A pictorial review of Menkes disease: wide spectrum of connective tissue abnormalities

Poster No.: C-1099
Congress: ECR 2016
Type: Educational Exhibit
Keywords: Paediatric, Vascular, Musculoskeletal soft tissue, CT, MR, Education, Genetic defects
DOI: 10.1594/ecr2016/C-1099

Any information contained in this pdf file is automatically generated from digital material submitted to EPOS by third parties in the form of scientific presentations. References to any names, marks, products, or services of third parties or hypertext links to third-party sites or information are provided solely as a convenience to you and do not in any way constitute or imply ECR’s endorsement, sponsorship or recommendation of the third party, information, product or service. ECR is not responsible for the content of these pages and does not make any representations regarding the content or accuracy of material in this file.

As per copyright regulations, any unauthorised use of the material or parts thereof as well as commercial reproduction or multiple distribution by any traditional or electronically based reproduction/publication method is strictly prohibited.

You agree to defend, indemnify, and hold ECR harmless from and against any and all claims, damages, costs, and expenses, including attorneys' fees, arising from or related to your use of these pages.

Please note: Links to movies, ppt slide shows and any other multimedia files are not available in the pdf version of presentations.

www.myESR.org
Learning objectives

The aim of this presentation is to demonstrate the characteristics of and the radiological findings in patients with Menkes disease (MD).
Menkes disease (MD), also known as 'kinky hair kinky vessel syndrome', is an X-linked recessive defect in a copper (Cu) transporter, first described by Menkes et al. in 1962 (1). MD shows many manifestations in various organs such as the head, vascular system, urinary organs, and skeletal system (2-4). MD patients are sometimes misdiagnosed as child abuse victims due to multiple bone fractures and subdural hematomas. Early treatment is important to prevent deterioration of the nervous system (5, 6).

This presentation offers a better understanding of the disease by demonstrating several representative images.
Findings and procedure details

1. Prevalence

MD is an X-linked recessive disease occurring in 1 out of 100,000 to 250,000 live births. According to a survey in Japan during 2011-2012, 62 cases were reported. From this data, 8 affected boys are estimated among 1,000,000 live male births. Of the 62 MD patients, 2 patients were female (2, 7).

2. Etiology

MD is the disorder of a Cu-transporter in the intestine membrane and the blood-brain barrier (5, 6). This is due to mutation in the gene encoding the copper transporting P type adenosine triphosphatase, subtype A (ATP7A) (2). ATP7A plays an important role transporting copper into the Golgi apparatus where Cu-dependent enzymes are made (Fig. 1 on page 8 ) (2, 8). Thus, copper deficiency causes decreased activity of Cu-dependent enzymes.

3. Cu-dependent enzymes

Cu-dependent enzymes and their functions are summarized in Fig. 2 on page 8 (2). The lack of Cu-dependent enzymes mainly leads to CNS degeneration and collagen non-maturation. CNS degeneration is caused by decrease in activity of some Cu-dependent enzymes such as Cytochrome C oxidase, which is known as the key enzyme of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). On the other hand, collagen non-maturation is caused by decreased activity of lysyl oxidase, which is another affected Cu-dependent enzyme. Lysyl oxidase forms the copper-talon complex, which builds the crosslinks between each collagen fibril (Fig. 3 on page 9 ) (9, 10).

4. Symptoms

The clinical manifestations of MD include severe seizure, growth retardation, vascular abnormalities, kinky hair structure, hypopigmentation, episodic hypothermia, death in early childhood and so on (2, 7, 11-13).

The kinky hair structure, which is caused by malformation of keratin due to lack of sulfhydryl oxidase, is the most well-known physical finding and cause to suspect MD. However, kinky hair is difficult to identify (Fig. 4 on page 9 ). Unfortunately, as a result, most MD patients visit a hospital due to the CNS-related symptoms or growth retardation at about two months old (3-5).
5. Clinical features and radiological findings

5.1. CNS system

CNS degeneration is one critical manifestation of MD (3, 4, 7). MRI reveals extensive gray matter and associated white matter atrophy (Fig. 5 on page 10). Furthermore, due to shearing of the bridging cortical veins as atrophy progresses, subdural hematomas and hygromas occur frequently (Fig. 5 on page 10 b, Fig. 6 on page 11 a). Not only subdural hematoma but also epidural hematoma sometimes occurs due to the bone fragility in conjunction with vascular wall abnormality, as described in section 5.3 (Fig. 6 on page 11 b).

In addition, "temporary cystic change" is another well-known MRI finding (Fig. 7 on page 12 a). High intensity areas in T2-weighted imaging appear at the temporal lobes, however this imaging feature is not persistent (Fig. 7 on page 12 b). According to a previous report, it is caused by transient ischemic change, which is often observed in patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) (14).

