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CASE REPORT

Successful Management of a Neglected Case of Nephropathic Cystinosis

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إدارة علاج ناجحة لحالة مهملة من اعتلال الداء السيستيني الكلوي

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ABSTRACT: Cystinosis is a rare metabolic disorder characterised by lysosomal cystine accumulation leading to multi-organ damage; clinically, the kidneys are the first organ affected. Respiratory insufficiency caused by overall respiratory muscle myopathy is a life-threatening complication. Treatment with cysteamine should be initiated rapidly and continued lifelong to prolong renal function and protect the extra-renal organs. We report the case of a four-year-old Omani girl, diagnosed with infantile nephropathic cystinosis at 21 months. Cysteamine was prescribed but with no compliance to medications. She presented to the Child Health Department of Sultan Qaboos University Hospital, Oman, two years later with severe failure to thrive, electrolyte disturbance and respiratory failure. The hypoventilation and early respiratory dysfunction, due to intercostal and diaphragm myopathy, was treated by non-invasive positive-pressure ventilation. The patient was discharged after four months of intensive rehabilitation with no ventilator support. No standard treatment options have yet been established for respiratory dysfunction in cystinosis.

Keywords: Cystinosis; Cysteamine; Continuous Positive Airway Pressure; Positive-Pressure Ventilation; Failure to Thrive; Pediatric Intensive Care Units; Case Report; Oman.

الملخص: الداء السيستيني هو اضطراب أيضي نادر يتميز بتراكم السيستين في الجسيم الحال مما يؤدي إلى ضرر أعضاء متعددة. سريريا، الكلى هي أول الأعضاء تأثراً. القصور التنفسي الناجم عن الاعتلال العضلي العام في عضلات التنفس، هو من المضاعفات التي تهدد الحياة . الشروع في بدأ علاج "Cysteamine" بسرعة واستمرارة مدى الحياة يطيل بقاء وظيفة الكلى وحماية الأجهزة خارج الكلية. نعرض هنا تقرير لحالة فتاة عمانية تبلغ من العمر 4 سنوات، تم تشخيصها بإعتلال الداء السيستيني الكلوي الطفولي في عمر 21 شهرا. كان هناك عدم أمتثال لأخذ دواء "Cysteamine" الذي كان مقررا أعطاءة. قدمت الطفلة إلى قسم صحة الطفل في مستشفى جامعة السلطان قابوس في سلطنة عمان ، و هي تعاني من فشل حاد في النمو، و اضطرابات في الأملاح ، و فشل في الجهاز التنفسي . تم علاج نقص التهوية و ضعف الجهاز التنفسي المبكر نتيجة أعتلال العضلات الوربية و الحجاب الحاجز ، بواسطة جهاز تهوية إيجابي الضغط غير غير باضع (NIPPV). خرجت المريضة بعد أربعة أشهر من إعادة التأهيل المكثف مع عدم وجود دعم التنفس الصناعي . لم يتم حتى الآن تحديد مقياس للخيارات العلاجية في حالات اختلال وظيفة الجهاز التنفسي في الداء السيستيني .

مفتاح الكلمات: تهوية إيجابية الضغط؛ غير باضع؛ الفشل في النمو؛ الداء السيستيني؛ ضغط إيجابي مستمر لمجرى الهواء؛ وحدة العناية المركزة للأطفال؛ تقرير حالة، عمان.

Cystinosis is an autosomal recessive disorder characterised by an accumulation of the amino acid cystine in lysosomes throughout the body. *CTNS*, the responsible gene, is defective in this disease. Usually, this gene encodes the lysosomal cystine carrier cystinosin, which is a lysosomal transport molecule needed to carry cystine out of the cells. It was cloned in 1998 and is located on the short arm of the chromosome 17p13.[1,2] In virtually all tissues, cystine accumulation causes multi-organ damage, with the kidneys being clinically the first affected. Cystinosis generally manifests in infancy as Fanconi syndrome with severe renal proximal tubular dysfunction. End-stage disease develops around the age of 10 years without specific therapy using the cystine-depleting agent, cysteamine.[2] Cystine accumulation has also been detected in the muscular tissue; the first case of severe myopathy in cystinosis was reported in 1988.[3]

The association of nephropathic cystinosis with progressive distal vacuolar myopathy was described in more detail in 1994.[4] Anikster *et al*. studied the pulmonary function and myopathy of 12 patients with nephropathic cystinosis and concluded that restrictive pulmonary disease due to overall respiratory muscle dysfunction is characteristic of the disease.[5] It usually develops after patients reach 10 years of age in the majority of those not treated with cysteamine.[2]

