VIA MEDICA

PRACA KAZUISTYCZNA

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Lipoid pneumonia — a case of refractory pneumonia in a child treated with ketogenic diet

Tłuszczowe zapalenie płuc u dziecka leczonego dietą ketogenną — przypadek kliniczny

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Abstract

Lipoid pneumonia (LP) is a chronic inflammation of the lung parenchyma with interstitial involvement due to the accumulation of endogenous or exogenous lipids. Exogenous LP (ELP) is associated with the aspiration or inhalation of oil present in food, oil-based medications or radiographic contrast media. The clinical manifestations of LP range from asymptomatic cases to severe pulmonary involvement, with respiratory failure and death, according to the quantity and duration of the aspiration. The diagnosis of exogenous lipoid pneumonia is based on a history of exposure to oil and the presence of lipid-laden macrophages on sputum or bronchoalveolar lavage (BAL) analysis. High-resolution computed tomography (HRCT) is the imaging technique of choice for evaluation of patients with suspected LP. The best therapeutic strategy is to remove the oil as early as possible through bronchoscopy with multiple BALs and interruption in the use of mineral oil. Steroid therapy remains controversial, and should be reserved for severe cases.

We describe a case of LP due to oil aspiration in 3-year-old girl with intractable epilepsy on ketogenic diet. Diagnostic problems were due to non-specific symptoms that were mimicing serious infectious pneumonia. A high index of suspicion and precise medical history is required in cases of refractory pneumonia and fever unresponsive to conventional therapy. Gastroesophageal reflux and a risk of aspiration may be regarded as relative contraindications to the ketogenic diet. Conservative treatment, based on the use of oral steroids, proved to be an efficient therapeutic approach in this case.

Key words: lipoid pneumonia, refractory pneumonia, ketogenic diet, aspiration, epilepsy

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Streszczenie

Tłuszczowe zapalenie płuc jest przewlekłym śródmiąższowym stanem zapalnym zrębu płuca, wynikającym z akumulacji w nim endogennych i egzogennych tłuszczów. Egzogenne tłuszczowe zapalenie płuc wiąże się z aspiracją bądź inhalacją olejów obecnych w pokarmach, lekach, radiologicznych środkach kontrastowych. Manifestacja kliniczna jest różnorodna: od postaci bezobjawowych do ciężkich zapaleń płuc, przebiegających z niewydolnością oddechową; zależy od ilości aspirowanego tłuszczu oraz czasu trwania aspiracji. Rozpoznanie ustala się na podstawie wywiadu lekarskiego oraz obecności w badaniu histopatologicznym

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popłuczyn oskrzelowo-pęcherzykowych makrofagów wypełnionych wodniczkami z tłuszczem. Tomografia komputerowa klatki piersiowej wysokiej rozdzielczości jest obrazową metodą z wyboru w diagnostyce tłuszczowego zapalenia płuc.
Postępowanie terapeutyczne polega przede wszystkim na zaprzestaniu ekspozycji na substancje tłuszczowe, ich eliminacji z dróg oddechowych, poprzez powtarzalne zabiegi płukania oskrzelowo-pęcherzykowego metodą bronchoskopową. Leczenie glikokortykosteroidami jest kontrowersyjne i stosowane w ciężkich postaciach.
Autorzy opisują przypadek 3-letniej dziewczynki leczonej dietą ketogenną z powodu lekoopornej padaczki. Przedstawione problemy diagnostyczne wynikały z niespecyficznych objawów, sugerujących infekcyjne przyczyny zapalenia płuc. O tłuszczowym zapaleniu płuc należy pamiętać zwłaszcza w przypadkach zapalenia płuc i gorączki opornych na konwencjonalne leczenie, kluczowe znaczenie dla rozpoznania odgrywa szczegółowo zebrany wywiad lekarski. Obecność refluksu żołądkowo-przełykowego oraz innych czynników ryzyka aspiracji należy rozważyć jako względne przeciwwskazania do stosowania diety ketogennej.
W opisanym przypadku leczenie za pomocą glikokortykosteroidów okazało się skuteczne.

Słowa kluczowe: tłuszczowe zapalenie płuc, zapalenie płuc, dieta ketogenna, aspiracja, padaczka

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Introduction

Aspiration of oily substances into the respiratory system is one of very rare causes of pneumonia. Exogenous lipoid pneumonia (ELP) was first mentioned in the literature by Laughlin in 1925 – it was depicted on the basis of autopsy performed on 3 children and 1 adult [1]. Causative factors responsible for ELP in children are: oily intranasal drops, vaseline, high-fat milk, fish liver oils, egg yolk, using lipstick or nail polish, being fed in horizontal position, cleft palate, swallow disturbances [2–4]. Particles of oily substances may get into the lower parts of respiratory tract (including alveoli) without triggering cough reflex or irritation of throat mucosa. Oily lipase releases fatty acids, which destroy parenchymal lung tissue and cause necrotic bronchopneumonia with dramatic clinical course. Initially,oedema of alveolar wall with fibroblasts multiplication occurs. Subsequently, lipid-laden macrophages and giant cells appear in alveolar lumen, which lead to progressive fibrosis of lung parenchyma [1, 2, 5, 6]. Histopatologically types of changes are distinguished: 1) interstitial inflammation with exudative reaction 2) chronic diffused productive lesions leading to parenchymal fibrosis 3) numerous nodule-like adipose granulomas [1, 6].

