Early and fortuitous diagnosis of alkaptonuria while searching other inherited metabolic diseases. Three cases report.

Diagnostic fortuit de l'alcaptonurie lors de la recherche d'autres maladies métaboliques héréditaires. 3 cas cliniques.

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Abstract

Alkaptonuria is a rare metabolic disease. Its Diagnosis is frequently made in adulthood.

We report three unusually cases of alkaptonuria diagnosed fortuitously at early age while searching other inherited metabolic diseases. The first case was a boy aged 3 months presented for seizures resistant to treatment and hypotonia. The second patient was a girl aged 7 months, presented for repeated severe lung infections. She had severe hypotrophy, hepatomegaly and cardiomegaly. She was short in stature and had a small narrow rib cage and craniofacial disproportions. The third case was a boy aged 18 months presented for cardiomyopathy, liver failure, hepatomegaly, haemostasis disorder and anemia. In addition, a darkening of urine after standing was noted. For all these patients, urinary organic acids profiles determined by gas chromatography-mass spectrometry revealed the presence of high amount of homogentisic acid confirming the diagnosis of alkaptonuria.

Association of alkaptonuria with other inborn errors of metabolism hasn't been reported previously. Further studies may bring additional clarifications of relationships between these diseases.

Keywords: alkaptonuria, association, inborn error of metabolism.

Résumé

L'alcaptonurie est une maladie héréditaire rare. Elle est très souvent diagnostiquée chez l'adulte. Nous rapportons trois cas pédiatriques inhabituels d'alcaptonurie diagnostiqués fortuitement lors de la recherche d'autres maladies métaboliques héréditaires.

Le premier cas était un garçon de 3 mois, ayant des crises convulsives résistantes au traitement et une hypotonie. La seconde patiente était une fille de 7 mois, ayant des infections pulmonaires sévères, dyspnéisantes et récidivantes. Elle avait une hypotrophie sévère, une hépatomégalie et une cardiomégalie. Le troisième cas est un garçon de 18 mois ayant cardiomyopathie, insuffisance hépatique, hépatomégalie, troubles de l'hémostase et anémie. En outre, un noircissement des urines a été noté chez ce nourrisson. Pour tous ces patients le diagnostic d'alcaptonurie a été posé devant la présence d'acide homogentisique, par la chromatographie en phase gazeuse des acides organiques urinaires.

L'association de l'alcaptonurie avec d'autres erreurs innées du métabolisme n'a pas été signalée auparavant. D'autres études pourraient apporter une certaine clarification sur les relations entre ces maladies.

Mots-clés : Alcaptonurie, association, erreur innée du métabolisme.

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INTRODUCTION

Alkaptonuria (AKU) is a rare metabolic disease due to the homogentisate 1,2-dioxygenase deficiency. Diagnosis of AKU is frequently made in adulthood. We report in this study three unusually cases of AKU diagnosed fortuitously at early age while searching other inherited metabolic diseases

CASES REPORT

Case 1

A boy aged 3 months, presented to Béchir Hamza Hospital for seizures resistant to treatment and hypotonia. He was born of consanguineous marriage and there was a family history of similar clinical manifestations, with three brothers died in the same context. Clinical examination was normal. The amino acid analysis by ion-exchange chromatography (Beckman 6300) was normal. Urinary organic acids profiles were determined by gas chromatography-mass spectrometry [Hewlett Packard 5890/HP 5972]; they revealed the presence of high amount of homogentisic acid (HGA) at a concentration of 6 g/mmol creatinine (normally not present in urine) confirming the diagnosis (figure 1 and figure 2). His last hospitalization at the age of two years and half found a very hypotonic child with frequent seizures. Since this hospitalization, the patient did not consult.

