MULTIDISCIPLINARY APPROACH TO A COMPLEX CASE OF ACUTE CHILD PNEUMONIA

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Abstract

We present a non-vaccinated 2 years and 3 months old female patient with anti-convulsive therapy for Bourneville tuberous sclerosis (TSC) who was hospitalized for fever, polypnea, paroxysmal coughing episodes and post-tussive vomiting, respiratory failure and convulsive status. Basic paraclinical investigations revealed bilateral paramediohilar interstitio-alveolar infiltration, normal liver and renal parameters, elevated CRP and procalcitonin, but the presence of very high white blood cell count with lymphocytosis raised suspicion of leukemia. It was excluded by bone marrow aspirate examination and the diagnosis of convulsive cough was confirmed based on the clinical and laboratory parameters. Molecular genetic test confirmed the diagnosis of tuberous sclerosis type 2. Taking in account that the child had partially controlled seizures and cerebral, cardiac and renal characteristic lesions, this case raised a lot of questions regarding the infectious contact and the possibility of other potentially severe infectious diseases prevention by vaccination. A hope in this case is the new approved in children drug everolimus. In conclusion, pneumonia, a common disease in pediatric age, can raise many diagnostic and therapeutic problems mainly in patients with chronic pathology, requiring multidisciplinary collaboration for successful management of the case.

Keywords: pneumonia, pertussis, seizures, tuberous sclerosis, child

Introduction

Pneumonia is a common cause of morbidity in childhood. It can manifest as a severe form of the disease in patients with associated chronic pathology, especially in non-vaccination conditions, requiring complex investigations and multidisciplinary intervention.

Case report

A 2 years and 3 months old female patient with anti-convulsive therapy with carbamazepine retard and vigabatrin for Bourneville tuberous sclerosis (TSC) are hospitalized for fever, polypnea, and paroxysmal coughing episodes with post-tussive vomiting, and generalized tonic-clonic seizures. The onset of disease was one week before admission, with cough, followed 1 day after by fever up to 38.8° C. In spite of the anti-tussive treatment, the cough is aggravated, the patient exhibiting emetic paroxysms, thoraco-abdominal balancing, respiratory groaning noise, and, in the day of admission, generalized tonic-clonic seizures which did not respond to the intrarectal diazepam treatment. At the presentation in the emergency unit she was febrile, with generalized tonic-clonic seizures, loss of consciousness, with 70% SpO2 which is being corrected up to 97% under oxygen mask therapy. After exclusion of Influenza A and B infection by rapid test, it was admitted in the intensive care unit (ICU) with diagnosis of acute pneumonia with respiratory failure, convulsive status and TSC.

From the family history, we retain type II diabetes mellitus (paternal grandfather) and acute kidney failure due to renal lithiasis requiring nephrectomy (paternal grandmother). An important fact is that the patient's 10-year-old brother, who was vaccinated according to Health Minister's schedule, presented a prolonged cough for 1 month.

The physiological personal history reveals that the patient comes from a second followed pregnancy, born trough cesarean section with a birth weight of 2970 g, high of 50 cm and Apgar score of 10. She was breastfed for 8 months, then with formula milk, diversified correctly at 6 months of age, with correctly prophylaxis of rickets and was vaccinated only at birth for B hepatitis and tuberculosis.

Pathological personal history reveals the onset at the age of 5 months, of afebrile focal ± generalized and atypical absence type seizures.

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Test		Patient	Normal value
Haemoglobin	g/dl	11.3	10.7-14.1
Leucocyte	/mm^3	103 840	5 500-15 500
Neutrophil	%	23.6	18-44
Lymphocyte	%	71	42-61
CRP	mg/l	103.23	0-5
Procalcitonin	ng/ml	0.599	< 0.5

Table 1. Basic laboratory tests

	Clinical exam	Paraclinical investigations
Infectious mononucleosis	Absence of lymphadenopathy, pharyngitis, hepato/splenomegaly	IgM anti-VCA Epstein-Barr antibodies: negative
Scarlet fever	Absence of typical pharyngitis and exanthema	Pharyngeal culture negative for *Group A beta-hemolytic Streptococcus*
Rubella	Absence of lymphadenopathy, typical exanthema	
Varicella	Absence of contact and typical exanthema	
Tuberculosis	Absence of contact	Absence of typical radiological characteristics QuantiFERON TB gold test: negative
Pertussis	Not vaccinated Paroxysmal coughing episodes with post-tussive vomiting	IgM anti-*B. pertussis* antibodies: positive IgA anti-*B. parapertussis* = negative

IgA=immunoglobulin A; IgM=immunoglobulin M; TB=tuberculosis; VCA=virus capsid antigen
Table 2. Differential diagnosis of leukemoid reaction with lymphocytosis

