics and Medical Genetics, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
5)Pediatric II Clinic, “Alfred Rusescu” Clinical Pediatric Hospital, Institute of Mother and Child Health, Bucharest, Romania

Abstract
We report the case of a male patient with a normal development in the first three months of life, presenting for global regression, central axial hypotonic syndrome, pyramidal syndrome, focal epileptic seizures, and a particular aspect of the hair – almost absent, short, sparse, lightly colored, at age of five months, becoming coarse, twisted (kinky hair) by the age of 21 months. Different diseases associate similar neurological and macroscopic aspect of the hair (biotinidase deficiency, argininosuccinic aciduria, aminoaciduria, giant axonal neuropathy, trichothiodystrophy and Menkes syndrome). The microscopic aspect of the patient’s hair showing normal hair, silver colored hair, hair shafts twisting 180°, tricholysis, and trichoptilosis, was highly characteristic for Menkes disease. Diagnosis was further supported by the low concentration of serum copper and ceruloplasmin and exclusion of other metabolic disorders with similar macroscopic aspect of the hair. Molecular genetic testing by multiplex PCR indicated deletion of exon 22 in the ATP7A gene situated in Xq21.1 region, consistent with the diagnosis of Menkes disease. Physicians should use microscopic evaluation of the hair more often when suspicion of Menkes disease is raised, aiming a narrow further diagnostic workup and early positive diagnosis and genetic advice for the affected families.

Keywords: Menkes disease, hair microscopy, kinky hair, copper, pili torti, epilepsy.

Introduction
Menkes disease (MD) (also known as Menkes kinky hair syndrome or trichopoliodystrophy) is a rare lethal disorder of copper transport (one in 100 000–254 000 live-born babies) [1] caused by mutations in the copper-transporting ATPase gene (ATP7A) transmitted in an X-linked recessive manner [2]. Because of impaired copper absorption, there are low concentrations of copper in some tissues, accumulation of copper in other tissues, and reduced activity of copper-dependent enzymes such as tyrosinase (responsible for hypopigmented skin and hair) [3], lysyl oxidase (explaining aneurisms, bladder diverticula due to defects of conjunctive tissue) [4], dopamine beta hydroxylase (leading to defects in catechol synthesis and keratin) [5], absence of cytochrome c oxidase and superoxide dismutase (explaining progressive cognitive involvement) [6]. Diagnosis is suspected in male infants who develop hypotonia, loss of milestones achievement and seizures after age 2–3 months. They usually exhibit a special aspect of the hair – sparse, twisted and of light color. Diagnostic testing include serum concentration of copper and ceruloplasmin (low in MD), plasma and CSF (cerebrospinal fluid) catecholamine analysis, copper transport studies in cultured fibroblasts, molecular genetic testing [7]. Optic microscopy of the hair may allow early diagnosis suspicion at the infant/toddler age when the serum copper and ceruloplasmin levels are low for all children, or when the above-mentioned methods are unavailable or excessively expensive [8].

Patient, Methods and Results
A Caucasian male patient presented at age of five months for treatment resistant left hemisphere focal clonic seizures with onset at age of four months. He had apparently normal milestones achievement until age of four months, when, after a febrile illness, motor and cognitive regression, hypotonia and hypoactivity were observed.

Patient was born at term after a pregnancy with imminent abortion in the first months, by vaginal prolonged delivery (27 hours), 3100 g and Apgar score of 7, necessitating neonatal resuscitation. Parents affirmed complete lack of scalp and eyebrows hair at birth.

Clinical examination at age of five months revealed round face, light skin color, blue eyes, and right inguinal hernia.

The hair at eyebrows and scalp was almost absent, short, sparse, lightly pigmented, almost gray (becoming coarse, twisted – kinky hair – by the age of 21 months) (Figure 1a).

He had 8500 g and 43.5 cm head circumference. No thoracic deformities, no cardiac, respiratory, renal or digestive involvements were noted.
Neurological examination revealed global, predominantly axial hypotonic syndrome (absent head control and sitting, floppy infant when ventrally supported, with balant head and limbs), muscle strength diminished, movements possible only distally. Bilateral pyramidal syndrome with bilateral equinovarus, brisk tendon reflexes, plantar clonus and Babinsky sign was registered. Cognitive examination revealed decreased interaction with family, inconstant smiling, no interest for toys or faces, frequent episodes of inconsolable crying and irritability. His overall psychomotor developmental age was of 1–2 months and he presented combined pyramidal and hypotonic syndromes.

Due to initial normal development with subsequent regression adding neurological signs and epilepsy combined with the particular aspect of hair, a range of metabolic disorders producing macroscopic hair changes were considered: biotinidase deficiency, argininosuccinic aciduria, aminoaciduria, giant axonal neuropathy, trichothiodystrophy, and MD.

Light microscopy scalp hair analysis at age of five month revealed normal hairs, abnormally colored hairs (silver), pili torti (hair shafts twisting 180°), trichoclasis (transverse fracture of the hair shaft), and trichoptilosis (longitudinal splitting of the hair shaft) (Figure 2a), highly characteristic for MD.

