Case Report

Kenny Caffey syndrome with severe respiratory and gastrointestinal involvement: expanding the clinical phenotype

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Abstract: Kenny Caffey syndrome (KCS) is a rare syndrome reported almost exclusively in Middle Eastern populations. It is characterized by severe growth retardation—short stature, dysmorphic features, episodic hypocalcaemia, hypoparathyroidism, seizures, and medullary stenosis of long bones with thickened cortices. We report a 10-year-old boy with KCS with an unusually severe respiratory and gastrointestinal system involvement—features not previously described in the literature. He had severe psychomotor retardation and regressed developmentally from walking unaided to sitting with support. MRI brain showed bilateral hippocampal sclerosis, marked supra-tentorial volume loss and numerous calcifications. A 12 bp deletion of exon 2 of tubulin-specific chaperone E (*TBCE*) gene was identified and the diagnosis of KCS was confirmed. Hypercarbia following a sleep study warranted nocturnal continuous positive airway pressure (CPAP) when aged 6. When boy aged 8, persistent hypercarbia with increasing oxygen requirement and increased frequency and severity of lower respiratory tract infections led to progressive respiratory failure. He became fully dependent on non-invasive ventilation and by 9 years he had a tracheotomy and was established on long-term ventilation. He developed retching, vomiting and diarrhea. Chest CT showed changes consistent with chronic aspiration, but no interstitial pulmonary fibrosis. He died aged 10 from respiratory complications.

Keywords: Kenny Caffey syndrome (KCS); respiratory system; gastrointestinal; tubulin-specific chaperone E (*TBCE*) gene

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Introduction

Kenny Caffey syndrome (KCS) is a rare syndrome initially described nearly 50 years ago reported almost exclusively in Middle Eastern populations and specifically in the Gulf countries (1-3). In most cases, KCS is inherited as an autosomal dominant trait, but autosomal recessive due to mutation of the tubulin-specific chaperone E (*TBCE*) gene has been also reported (4-6). It is characterized by severe growth retardation—short stature, dysmorphic features, episodic hypocalcaemia, hypoparathyroidism, seizures, and medullary stenosis of long bones with thickened cortices (3,5). We report a 10-year-old boy with KCS with an unusually severe respiratory and gastrointestinal system involvement—a feature not previously described in the literature of the field.

Case report

A 9-year-old boy was admitted from his local hospital in Kuwait to our institution's Pediatric Intensive Care Unit for respiratory investigations.

He was born at term by Caesarean section to second

cousin Bedouin parents. He had distinctive facial features with microphthalmia and short stature (<5th centile) (*Figure 1A,B*). He developed seizures at 2 months of age secondary to hypocalcaemia. He presented with multiple seizure types including status epilepticus, which were managed with antiepileptic medication and by correcting the hypocalcaemia. He first visited the United Kingdom (UK) at 6 years of age for a multidisciplinary respiratory and genetic assessment, which revealed hypercarbia following a sleep study and he was established on nocturnal continuous positive airway pressure (CPAP). He was also found positive for a 12 bp deletion of exon 2 of *TBCE* gene, supporting a diagnosis of KCS1. Microdeletion in the 22q11 region was excluded by FISH. Magnetic resonance imaging (MRI) of the brain showed bilateral hippocampal sclerosis, marked supra-tentorial volume loss and numerous calcifications, in keeping with his diagnosis (*Figure 2*). He was repatriated but he gradually developed diarrhea and food intolerance with episodes of vomiting. This was associated with worsening respiratory function needing multiple hospital admissions for chest infections. He progressed to requiring both day and night non-invasive ventilation at home. He regressed developmentally from walking unaided to sitting with support between 6 to 8 years of age. He developed

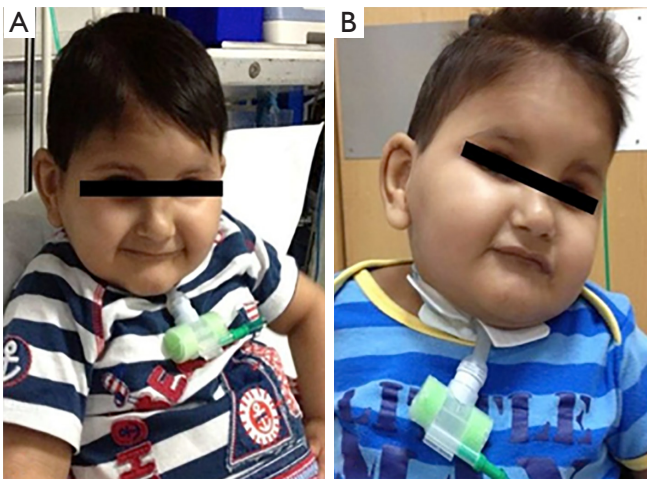

Figure 1 Note the microphthalmia and the distinctive facial features including sunken nasal bridge and pointed chin.