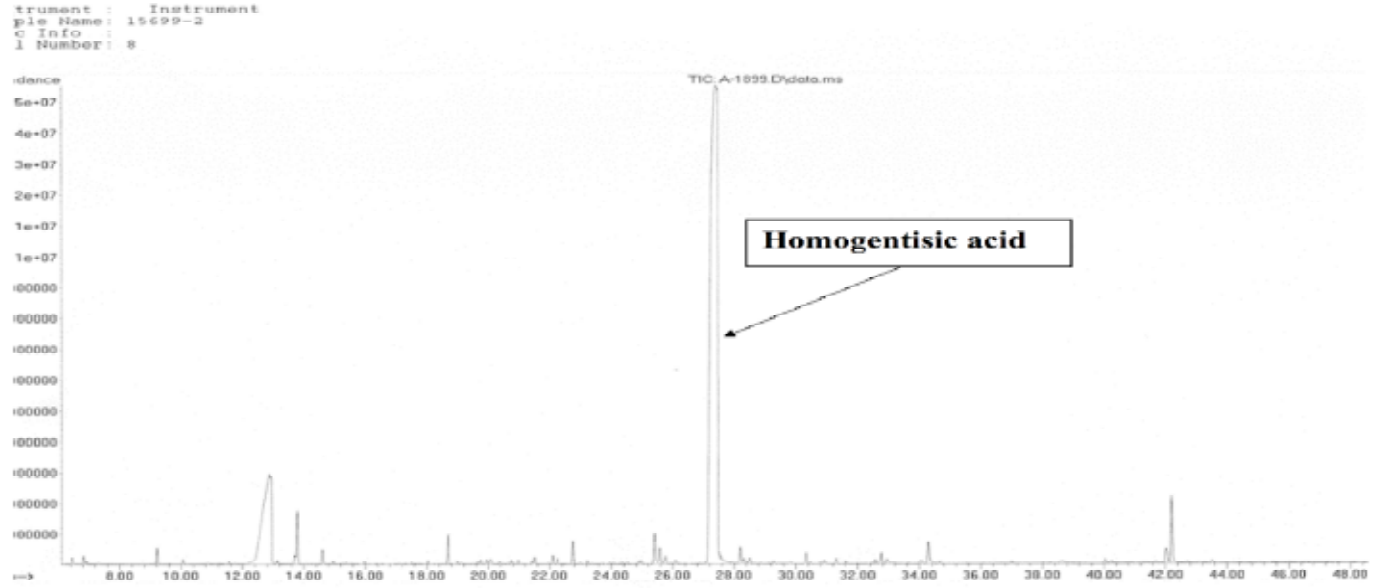

Figure 1: Chromatogram of Alcaptonuria patient (presence of homogentisic acid).