5.2. Skeletal system

Deformation of the skeleton is seen in the elbow, the clavicle, the hip and the pelvis (2, 15). For example, the heads of long bones show an abnormal shape. They widen towards the end this being known as "spurring" (Fig. 8 on page 12 a). Additionally, osteoporosis is a major symptom of MD (Fig. 8 on page 12 b), caused not by any Ca-P defects or hormone abnormalities, but by collagen dysfunction. The fragile bone exhibits a tendency to fracture (Fig. 8 on page 12 c) even though ordinarily bone fracture in childhood is rare. Bone fractures are sometimes multiple. Due to multiple bone fractures and the previously mentioned hematoma, patients with MD are sometimes misdiagnosed as child abuse victims.

5.3. Vascular system

One striking finding in the vascular system is elongation and tortuosity of the intracranial arteries (Fig. 9 on page 13). Intimal hyperplasia occurs, and abnormal elastic fibers form within the intima. These changes in elasticity are presumably the cause of vascular stretching and dilation (7). Cerebral artery tortuosity is one of the most well-known symptoms, and is the origin of another name for MD, "kinky vessel syndrome". Although kinky vessels are observed only in cerebral arteries, the reason for this is still unclear. However, previous studies have reported patients with MD who developed aneurysms of the brachial artery or the iliac (16, 17).

5.4. Urinary organs
Collagen non-maturation leads to the fragility of the bladder, which is associated with the formation of multiple diverticula (Fig. 10 on page 14 a) (12). This collagen non-maturation in the bladder sometimes also leads to vesico-ureteral reflux and hydronephrosis (Fig. 10 on page 14 b and Fig. 10 on page 14 c). Consequently, urinary tract infection is sometimes fatal for MD patients.

5.5. Herniation

The malfunction of connective tissue leads to non-mature inguinal ligaments, resulting in inguinal hernia (Fig. 11 on page 15 a). Cryptorchidism is another result (Fig. 11 on page 15 b) (7). According to our observations, MD also may lead to diaphragmatic hernia, in which the liver protrudes towards the thorax (Fig. 11 on page 15 c and Fig. 11 on page 15 d).

7. Treatment

MD patients suffer neurodegeneration leading to death before the third year of life. The current treatment is parenteral copper administration (5, 6). Subcutaneous injection of Copper histidine has been reported to be most effective. By injection, copper bypasses the normal route of absorption through the gastrointestinal tract, and directly increases plasma levels. Copper histidine subcutaneous injection can improve kinky hair, muscular tones and seizures. Neurodegeneration progresses despite copper histidine therapy when treatment is initiated after the onset of neurological symptoms, which usually occurs at 2 months old, when copper from the mother has been consumed. Thus, early detection is very important for the prevention of advanced CNS degeneration. We observed kinky vessels as one early stage symptom, so MRA may be useful to detect MD at an earlier stage. However, early detection of MD is very difficult from outward appearance of kinky hair this respect, so further study is needed to investigate how to screening MD with imaging techniques. On the other hand, the connective tissue dysfunctions such as kinky vessels are untreatable even if copper histidine therapy is initiated at an early stage (Fig. 12 on page 16 ).

8. Differential diagnosis

8.1. Wilson disease

Wilson disease (WD) is an autosomal recessive disorder caused by mutations in ATP7B, which is mainly expressed in the liver and implicated in biliary copper excretion (2). The prevalence of WD is estimated at 1 in 30,000 live births. ATP7B dysfunction results in a toxic buildup of copper in the liver. Brain copper accumulation develops secondary to the liver disease and leads to degeneration of the basal ganglia. MRI shows high intensity areas in T2-weighted imaging at the lentiform nucleus and brainstem (Fig. 13 on
Consequently, WD patients present movement disorders such as tremor, dystonia and Parkinsonism.

8.2. Occipital horn syndrome

A milder form of MD is known as occipital horn syndrome (OHS). "Occipital horn" means symmetric exostoses protruding from the occipital bone and pointing downwards (Fig. 14 on page 17) (2). Other manifestations of OHS are ataxia and loose skin. Incidence of OHS is estimated to be 1 patient per 680,000 live male births in Japan. The cause is also ATP7A deficiency, resulting in reduced copper absorption. There has been no effective treatment reported.
Fig. 1: Copper metabolism in normal cell and Menkes cell. In normal cells (a), copper (Cu) is transported into the Golgi apparatus by ATP7A. However, in the cell affected by Menkes disease (b), Cu cannot be transported into the Golgi apparatus due to malfunction of ATP7A. The deficiency of Cu in the Golgi apparatus causes decreased in activity of Cu dependent enzymes such as Lysyl oxidase.