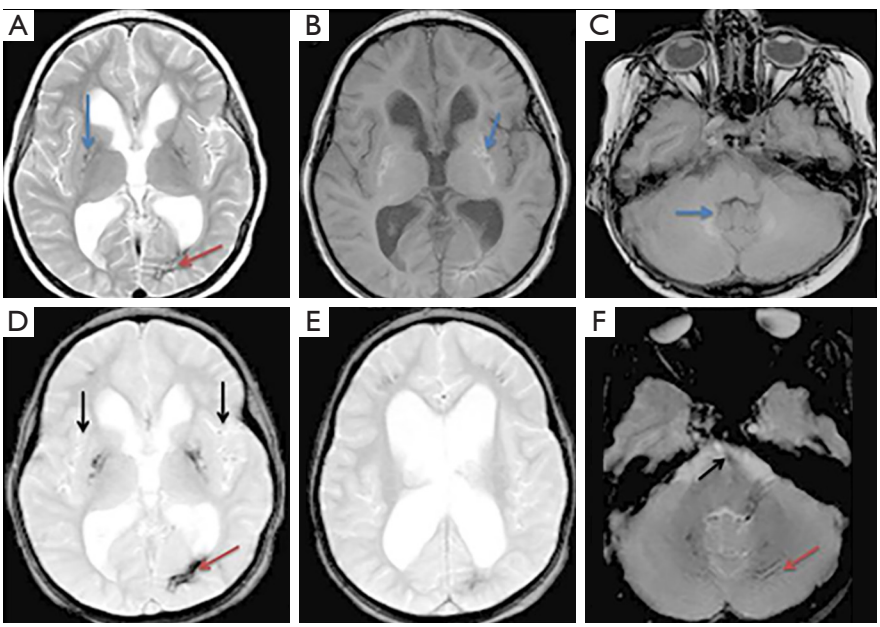

Figure 2 MRI brain performed on a 1.5T Philips Ingenia scanner. (A) Axial T2 weighted images (TR 5,000 ms, TE 100 ms, Voxel 0.7 mm, Matrix 328×198, flip angle 90 degrees, slice thickness 5 mm); (B,C) axial T1 weighted Fast Field Echo images (TR 341 ms, TE 3 ms, Voxel 0.65 mm, Matrix 356×226, flip angle 70 degrees, slice thickness 5 mm); Images confirm atrophy and mineralization in the basal ganglia and cerebellar dentate nuclei (blue arrows), note also evidence of previous hemorrhage in the left occipital lobe (red arrow); (D-E) gradient echo axial images (TR 792 ms, TE 23 ms, Voxel 0.9 mm, Matrix 256×163, flip angle 18 degrees, slice thickness 5 mm), widespread dystrophic calcification can be seen in the brain parenchyma, involving the frontal grey-white matter interfaces, globus pallidi, internal capsules, thalami, and in the cerebellum (black arrows), the region of susceptibility in left occipital lobe is most likely to represent a focus of old hemorrhage (red arrow).

psychomotor retardation and was able to speak only few words and use facial and body gestures to communicate.

Respiratory involvement

At 8 years of age his respiratory function deteriorated further with more frequent hospital admissions due to chest infections, hypercarbia and increasing oxygen requirements. A respiratory evaluation in his home country at this stage had raised a suspicion of interstitial lung disease and was treated with pulse methylprednisolone with no significant improvement. At 9 years of age due to worsening respiratory parameters and increasing requirement of non-invasive ventilatory support he was intubated and ventilated and transferred back to the UK for further respiratory management. He suffered further acute respiratory deteriorations requiring high frequency oscillatory ventilation (HFOV) including an episode of metapneumovirus infection. While under investigation, he deteriorated and was treated with further course of intravenous methylprednisolone along with standard supportive treatment. He was gradually weaned and extubated on to BiPAP via non-invasive ventilation. Following impedance and barium meal study, a convincing picture of chronic aspiration was considered as a possible reason for his respiratory deterioration. A CT scan of the chest suggested changes compatible with chronic aspiration and no pulmonary fibrosis. Further deteriorations and recurrent intubations for invasive ventilation led to a tracheostomy in order to facilitate long-term ventilatory support and to improve his quality of life. Post tracheostomy he became more stable but still had very limited respiratory reserve. Despite several attempts to gradually reduce his level of respiratory support, he remained on BiPAP with inspiratory pressures of 20 and expiratory pressures of 5 and a set rate of 20 breaths/minute. Although he was in room air, he gradually needed 1 L/min of oxygen due to frequent desaturations. High baseline $PaCO_2$, with metabolic compensation was deemed acceptable for him (permissive hypercapnia).