The aminothiol cysteamine depletes lysosomal cystine content by a disulfide exchange reaction with cystine, resulting in the formation of cysteine-cysteamine mixed disulfide and cysteine. This exits

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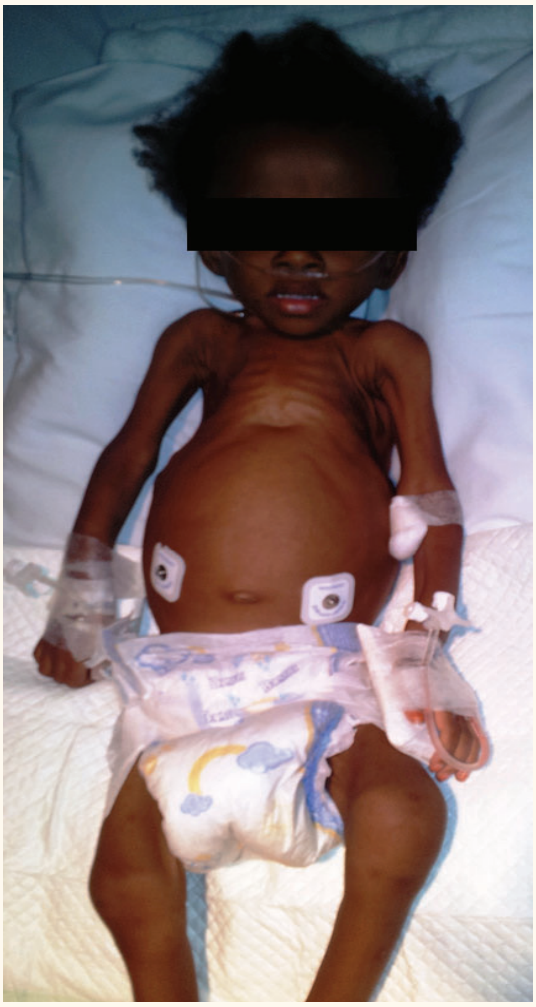

Figure 1: A photograph of the child on presentation with severe failure to thrive and severe muscle wasting. Note the small rachitic deformed chest.

the lysosomes via a system c transporter and the remaining cysteine via a cysteine carrier.[6,7] The system c transporter was recently identified to be the PQLC2 transporter.[8]

We report a case of cystinosis with myopathy whose hypercapnic respiratory failure was treated with non-invasive positive-pressure ventilation (NIPPV). Due to this treatment modality, the patient was moved from prolonged admission in the Paediatric Intensive Care Unit (PICU) and gradually weaned from NIPPV to nocturnal ventilation. She was weaned off ventilation completely after approximately two months.

Case Report

This Omani female child had been previously reported as the first case of nephropathic cystinosis in Oman when she was 21 months old.[9] At that time, the patient was started on cysteamine (30 mg/Kg/day) but the family had poor compliance to medications

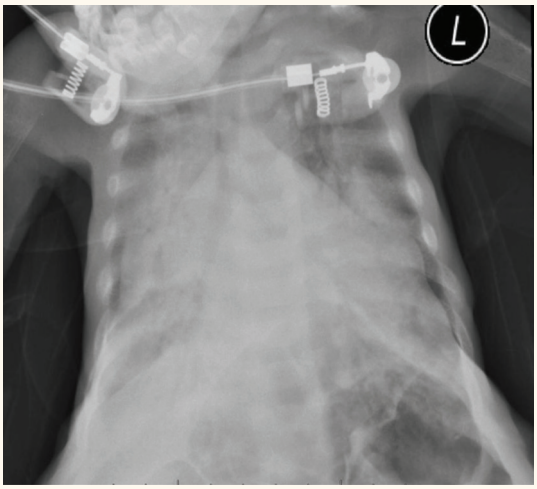

Figure 2: Chest X-ray on admission with extensive bilateral infiltration showing the hypoplastic chest and rachitic rosary.

and she was lost to follow-up for the following two years.[9] Subsequently, the patient presented to the Child Health Department of Sultan Qaboos Hospital, Oman, at the age of four years with a severe failure to thrive (weighing 6.1 Kg and below the third centile), pallor, metabolic acidosis, hypophosphataemia, hypokalaemia and a severe chest deformity with rachitic manifestations [Figure 1]. Additionally, she presented with bronchopneumonia with respiratory failure which required her to be admitted to the PICU for respiratory support [Figure 2].