© - Kobe/JP

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Function</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphhydryl oxidase</td>
<td>Keratin crossing</td>
<td>Abnormal hair</td>
</tr>
<tr>
<td>Cytochrome C oxidase</td>
<td>Energy production</td>
<td>Brain damage</td>
</tr>
<tr>
<td>Cu/Zn super oxidase</td>
<td>Super oxide radical detoxication</td>
<td>Brain damage</td>
</tr>
<tr>
<td>Peptidyl α-amidating monooxidase</td>
<td>Neuropeptide bio activation</td>
<td></td>
</tr>
<tr>
<td>Lysyl oxidase</td>
<td>Crosslinking of collagen/elastin</td>
<td>Arterial abnormality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subdural hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bladder diverticula</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hernia</td>
</tr>
</tbody>
</table>
Fig. 2: Copper dependent enzymes, their functions and symptoms due to decreased activity

© - Kobe/JP

A. Collagen maturation

Lysyl oxidase (Cu-dependent enzyme) → Cross-link formation

collagen fibril → collagen fibril

B. Collagen-rich organs

Bone → Vessel → Bladder

Bone fracture → Kinky vessel → Bladder diverticula

Menkes patients

Fig. 3: Collagen maturation and its function in organs. Lysyl oxidase is a copper-dependent enzyme, which combines with copper to form the copper-talon complex. This enzyme has a critical role in collagen maturation; therefore its deficiency leads to malformation of organs, which rely on collagen to provide structure, such as bones, blood vessels, and urinary organs.

© - Kobe/JP
Fig. 4: Kinky hair immediately after birth. This picture shows 'kinky hair', which means abnormal and brittle hair. However, babies often have a thin head of hair, making kinky hair difficult to identify.

© - Kobe/JP
Fig. 5: CNS degeneration and progression in patient who was diagnosed at a late stage. At 2 months old, atrophy was not obvious in MRI (a). There were no white matter lesions. However, MRI at 8 months old exhibited progressive atrophy and white matter lesions (red arrows) at frontal lobe (b). Diffuse myelin deficiency and bilateral hematoma is an associated finding.

© - Kobe/JP
**Fig. 6:** CNS hematoma. MRI at 9 months old shows a bilateral subdural hematoma caused by brain atrophy (a). CT at 6 days old reveals left subcutaneous and epidural hematoma due to bone fracture and vascular wall abnormality (b).

© - Kobe/JP

---

**Fig. 7:** Transient temporal lobe changes. In MRI at 6 months old (a), cortical atrophy and white matter change in temporal lobe (red arrows) were shown. Myelination was delayed. On the other hand, in MRI at 4 years old (b), though cortical atrophy remained, the white matter lesions had disappeared and myelination was not delayed.

© - Kobe/JP
Fig. 8: Skeletal changes due to collagen non-maturation. In the radiogram of the upper arm at 12 years old (a), the radial head shows an abnormal shape. It widens towards the end. Radiogram of the hand at 3 years old (b) shows findings of osteoporosis such as cortical thickness and low dense cancellous bone. Radiogram of the femur at 3 years old shows fracture (c).

© - Kobe/JP
**Fig. 9:** Tortuous cerebral arteries of one 8-year-old boy. MRAs of internal carotid arteries (a, b) and vertebral arteries (c, d) show markedly tortuous 'kinky' cerebral arteries.

© - Kobe/JP
**Fig. 10:** Image findings in the urinary organs of a 3 years old boy. Collagen maturation causes formation of multiple bladder diverticula, which leads to various urinary system troubles. CT reveals multiple bladder diverticula formation (a) and left hydronephrosis (b). Retrograde urography reveals vesico-ureteral reflux (c).

© - Kobe/JP
**Fig. 11:** Various herniation observed in Menkes patients. Non-mature inguinal ligaments cause inguinal hernia (a, red arrow) and cryptorchidism (b, red arrow). In addition, we observed diaphragmatic hernia (c, d, white arrow) in some patients with Menkes disease.

© - Kobe/JP

**Fig. 12:** Therapeutic effect of copper histidine therapy. Although copper histidine subcutaneous injection can prevent CNS degeneration, cerebral artery tortuosity, which is one connective tissue disorder, is untreatable even if copper histidine therapy is
initiated at an early stage. Cerebral artery tortuosity (a, before treatment) remained even after 7 years (b) and 12 years (c) of the treatment.

Fig. 13: The typical imaging features of Wilson disease. Symmetric high intensity areas (red arrows) in FLAIR imaging at the lentiform nucleus (a) and brainstem (b) were observed.

© - Kobe/JP
**Fig. 14:** The characteristic imaging findings in occipital horn syndrome. The exostosis of the occipital bone, which is known as "occipital horn" (red arrow) is depicted.

© - Kobe/JP
Conclusion

Although MD shows a wide spectrum of manifestations, not only pediatric radiologists but also general radiologists should be familiar with this disease, and make an effort to detect it in its early stages.
References


