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Case Report

Pulmonary vascular malformations in genetic epileptic encephalopathy: A rare, fatal case report

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ABSTRACT

Mutations of KCNT1 gene, encoding for a sodium-gated potassium channel, are causative of a wide spectrum of epilepsies and neurodevelopmental disorders; cardiovascular involvement also seems to be significant, with cardiac arrhythmia and, less frequently, the development of Systemic to Pulmonary Collateral Arteries (SPCAs) has been reported. We report the case of M., affected by a KCNT1-related drug-resistant epileptic encephalopathy, who presented fatal complications with massive hemoptysis due to SPCAs. We aim to increase the awareness regarding this infrequent but potentially severe clinical condition.

1. Background

Pediatric pneumologists frequently deal with patients suffering from neurological impairment, who are more susceptible to recurrent respiratory infections. These patients frequently need antimicrobial therapy and hospitalisation, due to complications like hypomobility or aspirationcaused by inefficient swallowing and coughing. This results in a low quality of life for them and their family. Here, we describe a rare case of an unusual but potentially life-threatening complication of a specific genetic encephalopathy, namely the development of Systemic to Pulmonary Collateral Arteries (SPCAs) in KCNT1-related epilepsies.

Mutations of KCNT1 gene, encoding for a sodium-gated potassium channel, are causative of a wide spectrum of epilepsies and neurodevelopmental disorders, particularly Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) and Autosomal Dominant or sporadic Sleep-related Hypermotor Epilepsy (ADSHE). Less commonly, KCNT1 mutations are associated with other seizures phenotypes, such as West syndrome, Ohtahara syndrome, early myoclonic encephalopathy, leukodystrophy and/or leukoencephalopathy, focal or multifocal epilepsy, which are all included in the heterogeneous group of Developmental and Epileptic Encephalopathies (DEE) [1]. Other systemic manifestations are considered to be part of this clinical spectrum. Notably, cardiovascular involvement seems to be significant, with cardiac arrhythmia such as Brugada syndrome having been reported and, more rarely, SPCAs [2], namely abnormal blood vessels originating from the aorta or its first-order branches and connecting to the pulmonary circulation causing a volumetric overload [3].

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2. Case presentation

M. was a full-term newborn, with normal pre-natal period and screenings, including fetal ultrasounds. Family history was negative for hereditary or chronic diseases. A few hours after birth (Apgar score 9–10), he started suffering from recurrent episodes of desaturation with cyanosis associated with clonic seizures. Blood and cerebrospinal fluid tests were negative and neuroimaging (MRI and transfontanellar ultrasound) did not identify any structural abnormalities. However, the EEG showed an interhemispheric asynchrony with overlapping rapid rhythms and modest sharp wave spikes in the central and right temporal regions. In suspicion of a genetic/metabolic condition, a full screening was performed with echocardiogram, chest X-ray, abdominal ultrasound and eye examination, all resulting unremarkable. Concurrently, the genetic investigation for the principal genes involved in epileptic encephalopathies led to the diagnosis of a channelopathy by the mutation of KCNT1 gene, encoding a sodium-gated potassium channel. The neurological pattern, consistent with West syndrome, quickly degenerated into a drug-resistant epileptic encephalopathy with polymorphic seizures (Gross Motor Function Classification System level V); no therapeutic approach had a real impact on the course of the disease, including the compassionate use of quinidine (started because of its effect on potassium and sodium channels).

Since the first months of life, M. always presented stertorous breathing, ineffective cough and impaired secretions clearance, necessitating frequent suctioning of the upper airways, respiratory physiotherapy and the use of a cough stimulator. Due to recurrent pulmonary infections, sometimes associated with bronchospasm and requiring frequent antibiotic therapy and hospitalisation, M. underwent pneumological evaluation and follow-up; therapy with inhaled corticosteroids and azithromycin was initiated, providing mild benefit. Allergy tests were also performed because of recurrent episodes of wheezing, resulting negative. Serial chest X-rays performed during exacerbations showed a progressive worsening of the lung pattern through time (Fig. 1).

At the age of three, a thorax CT scan was performed, showing a mild involvement of lung parenchyma (mosaic pattern due to air trapping with no evidence of bronchiectasis) while, surprisingly, bronchial arteries were significantly involved, with a marked ectasia as per hypertrophy, both in the mediastinum and around the bronchi up to the sub-segmental branches; a modest ectasia of the common trunk of the pulmonary artery was also found (Figs. 2 and 3).