During her three-month stay in the PICU, she was ventilated using pressure-regulated volume control (PRVC) mode. The patient was ventilated with high ventilator settings for a short period, but for most of the time in the PICU she was ventilated with moderate ventilator settings. She remained on low ventilator settings after two failed attempts to extubate her to continuous positive airway pressure (CPAP). The extubation failed because of respiratory dysfunction due to myopathy, the chest deformity, electrolyte disturbance, feeding intolerance and infections.

A multidisciplinary team was involved in her treatment. It was decided to start the patient gradually on cysteamine until a good response was seen. During this time, efforts were made to increase her weight using total parenteral nutrition and a high-caloric formula through continuous nasogastric tube feeding; this was successful and the patient gained 3 Kg in weight. Additionally, her electrolytes were corrected and she spent time in physiotherapy and play therapy with familial support. CPAP was begun after three months of conventional ventilation.

Whilst on CPAP (at a flow of 12 and 40% fraction of inspired oxygen [FiO_2]), the patient was conscious,

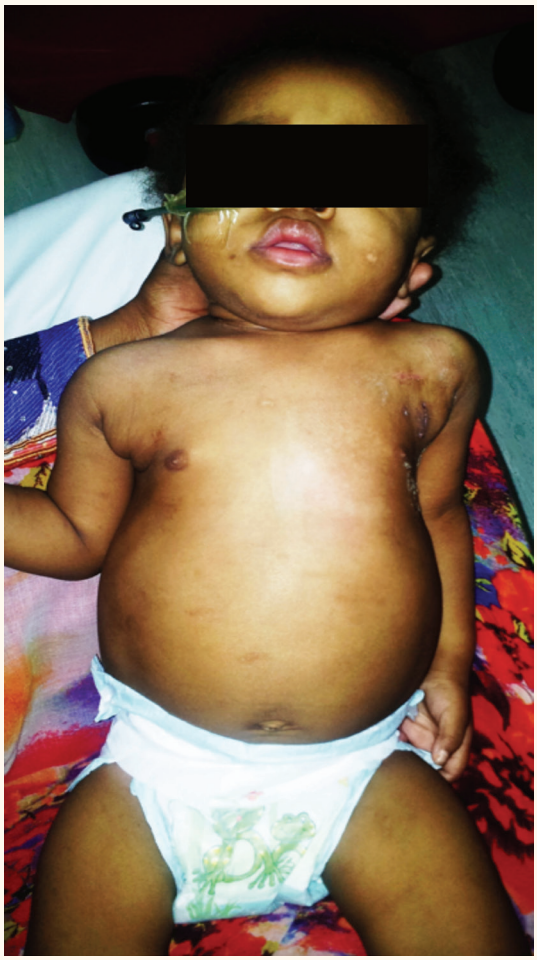

Figure 3: A photograph of the patient after treatment. Note the marked increase in weight and the improvement of the muscle wasting and rachitic rosary. A nasogastric tube was used for continuous feeding.

alert, tachypnoeic (at 50 breaths/min), with subcostal recession and poor bilateral air entry. An arterial blood gas (ABG) test showed partial compensated respiratory acidosis with a pH of 7.30; partial pressure of carbon dioxide (PCO_2) at 7 kilopascals (kPA); bicarbonate (HCO_3) of 25.2, and partial pressure of oxygen (PO_2) at 9.6 kPA.

After 24 hours, the patient began ventilation using the BiPap® Vision® Ventilatory Support System (VVS, Respironics, Philips Healthcare, Andover, Massachusetts, USA) at inspiratory positive airway pressure (IPAP)/expiratory positive airway pressure (EPAP) setting of 16/7, rate of 25 and 40% FiO_2. Clinically, the patient was conscious and alert with improvement in air entry. Her ABG test showed a pH of 7.42; PCO_2 at 6.9 kPA; HCO_3 of 31, and PO_2 at 10 kPA. After two weeks, the BiPap® VSS settings were changed to an IPAP/EPAP setting of 12/6, a rate of 20 and 30% FiO_2. Initially, her weight increased incrementally at a rate of almost 0.4 Kg per day due to the effects of the high calorie intake, medication