There are no pathognomonic clinical signs for ELP. Most common are cough and dyspnea [1, 5]. Schwartz distinguished 3 clinical forms of ELP: 1) without clinical signs (except changes in imaging investigations) 2) with fever and productive cough (infiltration in the basis of the lungs in chest X-ray) 3) chronic cough, constant dyspnea (nodal-reticular changes in chest X-ray) [2]. In additional investigations, occasionally, there are increased number of white blood cells, elevated C-reactive protein, erythrocyte sedimentation rate and procalcytonine concentration. Hypercalcemia may also be present. Results of pulmonary function tests could be normal, but most often they reveal obstructive and restrictive disturbances in ventilation with diminished diffusing capacity. In chest X-ray there are different images. In acute forms of ELP the most frequent findings are interstitial and alveolar infiltrations. In a chronic form — cirrhosis, fibrosis, bronchiestasis and lesions mimicking tuberculosis. Chest high resolution computed tomography (HRCT) is a crucial investigation, as it reveals foci of fat accumulation, described in Haunsfield units. Values between — 150 and 30 confirm the diagnosis of ELP [5, 7]. Bronchioalveolar lavage fluid (BALF) reveals the presence of lipid-laden macrophages.

The majority of authors claim that properly taken history, imaging investigations (mainly chest HRCT) and bronchioalveolar lavage are sufficient for ELP diagnosis [5, 6, 8]. Invasive investigations (biopsy) may be applicable only in suspicion of a neoplastic disease [5].

Elimination of causative factor is fundamental for ELP treatment. There is no recommended pharmacological treatment. Decision of using steroids depends on clinical signs and results of additional examinations [5, 8]. Prognosis is poor, especially in the youngest children (infants and toddlers). Changes, especially radiological, may persist for a long period. We report a rare case of lipoid pneumonia treated successfully.

Case report

A 3-year-old girl with intractable epilepsy due to congenital cytomegalovirus infection, treated with ganciclovir, sodium valproate, vigabatrin, levetiracetam, lamotrigine since infancy

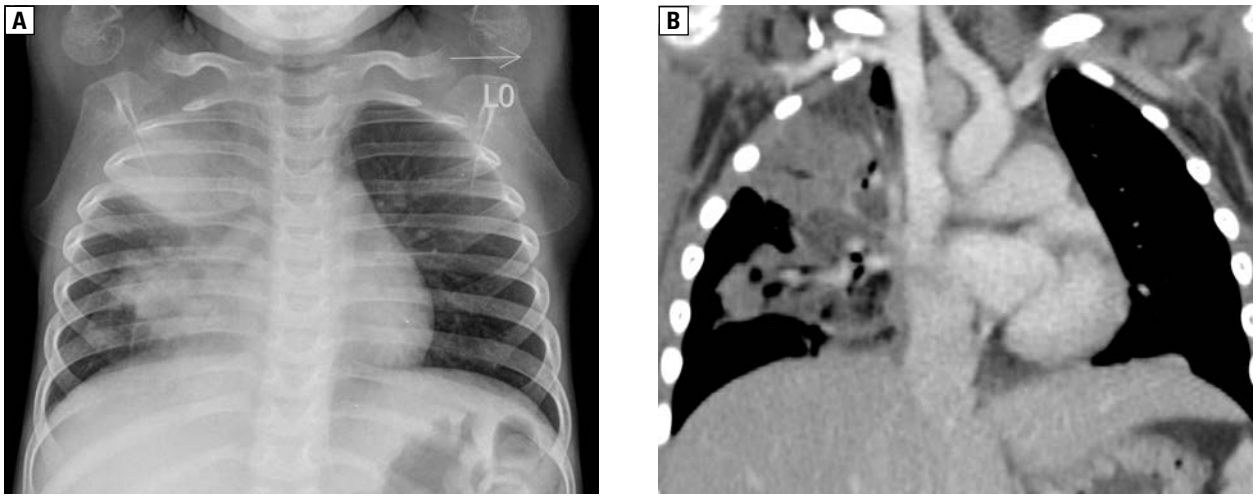

Figure 1 A, B. Massive and diffuse parenchymal infilitration of the right lung

and with ketogenic diet for one year (seizures-free period) was admitted to the hospital due to fever, dyspnoea of two month's duration with general weakness and marked weight loss. There were no other signs of an upper respiratory infection (cough, rhinits).

