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Case Report Open Access

Bilateral Aneurysm of the Internal Jugular Vein Associated with Menkes Disease: Diagnosis, Risk Factors and Management

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Abstract

Menkes disease is a rare genetic disease due to an abnormality in copper metabolism. Clinical picture mainly includes neurological and cutaneous symptoms, and may present vascular complications. We report two cases of bilateral aneurysms of the internal jugular vein associated with Menkes disease, which were discovered by the appearance of cervical swellings a few months after birth. Diagnosis was set by Doppler ultrasonography and no specific treatment was decided for both cases. A review of literature then presents the diagnosis method, risk factors and management of aneurysms of the internal jugular vein in Menkes disease.

Keywords: Menkes disease; Venous aneurysm; Internal jugular vein; Risk factors; Management

Introduction

Menkes disease is a genetic recessive X-linked disease, due to a mutation in the ATP7A gene (Xq21.1), which encodes a transmembrane copper transporter in enterocytes [1,2]. The different known mutations are responsible for quantitative or qualitative abnormalities of this protein [3,4], causing a food-provided copper deficiency in target tissues, such as brain, liver, skin appendages and blood vessels [5]. Inactivity of lysyl oxidase, a copper-dependent enzyme, cannot create covalent bonds that normally stabilize elastin and collagen fibres, leading therefore to fragility and deformability of connective tissues [6,7]. Some symptoms appear at birth, but clinical picture becomes really characteristic around the age of 3 to 6 months: failure to thrive, slow psychomotor development, iterative convulsive seizures, cerebral and cerebellar focal lesions, tendency for hypothermia, and atypical hair, hence its name "kinky hair disease" [8,9]. Several complications were described: skin and musculoskeletal fragility [10], bladder diverticula, gastric polyps [11] and diffuse pulmonary emphysema [12]. Vascular complications were also described. We report here two cases of bilateral aneurysms of the internal jugular vein (IJV) associated with Menkes disease. Then a review of literature presents the diagnosis method, risk factors and therapeutic management of these IJV aneurysms.

Case 1

A 6-weeks-old male infant was admitted to hospital for *status epilepticus*. Diagnosis of Menkes disease was rapidly considered because the child had white fine brittle hair, a partial alopecia, an hypopigmentation and a skin xerosis, an hypothermia and several neurological abnormalities: slow psychomotor development, generalized hypotonia, limb dystonia. Cerebral imaging (CT-scan and MRI), at the time of diagnosis, revealed a cortical and infracortical atrophy in both temporo-occipital areas, a widening of pericerebral areas and a cerebellar atrophy. *Pili torti* were found on histological examination of a patient's hair sample. Cupraemia was less than 50 µg/L (normal values: 800 to 1400 µg/l) and ceruloplasmin was 0,02 g/l (0,2 to 0,5 g/l). Diagnosis of Menkes disease was confirmed by findings of a mutation in the exon 5 of the ATP7A gene (c.1497C>A ; p.Cys499*). A parenteral copper-histidinate treatment (250 micrograms twice a day) was rapidly introduced.

A catheter was set in the right IJV because of iterative urinary infections during the first months of life. At 9 months of age, the young patient's parents noticed the appearance of bilateral cervical swellings. On examination, they were soft, compressible and without skin modifications. They noticeably increased in size during crying and defecating periods. Doppler ultrasonography, and then cervicothoracic CT-angiography, confirmed the venous nature of these lesions; there was a major twisty distension of both internal jugular veins which measured 60 by 50 mm in diameter on the left side, with partial vein thrombosis (Figure 1), and 31 by 18 mm in diameter on the right side, with complete vein thrombosis (Figures 1 and 2). Thoracic imaging showed important emphysematous lesions of both lung bases. The medical staff unanimously decided not to perform any additional imaging tests, looking for other vascular abnormalities, given the patient's poor prognosis (neurologically in particular), and because it had been decided not to proceed with surgery if such lesions were discovered. The young patient died at the age of 13 months, following his drug-resistant epilepsy and a respiratory distress due to a lung infection, which was a complication of a major bronchoemphysema.