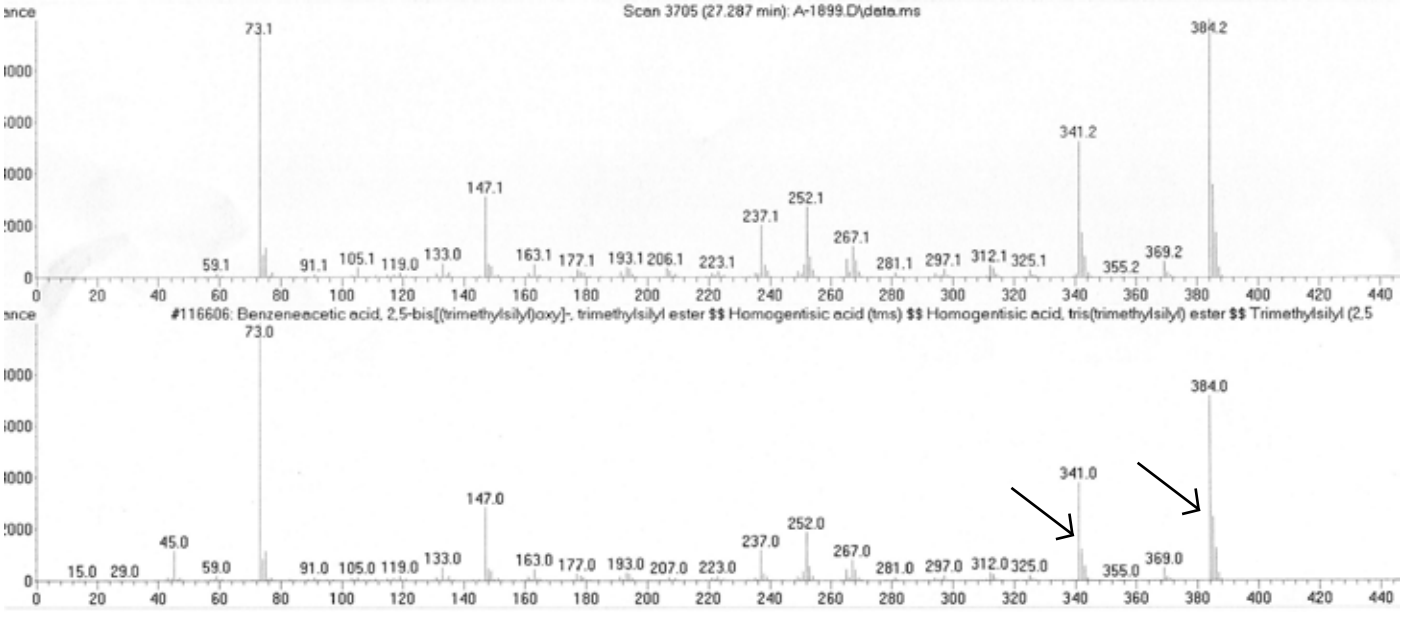

Figure 2: gas chromatography-mass spectrometry (GC/MS) of homogentisic acid (two characteristic peaks m/z, 341 and 384)

Case 2

A girl aged 7 months, was presented to the pediatric hospital of Kairouan for repeated, severe lung infections with breathing troubles. She was born of non-consanguineous marriage and no family history of similar clinical manifestations was found. After examination, the following symptoms were noted: severe hypotrophy, breathing trouble with blue skin and lips, failure to feed, hepatomegaly and cardiomegaly. She had a short stature, a small narrow rib cage, and a craniofacial disproportion. Laboratory tests showed severe anemia with hemoglobin at 7.4 g/dL. After standing, urine turned brown. Analysis of plasma amino acids was normal. Analysis of organic acids revealed the presence of high amount of HGA at a concentration of 3 g/mmol creatinine, confirming the diagnosis of AKU. Radiography of the thorax showed abnormal horizontal short ribs. She was died 20 days after hospitalization.

Case 3

A boy aged 18 months and born of consanguineous marriage was presented to Béchir Hamza Hospital for cardiomyopathy, liver failure, hepatomegaly, haemostasis disorder, and anemia. In addition, a darkening of urine after standing was noted. Analysis of plasma amino acids was normal and analysis of organic acids revealed the presence of high amount of HGA at a concentration of 4.8 g/mmol creatinine confirming the diagnosis of AKU. Evolution was unfavorable leading to quick death of patient.

DISCUSSION

AKU has a very low prevalence (1:100,000-250,000) in most ethnic groups (1). It is an autosomal recessive disorder caused by a deficiency of homogentisate 1,2-dioxygenase enzyme (figure 3). The defect is caused by mutations in the HGD gene, which maps to the human chromosome 3q21-q23, it consists of 14 exons and encodes a protein of 445 amino acids. 71 different mutations of the HGD gene have been identified in approximately one hundred unrelated patients from different countries (2, 3, 4). AKU is marked by the accumulation of HGA, its diffusion into blood, then in all connective tissues of organism and its excretion by urine. The oxidized metabolite of HGA, benzoquinone acetic acid, is transformed, after polymerization, into melanin-like pigment that present high affinity for connective tissue, especially cartilage, resulting in an ocher color (for this reason it carries the name of ochronosis) and causing darkening of alkaline urine exposed to light and pigmentation of cartilage tissue (5). AKU is characterized by a triad of signs according to chronology of appearance: homogentisic aciduria evidenced by a darkening of urine, ochronosis, and ochronotic arthropathy (2,6,7). Diagnosis of AKU is rarely made in the childhood by a darkening of urine which represents the only sign. In fact, acid urine may not darken after many hours of standing and fresh urine looks normal. Diagnosis of AKU is most commonly made in adulthood when ochronosis and ochronotic arthropathy appear (2,6,7). Ochronosis is generally noted in the third decade of life with darkening of tissues due to the slow accumulation of the black polymer of HGA in cartilage and other mesenchymal tissues. It is manifested clinically as dark spots mainly on the sclera and ears (5). Around the fourth decade of life, ochronotic arthropathy of major joints and calcification of cartilaginous tissue may cause disabilities (2,6). Besides this characteristic triad of AKU, the visceral damage including heart and kidney disorders have been reported at an advanced stage of this disease (6). Diagnosis is confirmed by urinary organic acids profiles determined by gaz chromatography-mass spectrometry and detecting abnormal high levels of HGA (3 to 7 g / 24 h) usually undetectable in healthy subjects (8). Currently, no effective treatment for AKU is known and focus is on symptomatic care, however, ascorbic acid, low-protein diet with restriction of phenylalanine and tyrosine are recommended. Recent trials with nitisinone (drog that blocks HGA production) showed that it effectively decrease HGA levels, but it increases plasma tyrosine (9)