Low serum ceruloplasmin of 15 IU/mL (normal values 70–125 IU/mL) and low serum copper – 62 μg/100 mL (normal values 70–140 μg/100 mL) suggested MD. CBC (complete blood count), blood glucose, serum electrolytes, bicarbonate, and blood gases levels, blood urea nitrogen, creatinine levels, bilirubin level, transaminases levels, prothrombin time, and activated partial thromboplastin time, ammonia levels, lactate dehydrogenase, creatine kinase, and urine screening showed normal values.

Metabolic workup (plasma quantitative amino acid analysis and urine organic acid analysis together with the above-mentioned general screening) showed normal values confirming the initial microscopic diagnosis. Genetic analysis by multiplex PCR indicated deletion of ATP7A exon 22.

Further evaluation later in the evolution, at age one year nine months identified characteristic macroscopic (Figure 1b) and microscopic hair aspect (Figure 2b) for MD, multi-organ involvement, concordant with this entity: radiography of the long bones showed metaphyseal spurring and periosteal reaction in the diaphysis (Figure 3), urinary bladder diverticulum at abdominal ultrasonogram (Figure 4) and bilateral, left more than right temporo-frontal subdural blood collection, left temporal subcortical cerebral massive destruction at MRI examination (Figure 5).

Patient was treated with antiepileptic drugs and intravenous copper-histidine medication, but he evolved to rapid deterioration and died at age 2.5 years.

Genetic advice was offered for the next two pregnancies; chorionic villous biopsy and sex determination were performed for both pregnancies; parents choose to terminate the first with male fetus and to keep the second, resulting a healthy baby girl.
Discussion

The values of serum copper and ceruloplasmin, used for diagnosis of MD, may be physiologically low in all children under the age of six months [9], therefore not always reliable for early diagnosis at this age [7, 10]. In these cases, microscopic evaluation of the hair, characteristic in MD and different from other neurodevelopmental progressive disorders having similar clinical and macroscopic hair aspect, and sharing also some of the microscopic changes may point to the diagnosis. Although macroscopic aspect is unpecific [11], and MD children may show very short and sparse hair, microscopic changes may be visible at early age.

Other diseases associating hair changes should be excluded. Biotinidase deficiency is accompanied by alopecia due to early hair loss with no microscopic changes [12, 13]. Argininosuccinic aciduria may produce hair loss [14], brittle hair [15], or even pili torti as described in one case, but microscopic aspect differs, with perifollicular chronic inflammation and fibrosis, abnormal hair follicles with keratin plugs and misshapen hair shafts (pili torti) [16]. Aminoaciduria [17] may be accompanied by either hair loss [18] or by abnormal hair (coarse, fair, fuzzy), but with no macroscopically abnormal aspect [19]. Trichoiodidistrophy [20] may show at microscopic evaluation shaft abnormalities of trichoschisis and trichorrhexis nodosa-like fraying, but no twisting of the hair shaft or trichoptilosis/trichoclasis, which are characteristic for MD [21]. Giant axonal neuropathy may also associate hair changes, but nerve velocities usually clarify the diagnosis [22]. Genetic analysis by multiplex PCR was previously proved by Liu et al., as a rapid and robust screening method for diagnosing Menkes disease [23]. The multiorgan involvement and gravity of the case may be correlated with the large described deletion of ATP7A exon 22, although generally it is difficult to establish a clear phenotype-genotype correlation, clearly illustrated by the presence of inter- and even intra-familial variability [24]. The metaphasal spurring and periosteal reaction in the diaphysis are similar to the changes seen in scurvy [25]. Copper-histidine treatment was previously used with variable outcome for MD patients [26, 27], most probably due to the genetically diverse condition [28]; our patient revealed a rapid deterioration. Our case was extensively evaluated and the whole clinical, biological and genetic picture was documented, but the actual diagnosis was suspected and rapidly demonstrated by microscopic evaluation of the hair, and allowed proper genetic advice [29].

Conclusions

This article highlights the importance of optic microscopy of the hair for early diagnosis of MD, allowing differentiation when clinical differential diagnosis is broad and other tests are not conclusive and genetic testing unavailable or very expensive. Physicians should use this simple method, available in any hospital, more frequently when suspicion of MD is raised. Early diagnosis will allow correct genetic advice, with the possibility of avoiding occurrence of new cases in the same family.

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References


Figure 3 – Long bones X-ray: metaphyseal spurring and periosteal reaction. Figure 4 – Diverticulum of urinary bladder. Figure 5 – MRI: flair sequence showing bilateral, left more than right temporal-frontal subdural blood collection, left temporal subcortical cerebral massive destruction.
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Corresponding author
Dana Craiu, Associate Professor of Pediatric Neurology, MD, PhD, Discipline Pediatric Neurology, Department of Neurology, Pediatric Neurology, Psychiatry, Neurosurgery, Psychiatry for Children and Adolescents, “Carol Davila” University of Medicine and Pharmacy, Bucharest; Clinic of Pediatric Neurology, “Alexandru Obregia” Clinical Psychiatric Hospital, 10–12 Berceni Road, Sector 4, 041915 Bucharest, Romania; Phone/Fax +4021–334 79 94, e-mail: dcraiu@yahoo.com

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