Case 2

A 3-months-old male infant was admitted to hospital for food trouble and neurological disorders: abnormal ocular movements,

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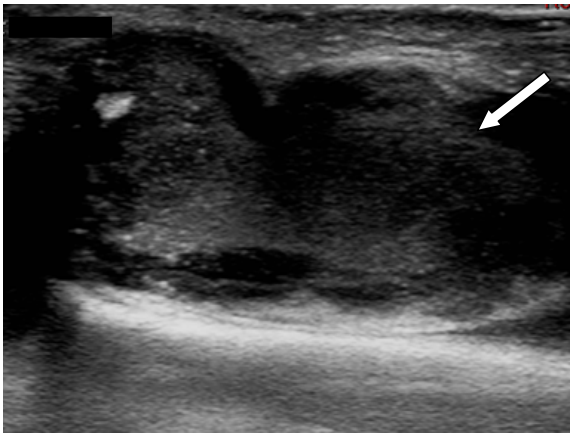

Figure 1: Cervical ultrasonography, B-mode axial view: partial thrombosis (arrow) of a left IJV aneurysm.

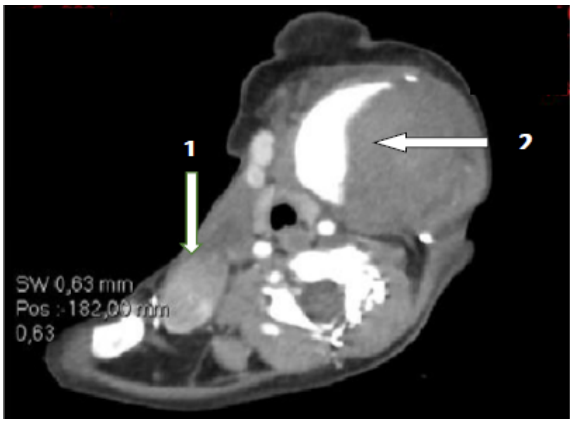

Figure 2: Axial cervical CT-angiography: complete thrombosis of a right IJV aneurysm (arrow 1) and partial thrombosis of a left IJV aneurysm (arrow 2).

slow psychomotor development and *status epilepticus*. Menkes disease was considered because of the presence of hypothermia and *pili torti*. Cupraemia was 60 µg/l (800 to 1400 µg/l) and ceruloplasmin was less than 0, 05 g/l (0,2 to 0,5 g/l). Diagnosis was confirmed by findings of a mutation in the exon 4 of the ATP7A gene (c.1011del; p.Val338Tyrfs*31), and a parenteral copper-histidinate treatment was rapidly introduced.

A sleep apnoea syndrome was diagnosed at 19 months of age, leading to a ventilation with continuous positive airway pressure. A catheter was initially set in the right IJV because of iterative urinary infections associated with bladder diverticula. Four catheter replacements on both sides were necessary because of iterative catheter-related deep vein thrombosis. One month later the patient's parents noticed the appearance of a small left cervical swelling, but no medical examination and no imaging tests were performed at this moment. At the age of 3, the child was admitted to hospital for acute respiratory failure, during which the swelling increased in volume. Doppler ultrasonography showed a left IJV aneurysm, which was 12 mm in diameter, without thrombosis. In this context of respiratory distress, a controlateral aneurysm appeared a few days later. Chest X-ray revealed a pneumomediastinum and a severe bronchoemphysema. These two aneurysms were confirmed on cervical CT-angiography (Figure 3) and they rapidly increased in volume within the next 24 hours, leading the young patient to death by upper airway compression.

Discussion

Vascular manifestations in menkes disease

Arterial manifestations are the most frequent. It mainly relates to twisty arteries [13,14], but also kinkings, ectasia and aneurysms. Aneurysms were described for the common iliac artery [15], lumbar artery [15], splenic and hepatic [16], brachial [17], coronary, pulmonary and cerebral [10] arteries. Venous manifestations are rarer. It especially relates to twisty veins, but aneurysms are also described in literature: 2 articles are about cases of unilateral aneurysms of the internal jugular vein (IJV) [12,18]. Several cases of bilateral IJV aneurysms were previously reported, but, to date, none of them was associated with Menkes disease [19-21]. One case report described a diffuse and mixed (arterial and venous) cerebral injury [22]. Up to now, no lymphatic manifestations were described in Menkes disease.

