

Early screening of treatable metabolic diseases: case report of menkes syndrome

Abstract

Introduction: Congenital anomalies, among these metabolic disorders, are largely asymptomatic at birth. The diagnostic suspicion ends up being delayed and defined in a moment of irreversibility of the disease. Menkes Syndrome (MS) is an example of these asymptomatic changes, which makes the suspicion and diagnostic investigation difficult, through the serum dosage of copper and ceruloplasmin, delaying the therapy. This is based on early parenteral copper supplementation to ensure prognostic implementation.

Objective: Report the case of a patient diagnosed with Menkes Syndrome, review the subject literature and discuss the impacts of the implementation of new diagnostic methods through neonatal screening.

Case report: Ten-month-old white male patient with a history of neuropsychomotor developmental delay and difficult-to-control seizures, beginning at 6 months. Given the possibility of inborn error of metabolism, Neonatal Molecular Screening (TNM) was requested via oral swab. The result evidenced Homozygous n the ATP7A gene with low dosages of copper and ceruloplasmin confirming the diagnosis of Menkes Syndrome.

Conclusion: Scientific advances pressure the expansion of neonatal screening in order to improve rare disease screening. The emergence of new generation sequencing contributes to the identification of gene alterations that lead to complex and challenging management diseases. Neonatal screening directly impacts infant morbidity and mortality by early detection and treatment. Genetic diagnosis of congenital anomalies allows optimizing the search for resources and specific therapy for each case. Despite these benefits, the NGS exam has a considerably high cost, both economically and psychosocially, that must be taken into account before the universalization of these technologies.

Keywords: menkes syndrome, genetic screening, newborn screening

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Abbreviations: MS, menkes syndrome; NGS, new generation sequencing; ICU, intensive care unit.

Introduction

Every year an estimated 7.9 million children are born with a congenital anomaly, many of them are asymptomatic at birth and with no family history.¹ Most individuals affected with metabolic diseases begin the diagnostic investigation from the onset of signs and symptoms, by that time, the treatment is often irreversible.² One of the metabolic diseases with early treatment is Menkes Syndrome (MS).

MS is a lethal neurodegenerative disease with an X-linked inheritance pattern known as “Kinky hair disease”.³ The incidence is estimated at 1 to 300,000 births in Europe, but in Australia these numbers increase to 1 to 40,000 births.³ It occurs due to deficiency in the ATP7A gene-coded copper transmission transporter located in the long arm of the X chromosome at the Xq13.3 locus.⁴ It is a multisystemic disease with a progressive clinical course. Most individuals are asymptomatic in the firsts months of life and progress with rapid decline in neuropsychomotor development associated with seizures, hypotonia, changes in connective tissues and hair structures.⁵

The classical diagnosis is based on an association between clinical manifestations and reduced serum copper and ceruloplasmin levels.⁶ The most common treatment for Menkes disease is copper injection

therapy indicated for asymptomatic patients under 28 days of age. Research shows the disease presents a variable response to therapy according to the type of mutation and the level of copper transport impairment. Some patients show great improvement, while others have minimal improvement or die despite the early intervention, but those who are diagnosed and begin treatment within days after birth show the best outcomes.⁷ However, because the current newborn screening methods do not detect Menkes disease and the clinical symptoms are hard to spot in newborns, most infants do not get diagnosed or treated early enough to benefit significantly from treatment.

Case Report

Ten-month-old, white, male patient with history of delayed onset of neuropsychomotor development and loss of developmental milestones at six months, associated with West syndrome. Physical examination showed a significant drowsiness, difficulty swallowing, generalized hypotonia, deep hyporeflexia with frequent spasms. He had already been subjected to outpatient investigation with skull magnetic resonance imaging demonstrating a mild cortical atrophy and normal ammonia level. As the possibility of innate metabolism error was suggested, Molecular Neonatal Screening (TNM) was requested by oral swab. The result evidenced presence of variant in Hemizygosis in the ATP7A gene suggesting the diagnosis of Menkes Syndrome. The diagnosis was confirmed with low dosages of copper

and ceruloplasmin. The patient evolved with accentuation of the capillary hypochromia, previously observed only with dermatoscopy, and worsening of muscle tone, despite the beginning of motor physical therapy and occupational therapy. The convulsive seizures were controlled with Levetiracetam.