Pneumonia	Respiratory failure	Convulsive status
-tachypnea -bilateral fine crackles rales -chest roentgenogram -leucocytosis -increased CRP	-cyanosis -SpO2 of 70% - thoraco-abdominal balance, -intercostal and subcostal retraction -respiratory groaning noise	- succession of tonic-clonic seizures without recovery of consciousness between individual attacks

Table 3. Positive diagnosis criteria of pneumonia, respiratory failure and convulsive status

Major criteria	Minor criteria
1. Hypomelanotic macules (≥ 3, at least 5mm diameter) 2. Angiofibromas (≥ 3) or fibrous cephalic plaque 3. Ungual fibromas (≥ 2) 4. Shagreen patch 5. Multiple retinal hamartomas 6. Cortical dysplasias* **7. Subependymal nodules** 8. Subependymal giant cell astrocytoma **9. Cardiac rhabdomyoma** 10. Lymphangioleiomyomatosis (LAM)# 11. Angiomyolipomas (≥ 2)#	1. "Confetti" skin lesions 2. Dental enamel pits (>3) 3. Intraoral fibromas (≥ 2) 4. Retinal achromic patch **5. Multiple renal cysts** **6. Nonrenal hamartomas**
Definite diagnosis: Two major features or one major feature with ≥ 2 minor features Possible diagnosis: Either one major feature or ≥ 2 minor features	
* Includes tubers and cerebral white matter radial migration lines. # A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.	

Table 4. Diagnostic criteria for TSC

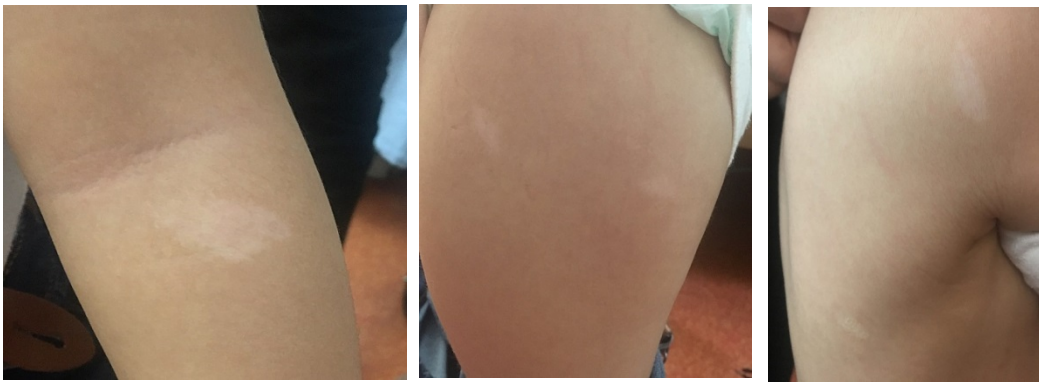

Fig. 1. White spots at the level of both upper and lower limbs and at the level of the posterior thorax