IJV aneurysms in menkes disease: Diagnosis

Venous aneurysm is a rare cause of cervical swelling in children [20]. The most common etiologies are: lymphadenopathy, parotiditis, laryngocele, branchial arc cyst, thyreoglossal tract cyst, upper mediastinal cyst [18,23]. On physical examination, the soft, compressible and painless nature of the swelling, and its size increasing under intrathoracic pressure efforts (coughing, sneezing, defecation, shouting or crying) usually points to the venous nature of the swelling, even if these characteristics are also present with laryngocele and upper mediastinal cyst. Doppler ultrasonography remains the gold standard for diagnosis [24]. This test can easily show the vascular dilation (B-mode) and its venous nature (non-pulsatile and breath-depending flow, on pulsed Doppler). Valsalva maneuver shows an increase in venous diameter, which can reach up to 2.2 times the original size [23]. Color Doppler imaging searchs for a blood flow in the vein: its partial presence or its absence are respectively signs of partial or complete thrombosis [25]. Doppler ultrasonography has the advantage of being easily available, not expensive and reproducible, especially for the supervision of the aneurysm [24]. Cervicothoracic CT-angiography and angio-MRI show the same features and can be needed for a detailed study of the relationship between the venous aneurysm and its adjacent organs, especially if a surgical treatment is considered [24,26]. These imaging tests can also be needed for differential diagnosis, as

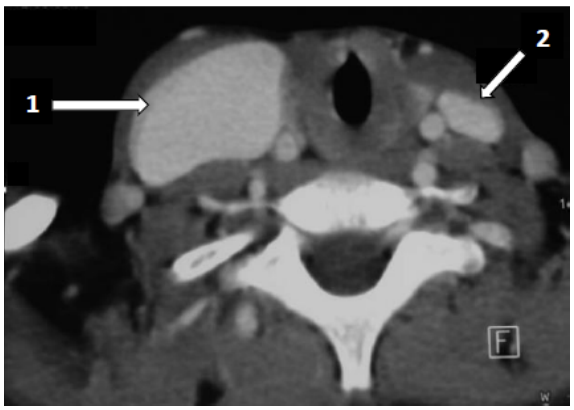

Figure 3: Axial cervical CT-angiography: right IJV aneurysm (arrow 1) and left IJV aneurysm (arrow 2) without thrombosis.

seen above, and etiological diagnosis: upper mediastinum venous hypoplasia or compression, for example by an haematoma or a bone fracture [23].

Risk factors

Long-term increase of intrathoracic pressure, transmitted to the IJV, seems to be the main provoking factor of these aneurysms. This condition can be observed for example in severe pulmonary emphysema, as it was previously described in literature [12] and in our two cases, and may also be caused by chronic coughing [27] or prolonged ventilation with continuous positive airway pressure [28]. Extrinsic compression of major deep veins in upper mediastinum should be considered as another predisposing factor of IJV aneurysms. This situation can be observed with pneumomediastinum, which itself can be caused by bronchoemphysema. IJV catheterization, related to parenteral treatments which are frequently needed in Menkes disease, seems also to be an important risk factor in this ground of vascular fragility.

Some cases of IJV aneurysms associated with Menkes disease are reported in literature [12,18], but without explicitly mentionning the possible mechanisms. Even if there are only six cases on the subject now (the four ones cited earlier, plus our two cases), it stands to reason that a general mechanism (intrathoracic hyperpressure) could be preferentially responsible for bilateral aneurysms, and that unilateral aneurysms could be caused by a local factor (extrinsic venous compression, venous catheterization). However, appearence of bilateral aneurysms is not always simultaneous on both sides, as in our case 2.

Management

As far as possible, preventive treatment should logically consist of avoiding or treating the risk factors mentionned above. Venous catheterization could be less invasive if performed by a trained technician. Pulmonary emphysema should be searched and treated as soon as possible.

Curative treatment of IJV aneurysms in children should remain conservative according to most authors [18,23,25,28-32], because this lesion is not severe and complications are rather rare. A wait-and-see decision seems to be all the more justified in Menkes disease because of vessel wall fragility and poor short-term prognosis. A regular supervision is thus recommended with Doppler ultrasonography, whose frequency is adapted according to the aneurysm size and the symptoms. Surgery should be indicated only for symptomatic (subcutaneous tension) or complicated aneurysms [28], or for aesthetic discomfort [28,32]. If performed, surgical procedure consists of aneurysm resection and anastomosis, longitudinal constriction suture venoplasty, or IJV ligation [23,28]. This surgical technique is contraindicated for bilateral IJV aneurysms because of probable intracranial hypertension related to cerebral oedema [33].

Conclusion

Owing to connective tissue abnormalities, Menkes disease may present vascular complications, such as aneurysms of the internal jugular vein. Diagnosis is easily set by Doppler ultrasonography. IJV aneurysms may be provoked by long-term intrathoracic hyperpressure related to pulmonary emphysema, which is a common complication in Menkes disease. They also may be caused by vein catheterization, which is frequently needed for parenteral treatment. Management should be as conservative as possible because of tissue fragility and usually short life expectancy of these young patients.

Disclosure of Interest

The authors declare that they have no conflicts of interest concerning this article.

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