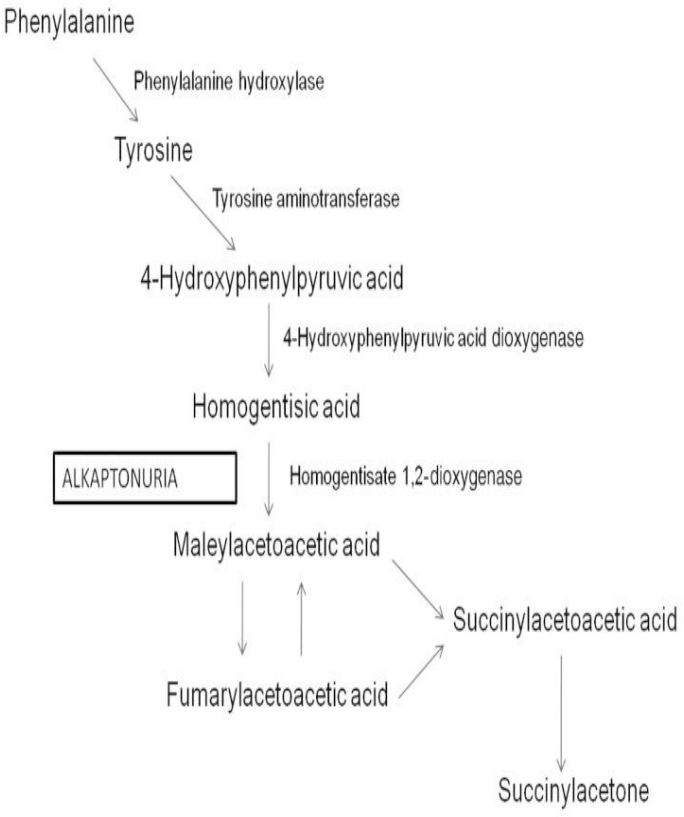

Figure 3- Biochemical pathway of the disease. Deficiency of homogentisate 1,2-dioxygenase (HGO) in the tyrosine degradation pathway leads to alkaptonuria.

In the literature, AKU is very rarely reported in childhood and exceptionally in babies (8,10). In this work, three unusually cases of AKU are reported. The diagnosis of AKU was made fortuitously at early age when searching other inherited

metabolic diseases. In fact, clinical signs were not pointing to AKU. The association, of AKU in these patients with probable other inherited metabolic diseases is remarkable since no similar association has been reported previously in the literature to our knowledge. In the first case, the diagnosis of AKU did not explain the early onset of severe and persistent seizures and hypotonia which were common with another inherited disorder, especially as this patient had similar cases in siblings with the concept of consanguinity. For this patient, and because of the lack of equipments in Tunisia, we were not able to diagnose the other inherited disease. Concerning the second case, AKU was most probably associated to a rare genetic disorder called Jeune syndrome, which is originally described as asphyxiating thoracic dystrophy by Jeune et al. (11). For the third case, the symptoms found were not reported previously in AKU. Indeed, this patient had an association of AKU with another serious inborn error of metabolism causing quick death, but that was not diagnosed. For all these cases, it is unlikely that the homogentisic acid oxidase deficiency itself or the accumulation of HGA is related to the other associated disorders since no report has ever mentioned such associations. The existence of a common genetic factor inducing both AKU and other diseases may be suggested because of the extremely low incidence of these disorders. In addition, other different types of genetic alterations may be implicated in these inherited errors of metabolism. In the literature, AKU was diagnosed in Tunisia in a 49-year-old man at a stage of ochronotic arthropathy (12). Concerning association of AKU with other diseases, we noted a case of association with astrocytoma and pituitary adenoma in a female patient (13) and with diabetes mellitus in another case (14).

Interrelationship between AKU and other metabolic abnormalities is not yet elucidated. Research may bring some clarification about relationships between these diseases.

CONCLUSION

AKU is rarely associated with other disorders. Its association with other inborn errors of metabolism hasn't been reported previously. Interrelationship between AKU and other metabolic abnormalities is not yet elucidated. Research may bring some clarification about relationships between these diseases. Long-term clinical trials might be necessary to demonstrate the clinical efficacy of oral nitisinone in alkaptonuria patients at early age before the onset of complications.

Abbreviations:

Alkaptonuria (AKU); homogentisic acid (HGA)

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