Gastrointestinal involvement

He was also noted to have hypoparathyroidism, hypothyroidism, hyponatremia with low cortisol response needing supplements of calcium, sodium and levothyroxine and hydrocortisone during periods of stress. He was treated with parenteral nutrition during episodes of acute illness. Due to features of malabsorbtion with large loose stools, retching and vomiting episodes, a detailed gastrointestinal work up was performed including endoscopy and biopsy. An OGD, colonoscopy and GI biopsies were carried out with an electron microscopy study of the biopsy sample suggestive of microvilli and was otherwise reported to be normal study. The endoscopy showed a featureless small stomach, short colon with bilious reflux into stomach and lower oesophagus with increased amount of bile seen in the proximal colon resulting in bile salt induced diarrhea. The lower esophageal sphincter appeared to be widely open. He had a surgical gastro jejunostomy tube, which was revised to jejunostomy due to complication of migration of the GJ tube and obstruction at the DJ flexure needing release surgery. He was tried on various elemental feeds and was established on Galactamannan-19. He was tried on probiotics like BioGia and also on Loperamide bile salt chelating agents after which there was some improvement in his stool frequency but consistency remained loose. The jejunostomy was revised and he tolerated PEG feeds and he continued to enjoy eating small bites of solids like crisps as before. He was repatriated with the aim of continuing his care at home. At this stage prognosis of KCS especially with severe respiratory and gastrointestinal system involvement, was discussed with the family and the progressive life limiting course nature was explained. He remained stable with long term invasive ventilation until the age of 10 years and 2 months but unfortunately deteriorated and died from his respiratory complications.

Discussion

In 1966, Kenny and Linarelli described a mother and son who had severe short stature, thin long bones with narrow diaphysis, and bouts of hypocalcaemia (1). In 1967, Caffey described the radiographic features of the same individuals (2). The condition has since been known as KCS (MIM 127000). The classical facial features of KCS were later on fully described by Lee in 1983 (3). KCS is due to mutations in the *TBCE* gene. The *TBCE* gene encodes a protein that participates in beta-tubulin folding (4,6). Mutations in the *TBCE* gene have been also associated with the recessive disorder Sanjad-Sakati syndrome (SSS) [MIM 241410; hypoparathyroidism, short stature, intellectual disability, and seizures]; also known as recessive KCS or KCS1, which has partial clinical overlap with KCS (7). In most cases, KCS is inherited as an autosomal dominant trait and this has been known as KCS2, but autosomal recessive cases known as KCS1 have been reported and also X-linked recessive

inheritance has been speculated. Our case differentiated from KCS1 and SSS on clinical presentation and at a molecular level.

There is also overlap with other syndromes such as CHARGE association, Di George, velo-cardio-facial and CATCH 22 with common findings such as hypocalcaemia, growth retardation, hypoparathyroidism, and abnormal facial features. The presence of characteristic phenotype of KCS1 and normal chromosomal and FISH studies helped to differentiate. There was also characteristic molecular pathology with no mutations identified in the 22q (8,9). Our index case was confirmed to have a 12 bp deletion of exon 2 of *TBCE* gene following a clinical diagnosis.

Currently, therapeutic options for KCS patients are limited to palliative therapy and symptomatic management of seizures by correction of hypocalcaemia (1). Our patient required several corrections of hypocalcaemic seizures and eventually stabilized on levetiracetam. Severe respiratory and gastrointestinal systems involvements, as part of KCS's clinical phenotype, have not been previously described in the literature. Early respiratory specialist involvement in the multidisciplinary treatment of these patients could prevent associated co morbidities and improve their quality of life and potentially prolong survival. Our patient sadly died from respiratory complications, which were thought to be secondary to lack of specialist care in his home country.

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