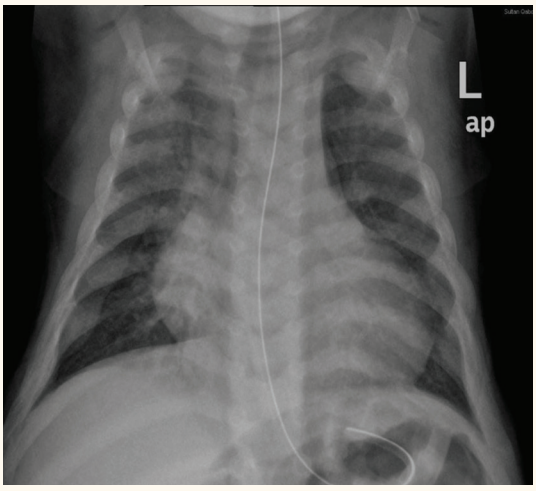

Figure 4: Chest X-ray before discharge showing the almost completely clear bilateral lung fields with improvement of the rachitic rosary.

and electrolyte supplementation. On follow-up of her respiratory status, there was a significant improvement of respiratory stress and chest air entry with the ABG test recording a pH of 7.35, PCO_2 at 5.4 kPA, a HCO_3 of 25 and PO_2 at 10.8 kPA. From that point, the patient was gradually weaned from the BiPap® VSS; within two weeks, she was only using the ventilation system during her sleep. During the day, the patient maintained saturation on room air.

After a further two weeks, the patient had gained 0.6 Kg and was weaned completely from the BiPap® VSS even while asleep. She displayed no early morning lethargy, cyanosis or tachypnoea [Figure 3]. Her ABG test in the morning recorded a pH of 7.4; PCO_2 at 4.2 kPA; HCO_3 of 20.1, and PO_2 at 10.9 kPA. Before she was discharged, a chest X-ray was performed which showed a marked improvement [Figure 4].

The patient was discharged with no ventilator support after four months of intensive rehabilitation, repeated counselling and familal support. Nutritional support was continued with a feeding tube at home. The patient was followed-up and her respiratory status was closely monitored; she continued to show improvement in her respiratory dysfunction with normal blood gas results.

Discussion

Cystinosis is a rare metabolic disorder and the respiratory insufficiency caused by the overall respiratory myopathy is a severely invalidating and sometimes life-threatening complication.[5] The current patient, initially diagnosed at 21 months, presented—after two years of non-compliance to the cystine-depleting agent, cysteamine—with failure

to thrive, myopathy, respiratory dysfunction and failure and other associated conditions. There was evidence of diaphragmatic myopathy as the patient was hypoventilating, as proven by the ABG tests and clinical evidence of emaciated intercostals, paradoxical chest movements during the first few days of admission and the preference to remain in a sitting position even during sleep. This improved with cysteamine and other modalities of support.

Cysteamine is the only available treatment for cystinosis, slowing the deterioration of renal function and the occurrence of extra-renal complications. It can deplete cystine from the muscles and can stop or delay the myopathy; however, it should be started early and continued for the rest of the patient's life. Although no study has yet addressed the question of whether cysteamine is an effective treatment for cystinosis-associated myopathy, Gahl *et al*. demonstrated that cysteamine is able to deplete muscular tissue of cystine.[3]

Through multidisciplinary teamwork—with the reintroduction of cysteamine, the correction of the electrolyte disturbance, physiotherapy, play therapy, feeding supplementation of a high-caloric formula through a nasogastric tube and a change of respiratory support to BiPap® VSS—the patient's general condition and respiratory function improved and she was discharged from the PICU. The patient had been tachypnoeic and showing signs of distress even with CPAP ventilator support and her blood pH was suboptimal due to a high carbon dioxide concentration. The patient initially awoke drowsy in the mornings due to carbon dioxide retention. After treatment, she was fully conscious and alert in the mornings with normal blood pH and carbon dioxide levels and no signs of respiratory distress despite no ventilator support. It was evident that her carbon dioxide levels had reduced by almost 20% even after the BiPap® VSS was discontinued.

Eden *et al*. reported the use of nocturnal NIPPV in a 38-year-old male suffering from respiratory dysfunction due to cystinosis. The diagnosis was initially made when the patient was 2 years old and treatment was started at the age of 25 years.[10] Although mostly used for other disease processes, NIPPV can improve the patient's quality of life and reduce the hospital stay and expenses for cases of cystinosis and respiratory dysfunction, as can be evidenced from the current reported case.

Conclusion

Cysteamine is currently the only available treatment for cystinosis. It is assumed that cysteamine depletes the accumulation of cystine in the muscles. In cases of established respiratory dysfunction, no treatment options have so far been describe. As evidenced in the case of nephropathic cystinosis reported here, NIPPV can be used in cases of myopathy for the correction of hypoventilation and respiratory dysfunction.

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