Discussion

The established diagnosis of MS is made by plasma copper and ceruloplasmin dosage after the third week of life.⁶ Currently, this method has been replaced by genetic testing that can be performed at any time. Subcutaneous copper supplementation, when started before the onset of symptoms, has reduced seizure frequency and severity as well as increased survival rates.^{6,7}

Therefore, the urgency in the diagnostic is justified by the rush to initiate the therapy, whose benefit is only well established in the neonatal period.³ Accordingly, the presentation of this report aims to discuss the indication and expansion of molecular genetic screening, from the perspective of a diagnostic anticipation, and providing an improvement in the prognosis of the syndrome.

Children with epileptic encephalopathy often carry diagnostic labels such as West syndrome, which are based on clinical manifestation and not differentiated by the underlying genetic condition.⁹ The management of a child with refractory epileptic status in the first months of life is challenging and frustrating, and may require admission to the intensive care unit (ICU) as well as invasive measures. The contribution in identifying altered genes for this spectrum of diseases has been increasingly valued, especially after the emergence of New Generation Sequencing (NGS).¹⁰ Genetic diagnosis allows the adoption of increasingly accurate and effective therapies for seizure treatment.

Standard neonatal screening programs are justified by the fact that early detection and treatment have a positive impact on the morbidity and mortality of affected individuals.¹¹ Screening in Brazil includes blood, endocrine and metabolic diseases such as sickle cell disease and hypothyroidism, not including rare diseases such as MS.¹²

Although diseases included in neonatal genetic screening are individually rare, together they are fairly common, so it is very likely that a doctor will come across at least one of them throughout his career. In addition, advances in medicine have led to increased survival rates of children with genetic conditions and their demand for medical services. Although these constitute a relatively small number of cases, they collectively exert a disproportionate effect on health systems by requiring multiple hospital services.

Clinical diagnosis of such conditions is not always easy, therefore is often confirmed at a late stage. Such delay extends as an expensive and emotionally exhausting diagnostic odyssey, including unnecessary examinations, caregiver work absenteeism, repeated journey to distant medical services and increased risks of irreversible injuries.¹² This ends up constituting a heavy emotional, economic and physical cost, besides not contemplating genetic counseling.¹³ Although subcutaneous copper therapy is considered standard, there is great variability in therapeutic response. The types of mutations that have the best responses are those that do not completely prevent copper transport.⁷ In addition, occupational therapy and physical therapy can help maximize the potential and functioning of a child with MS. In the case described, it was not possible to perform copper therapy due to late diagnosis, but occupational therapy and motor physical therapy

were initiated, although the disease maintained the expected evolution with worse motor skills.^{14,15}

Despite the benefits cited, the cost associated with the NGS exam makes universal screening questionable. Confirmation of positive tests combined with the counseling and monitoring of families increases the value of the screening. Moreover, the identification of genetic alterations does not necessarily determined the occurrence of early childhood diseases, and may represent only one variant of undetermined meaning.^{16,17}

Conclusion

The clinical complexity of MS, its diagnosis and early neonatal therapeutic intervention united with the absence of published guidelines constitute a real challenge for professionals and families involved. Therefore, it is necessary to define the role of neonatal screening in this disease to better direct its clinical management.

Genetics diagnosis of a congenital anomaly alters the patient's management in several ways allowing for targeted, individualized and more effective therapy. Recognition of a genetic condition enables immediate diagnostic definition, reducing time and resource consumption, and serving as the basis for genetic counseling. However, proposals to expand the screening and complexity of such tests are not supported by the same level of evidence and unambiguous benefit. The approach to technical, logistical, psychosocial, ethical and economic aspects in the light of these advances should be evaluated before the implementation at the population level.

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Conflicts of interest

No conflicts to declare.

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