Given the poor neurological status and the diffuse vascular involvement, a wait-and-see strategy was initially preferred after a multidisciplinary discussion. After one year of relative clinical stability, a further CT scan showed no increase in bronchial arteries ectasia. On the other hand, while echocardiogram and EKG were normal and only few desaturations and apneas were found on polysomnography, with no indication for non-invasive ventilation, the swallowing evaluation tests confirmed the presence of dysphagia with signs consistent with inhalation, leading to the placement of a Percutaneous Endoscopic Gastrostomy (PEG).

At the age of six, M. presented the first severe complication with hemoptysis, which was well treated with intravenous tranexamic acid therapy. After selective arteriography, an embolization of the collateral arteries was performed (Figs. 4 and 5), without intra-operative complications. Unfortunately, the subsequent CT scan did not show any reduction in bronchial arteries size.

A few months later a second and a third episode occurred, the latter with acute respiratory failure, requiring intubation and invasive ventilation; due to hemodynamic instability aminic support was delivered. After a multidisciplinary meeting the family agreed not to performed further embolizations.

A few months later, at the age of 7, M. passed away due to complications from a fourth episode of massive hemoptysis.

3. Discussion and conclusion

Pneumonia are a worldwide leading cause of pediatric hospitalisation and children with neurological impairment are both frequently affected and particularly vulnerable to more severe complications. Factors such as an ineffective cough, a severe scoliosis preventing normal chest expansion and hypomobility result in a higher rate of hospitalisation and PICU admission (Pediatric Intensive Care Unit) [4]. Due to impaired swallowing ability and dysphagia, a PEG insertion is often required, both to prevent aspiration and to avoid malnutrition when oral intake is inadequate or takes too much time [5,6]. These are some of the reasons why children with neurological impairment are part of a pediatric pneumologist's daily clinical practice.

Whitin this scenario, our case report highlights two important issues. First, KCNT1 mutations, a gene encoding for a sodium-gated potassium channel, are responsible for a large group of epilepsies and encephalopathies, representing a rare condition even among

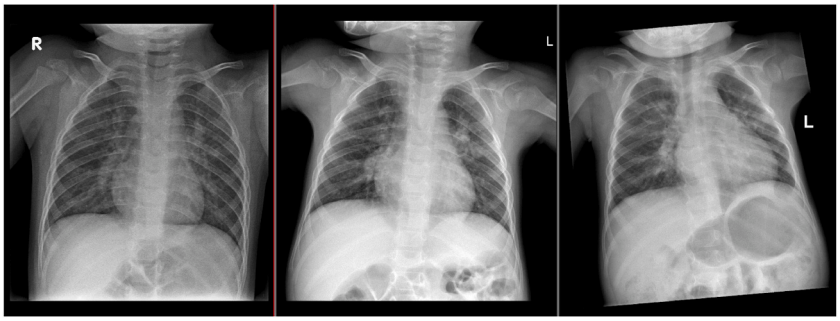

Fig. 1. Chest X-rays showing a progressive worsening of the lung pattern through time.

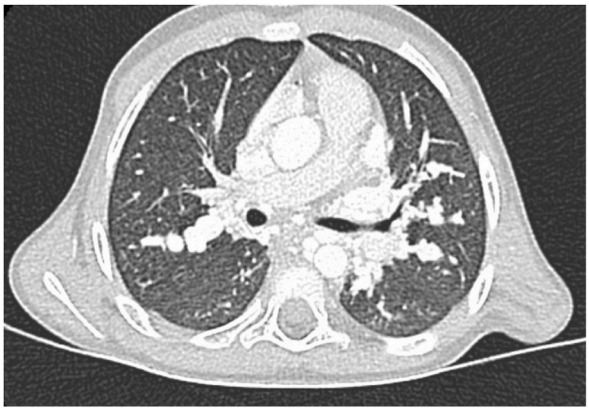

Fig. 2. Thorax CT, lung window: mosaic pattern, air trapping, no evidence of bronchiectasis.