On examination, her general condition was poor, with fever, tachypnoe (70 breathes per minute), tachycardia (170 beats per minute), signs of dehydration, hypotrepsia and mental retardation. Chest examination revealed decreased vesicular breath sound and dulness to percussion over the right lung. The liver was palpable 4 cm below the costal margin.

Laboratory tests on admission revealed the presence of an inflammatory process: white blood count (WBC) of 19×10^9/l (with a differential of 62% neutrophil leucocytes, 6% band cells, 18% lymphocytes, 6% monocytes), C-reactive protein (CRP) 12.27 mg/dl (normal range < 0.5 mg/dl), ferritine — 506 ng/ml, erythrocyte sedimentation rate (ESR) 110 mm/hour. Investigations also revealed a haemoglobin of 10.2 g/dl, hypoalbuminaemia (16 g/l), ketone bodies in urine, negative blood cultures. Blood gas analysis, the concentration of glucose and ions in the blood, serum levels of immunoglobulins were normal. Serological tests for Epstein-Barr virus, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Bordetella pertussis* infections were negative and IgG antibodies against CMV (cytomegalovirus) were present in the blood. Tuberculosis was excluded. Chest X-ray and computed tomography (CT) scan showed massive and diffuse parenchymal infiltration of the right lung, atelectasis of the left dorsal basal lung segment and enlarged pretracheal and hilar lymph nodes (Fig. 1, 2).

The patient received a course of antibiotics: ceftriaxone and clarithromycin, then clindamycin, ciprofloxacin, meropenem, vancomycin, fluconazole. Transfusions of red blood cells

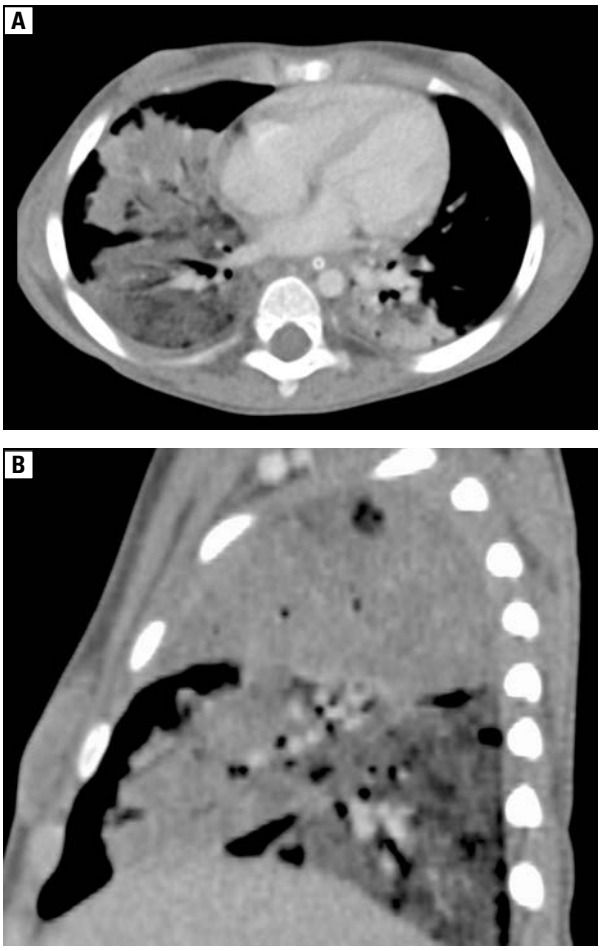

Figure 2 A, B. Atelectasis of the left, dorsal basal lung segment and enlarged pretracheal and hilar lymph nodes

(2 × 125 ml) and albumins were vital to treat anaemia and hypoalbuminemia. Due to suspition of ELP, immunoglobulins (3 × 0,4 g/kg) were given before bronchoscopy and material from bronchoalveolar lavage (BAL) analysis. Ketogenic diet was discontinued. She was better clinically after immunoglobulins, antibiotics, inhalation therapy (breath rate became normal), but fever and crackles persisted. Markers of inflammatory process were elevated despite the treatment. The patient was sent to other hospital with the suspiction of LP, to confirm the diagnosis. Bronchofiberoscopy revealed chronic inflammation in the bronchi, fragile bleeding and collapsing walls of the bronchi with small milky secretion. In the microscopic examination of the material from BAL, macrophages included deposits showing sudan positive staining, suggesting the presence of fat droplets. Similar deposits were visualized in the intercellular space in the material from BAL. On the base of BAL examination diagnosis of lipoid pneumonia was confirmed. Results of cultures from the bronchi towards bacteria and fungi were negative. Anti-inflammatory treatment with glucocorticosteroids (GCS) (1–2 mg/kg/day) was started, at first — parenterally, then — orally. After 2-week treatment significant clinical improvement was observed — decreased respiratory effort and tachypnea. The patient gained weight, in the chest X-ray control, radiological changes were persisted. Blood tests revealed a decline of CRP, ESR, WBC. Long-term treatment with GCS (every day) and azithromycin (three times a week) were recommended. During control visit after 6 weeks further improvement was observed — the girl was in good condition with no shortness of breath. Results of blood tests showed no abnormalities. Chest X-ray image showed significant improvement in the lungs. GCS were discontinued within 6 months after treatment initiation.