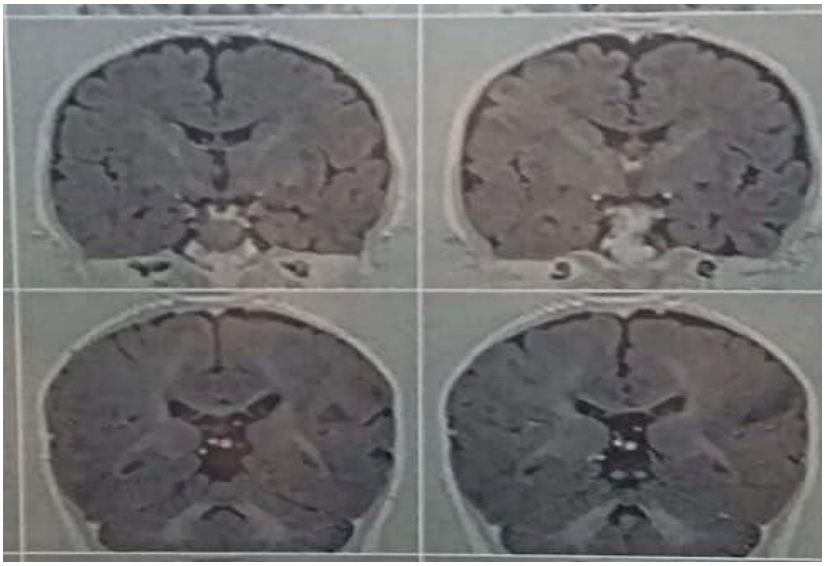

Fig. 2. Cerebral MRI: hamartomatous nodules

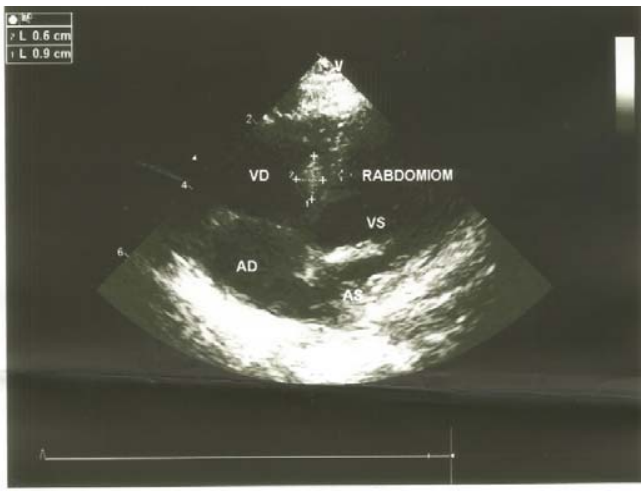

Fig. 3. Cardiac rhabdomyoma

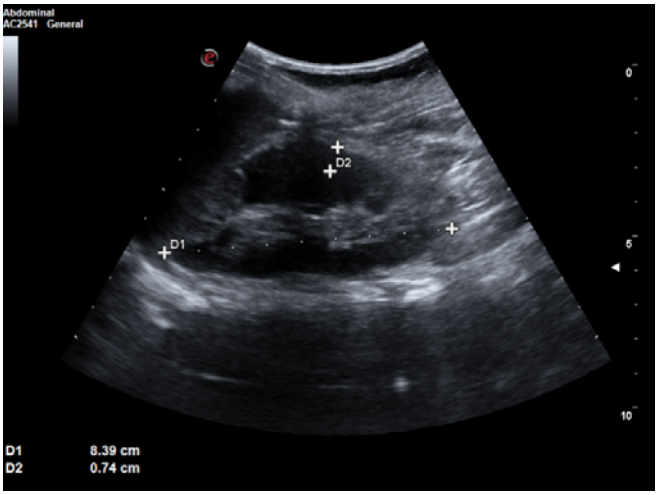

Fig. 4. Renal cysts

The clinical examination at admission showed a general influenced status, discrete pallor, white spots at the level of both upper and lower limbs and at the level of the posterior thorax (Figure 1), cyanosis, tachypnea (52 breaths/min), thoraco-abdominal balance, intercostal and subcostal retraction, presence of a symmetrical, bilateral pulmonary murmur, fine crackling rales, tachycardia, liver and spleen in normal range, loss of consciousness and no clinical signs of meningeal irritation.

Basic paraclinical investigations revealed bilateral paramediohilar interstitio-alveolar infiltration without pleurisy at chest roentgenogram, normal liver and renal parameters, elevated C reactive protein (CRP) and procalcitonin, but the presence of very high white blood cell count with lymphocytosis raised suspicion of leukemia (Table 1). The bone marrow aspirate examination showed erythroblast hypoplasia, reactive granulocyte series, lymphocytosis, 1% blasts, thus excluding leukemia and having the diagnosis of leukemoid reaction defined as leukocytes over 50 000 / mm3, with lymphocyte predominance [1].

Infectious mononucleosis, scarlet fever, rubella, varicella, tuberculosis and Bordetella parapertussis infection as a cause of lymphocytic leukemoid reaction are excluded based on clinical examination, chest roentgenogram, culture of pharyngeal exudate, serological investigations and QuantiFERON TB gold test (Table 2) [1, 2].

The neuropsychiatric examination revealed febrile infectious convulsive status.

Taking into account the presence of paroxysmal coughing episodes with post-tussive vomiting, absence of anti-pertussis vaccination and positive serology for Bordetella pertussis (B. pertussis), the diagnosis of pertussis infection complicated with pneumonia, acute respiratory failure and convulsive status was confirmed (Tables 2 and 3) [2,3].

The diagnosis of TSC requires 2 major criteria or 1 major criterion and at least 2 minor criteria mentioned in Table 4 [4]. To highlight them, cerebral MRI, cardiac and abdominal ultrasonography were performed. Cerebral MRI revealed supratentorial subcortical hamartomatous nodules and bilateral subependimal nodules suggestive for TSC (Figure 2). Cardiac ultrasonography showed the presence of cardiac rhabdomyoma with a maximum size of 1cm / 0.5cm (Figure 3), and abdominal ultrasound revealed a hypoechogenic lesion with a diameter of 0.5 / 0.5 cm in the median region of the right kidney medulla and bilateral cortical multiple small hypoechogenic lesions (Figure 4). Thus, with 3 major criteria and 2 minor criteria, the diagnosis of Bourneville syndrome can be supported. Since TSC is an autosomal dominant (AD) genetic disorder and the parents are clinically healthy, genetic testing was performed by sequencing for the TSC1 and TSC2 gene panel showing a pathogenic heterozygous mutation c.5138-5139del; p. (Arg1713Profs * 15) at the TSC2 gene level confirming definitively the diagnosis of TSC type 2.