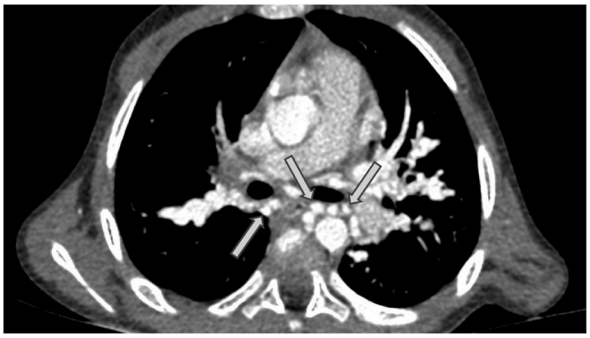

Fig. 3. Thorax CT, mediastinal window: marked ectasia of bronchial arteries, up to the sub-segmental branches, modest ectasia of the common trunk of the pulmonary artery.

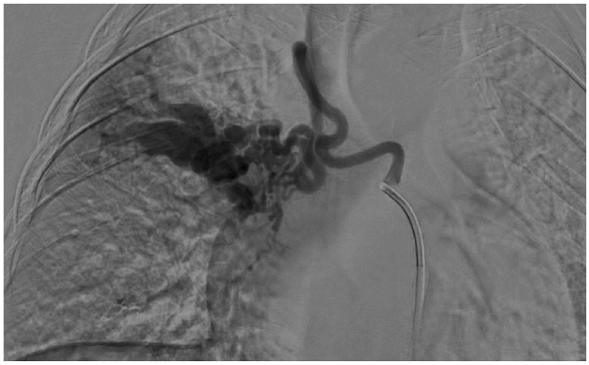

Fig. 4. Selective arteriography showing SPCAs.

pediatric neurological impairments. Their clinical spectrum may also include systemic involvement, notably cardiovascular, with cardiac arrhythmia and, more rarely, Systemic to Pulmonary Collateral Arteries. To our best knowledge, there are very few data reporting the association between KCNT1 gene mutations and the development of SPCAs [7]. It is therefore important for pneumologists to be aware of these potentially life-threatening comorbidities in order to manage them globally, starting from diagnosis which can sometimes be challenging without arteriography [8]. Since neurological status in these patients can be significantly compromised and given the risks of intraoperative complications, it is important to balance the pros and cons of selective arteriography and embolization. In this case, because of the initial clinical stability of the patient and the diffused vascular involvement, we decide to postpone these procedures; of note, this case may suggest that early embolization does not modify the course of the disease.

Secondly, it is known that Systemic to Pulmonary Collateral Arteries can be complications of end-stage chronic pulmonary diseases, mainly tuberculosis, malignancies, inflammatory lung diseases, cystic fibrosis while less commonly chronic obstructive pulmonary

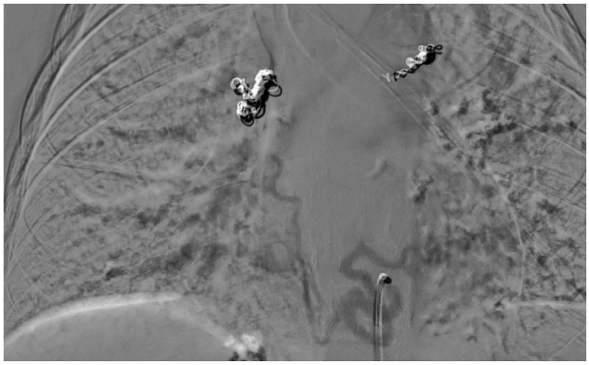

Fig. 5. SPCAs embolization.

disease and cardiovascular malformations. In such cases, bronchial arteries embolization has been proved to be a safe and effective intervention for controlling hemoptysis [9,10]. Since here the course of the disease was extremely rapid and SPCAs were present without a significant impairment of lung parenchyma, it is reasonable to think that KCNT1 gene mutations can be directly involved in SPCAs pathogenesis and, more in general, in cardiovascular angiogenesis [11]. Hypothesizing future scientific research developments, it would be therefore interesting to investigate KCNT1 expression, for example through mRNA PCR on Broncho-Alveolar Lavages collected from patients with chronic pulmonary diseases, to evaluate its causative role and consequently try to develop some target therapy.

CRediT authorship contribution statement

N. Garancini: Writing – original draft, Conceptualization. **M. Ghezzi:** Supervision. **A. Farolfi:** Supervision. **V. Guaia:** Writing – original draft. **G. Canali:** Writing – original draft. **V. Fabiano:** Supervision. **G.V. Zuccotti:** Supervision. **E. D'Auria:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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