Discussion

The ketogenic diet (KD) is a strict high-fat, low protein, low carbohydrate diet that has been used for the treatment of intractable childhood epilepsy since the 1920s. Researchers also investigate use of this diet for other neurologic disorders such as mitochondrial disorders, autism, depression and brain tumors [9, 10]. Althought ketogenic diet is still controversial, its clinical efficacy in epilepsy has recently been established through randomized, blinded trials [11, 12]. The mechanisms underlying its clinical efficacy remain unknown. The diet mimicks the biochemical changes associated with starvation, which create ketosis. Several hypotheses have been proposed about the anticonvulsant mechanism of the KD, including: changes in levels of gamma aminobutyric acid (GABA) and other cerebrospinal fluid amino acids, changes in mitochondrial biogenesis, neuroprotection [9, 10, 13, 14]. Recent studies suggest that the KD may have anticonvulsant or antiepileptogenic actions via mTORpathway inhibition [15].

Early-onset adverse effects of KD include: acidosis, hypoglycemia, dehydration, constipation, vomiting, diarrhoea. Later adverse effects are: hypoproteinaemia, dyslipidemia, elevated liver enzyme, gallstones, kidney stones, weight loss and gain [9, 16]. Ketogenic diets are categorized as either long-chain fatty acid based or medium-chain fatty acid based. Lipid oil mixtures are prepared for infants and young children.

In this case, common adverse effects were not found, but massive life-threatening refractory pneumonia required discontinuation of the diet. Only a few reports have described lipoid pneumonia (LP) due to oil aspiration in patient treated with ketogenic diet [17–19]. One of the main cause of oil aspiration in our patient was feeding on horizontal position: she had not cough reflex because of the damage of the central nervous system (CNS) due to congenital CMV infection. Non-specific symptoms mimicking infectious pneumonia were main diagnostic problems. It is worth to underline that LP is a specific case of aspiration pneumonia in which treatment with conventional antibiotics and those against anaerobic bacterias are not effective and sufficient (but it is known that there is a high risk of reccurent bacterial pneumonias in the area of LP) [20]. Mineral oil is an inert substance that is not metabolized by pulmonary enzymes when aspirated. Instead, it is emulsified and phagocytosed by alveolar macrophages, returning to the alveolar space after cell death. The release of inflammatory cytokines by the activated macrophages probably leads to fever and to the presence of infection markers, which causes the misdiagnosis of LP as bacterial pneumonia [21, 22].

Immunoglobulins were administered as additional pneumonia treatment, futhermore in literature review, in one case report immunoglobulins were shown to be effective in LP [23].

In this case, significant clinical improvement was observed after treatment with steroids.

In the literature, steroids and therapeutic BAL have not been demonstrated to be significantly effective and cannot be proposed as the treatment for all cases. Surgery is seldom required

in the treatment of LP. One patient underwent a lobectomy to treat recurrent infection in the area of the lipid pneumonia [24].

Intractable epilepsy often occurs in children with damage of the CNS that inhibits cough and swallow reflexes. A high-fat diet prolongs the gastric emptying time and causes vomiting, especially in patients with gastroesophageal reflux — they are at high risk of oil aspiration that can lead to LP [18, 24]. These conditions may be regarded as relative contraindications to the KD [25]. If diet is started or continued, strict instructions about prophylaxis against aspiration pneumonitis are necessery (adequate patient's position, anti-reflux surgery, gastrostomy feeding etc.).

In conclusion, our case report exemplifies that neurologists and pediatricians should remember about LP — rare complication of the KD. Diagnosis of this rare, serious disorder can be delayed for many weeks or months, because symptoms are non-specific, mimicking infectious pneumonia. The main goal is to identify patients at high risk of oil aspiration to prevent from LP before diet is prescribed. Gastroesophageal reflux and a risk of aspiration should be regarded as relative contraindications to the KD. In such cases strict instructions for patients and parents are necessary. Missing of lipoid pneumonia diagnosis can be fatal, therefore a high index of suspicion and precise medical history is required in cases of refractory pneumonia and fever unresponsive to conventional therapy. Conservative treatment, based on the use of oral steroids, proved to be an efficient therapeutic approach in this case.

Conflict of interest

The authors declare no conflict of interest.

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