Under treatment with intravenous meropenem, linezolid and clarithromycin, evolution was favorable, with CRP normalization after 14 days of treatment. Convulsions were immediately controlled with midazolam. Cough was present for a period of 7 weeks from onset and the number of leukocytes normalized after 8 weeks of evolution

Discussion

Pneumonia is a major cause of morbidity and in children it is the single largest infectious cause of death worldwide under the age of 5, accounting for 15% of all deaths [5]. In Romania, in 2010, the incidence of pneumonia at age 0-4 was 30 cases / 1 000 children, 26.7% of them being severe forms of illness, with a mortality of 9.3% [6]. B. pertussis pneumonia represents approximately 1.3% of cases of severe pneumonia at age 0-5 years [7]. Also several studies showed that about 9.5% of children with convulsive cough presented pneumonia as a complication [2]. This may be caused by B.pertussis or secondary bacterial invaders. The World Health Organization (WHO) estimated that in 2013, B. pertussis caused approximately 60 257 deaths in children <5 years of age [8]. In our country, in 2017 the incidence of convulsive cough was 0.5 / 100 000 inhabitants, lower than 2008 (2.4 / 100 000 inhabitants) when the last peak of incidence was registered [9].

Suggestive for the B. pertussis etiology in a child with acute respiratory failure is the presence of paroxysmal coughing episodes with post-tussive vomiting. Also very suggestive for diagnosis is very high leukocytosis with lymphocytosis, as in the present case. Leukocytosis is caused by the pertussis toxin and it is known that the severity of disease and the risk of death correlate directly with the white blood cell count and, in particular, the number of lymphocytes [2]. Considering that the patient is not vaccinated, does not attend the community and apparently has no infectious contact the question regarding who was the source of infection still remain. A number of studies showed that usually the source of infection with B.pertussis in infants and small children is a family member [10, 11, 12].

Both the disease and anti-B.pertussis vaccination do not provide lifetime immunity [2]. This explains why sporadic infection in the adolescent and adult reservoir is the major source of B. pertussis infections in nonimmune children. Studies of prolonged cough illnesses in adult and adolescents showed that 13-20% of the diseases are caused by B. pertussis infection (13, 14, 15). In our patient's case, the 10-year-old brother, considering that he had cough for 1 month before his sister's illness, may be the source of the infection even if he was vaccinated.

1.4-2.3% of patients with pertussis develop seizures and they are mainly caused by hypoxia [2]. In the presented case, seizures probably have a more complex etiology, caused by brain lesions from TSC, fever and hypoxia.

Bourneville's TSC is an AD genetic disorder characterized by skin, neurological (mainly seizures) manifestations and predisposition for tumors developing in any location. Although the diagnosis is based only on clinical criteria (Table 4), genetic confirmation is recommended, if possible, allowing for a proper genetic

counseling, prenatal diagnosis and therefore primary prophylaxis of the disease. TSC is a potentially progressive disease. This fact and the partially responsive to antiepileptic treatment seizures were the main justifiable causes of vaccination contraindication in our patient.

It is proved that the age-appropriate immunization coverage rate among children with TSC is low. In 72 children with TSC, the rate of adverse events or suspected adverse events after vaccination was 17% (12 cases), which was higher than the normal control children (2 cases, 3%) ($P<0.05$). The main side effects after immunization were seizure events, which accounted for 92% (11 cases). The high incidence of adverse events may be associated with the fact that there are nervous system abnormalities in patients with TSC. Despite of these, TSC children vaccination is considered relatively safe, with no serious adverse events [16]. Another study including 106 children with TSC showed that DTP immunization before seizure onset wasn't found to be a risk factor or predictor for mental retardation in children with TSC [17].

Since 2018, Food and Drug Administration (FDA) and European Medicine Agency (EMA) have approved the use of everolimus, a mechanistic target of rapamycin (m-TOR) inhibitor in TSC patients at least 2 years old presenting partial seizures, subependimal astrocytoma with giant cell and renal angiomyolipoma [18, 19]. This is a viable therapeutic option for our patient, because if the seizures and tumor progression are controlled, revaccination and thus the prevention of potentially fatal diseases could be performed.

Conclusions

In conclusion, pneumonia, a common disease in pediatric age, can raise many diagnostic and therapeutic problems mainly in patients with chronic pathology, requiring multidisciplinary collaboration for successful management of the case.

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