

Neurologic presentation of Erdheim-Chester disease

Objawy neurologiczne w chorobie Erdheima-Chesterera

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Abstract

Erdheim-Chester disease is a rare, systemic histiocytosis that involves multiple organ systems and causes symmetric sclerosis of the metaphysis and diaphysis of the long bones. We present 2 cases and reviewed 108 patients reported in the literature who had neurologic manifestations of Erdheim-Chester disease. After eye involvement or diabetes insipidus, cerebellar symptoms were most frequently encountered, followed by tumor, headaches, cord compression, mental status change, seizures, and change in libido. A wide range of neurological symptoms can be seen in ECD. Therefore we hope the review brings more awareness about this disorder.

Key words: Erdheim-Chester disease, non-Langerhans histiocytosis, neurological symptoms.

Streszczenie

Choroba Erdheima-Chesterera jest rzadką ogólnoustrojową histiocytozą, która zajmuje liczne narządy i układy oraz powoduje symetryczne stwardnienie przynasad i trzonów kości długich. W pracy przedstawiono opisy przypadków dwóch chorych i dokonano przeglądu odszukanych w piśmiennictwie danych 108 pacjentów z objawami neurologicznymi w przebiegu choroby Erdheima-Chesterera. Po zajęciu oka i po moczówce prostej objawy mózdkowe były trzecim najczęściej spotykanym objawem, ponadto występowały: objawy guza, bóle głowy, ucisk rdzenia kręgowego, zmiany stanu psychicznego, napady padaczkowe i zmiany dotyczące libido. W chorobie Erdheima-Chesterera może występować wiele różnych objawów neurologicznych, dlatego autorzy mają nadzieję, że przedstawiona praca zwiększy świadomość występowania tej choroby.

Key words: choroba Erdheima-Chesterera, histiocytoza bez komórek Langerhansa, objawy neurologiczne.

Introduction

Erdheim-Chester disease (ECD) is a rare, systemic, non-Langerhans histiocytosis characterized by symmetric long-bone osteosclerosis of the metaphyses. Histologically, ECD demonstrates infiltrate of non-Langerhans cell histiocytes that stain positive for CD68 and negative

for S-100 protein and CD1a but demonstrates no Birbeck granules on electron microscopy. Clinically, patients may have bone pain, retroperitoneal fibrosis, pulmonary fibrosis, and orbital manifestations. Neurologic manifestations are less common [1]. Here we describe the neurologic manifestations and magnetic resonance imaging (MRI) findings of ECD.

[Table 1 is available on www.neurologia.termedia.pl]

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Methods

We reviewed MEDLINE and PubMed for articles written in English and other languages and published between 1962 and 2005 with the key word „Erdheim-Chester disease.” Full articles were included in this review if the titles and/or abstracts described patients with any neurologic symptom, eye involvement, or diabetes insipidus (DI). Patients with eye involvement or DI were included because of the possibility of MRI abnormalities in the brain. These cases were further reviewed for neurologic symptoms, brain MRI findings, nonneurologic symptoms, radiographic findings, treatment, and outcome. Patients described in more than 1 article were included only once. Information was obtained from the abstract only in 4 cases because of difficulties obtaining the complete articles [2-5].

A review of medical records at Mayo Clinic in Jacksonville, Florida, using the key word „Erdheim-Chester Disease” yielded 4 patients with ECD, 2 of whom had neurologic symptoms.

Case reports

Case 1

A 55-year-old woman with a history of hypertension, hyperlipidemia, and type 2 diabetes mellitus developed a rash under her breast 5 years ago. Then 2 or 3 years later, she started having trouble with her balance and was walking unsteadily. Shortly after that, diplopia, dysarthria, and generalized bone pain developed. She lost 13.6 kg 3 years previously but since regained the weight. She believed her neurologic symptoms had worsened in the past few months.

Her physical examination demonstrated truncal ataxia, severe esotropia, hypometric saccades, horizontal nystagmus, dysarthria, and mild neck rigidity. She had left facial asymmetry and orbicularis oris-oculi synkinesis secondary to Bell palsy 16 years ago.

Metastatic bone survey demonstrated patchy sclerosis localized to the shafts of the long bones with periosteal new bone and sparing of epiphyses. Brain MRI showed scattered nonspecific focal T2-weighted

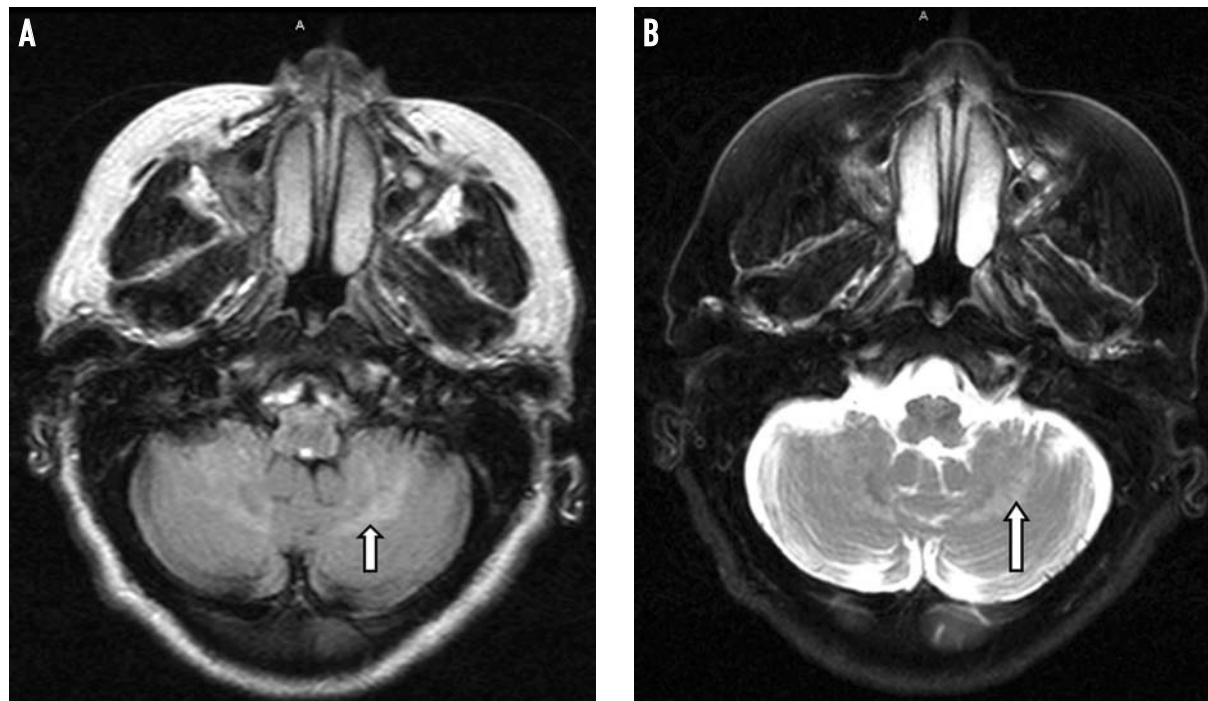


Fig. 1. Case 1. Magnetic resonance image of the brain. A, Arrow points to hyperdensity in the dentate nucleus and brainstem seen on fluid-attenuated inversion-recovery imaging. B, Similar findings seen on T2-weighted imaging

signal hyperintensity in the subcortical cerebral white matter and mild prominence of the superior vermicular sulci (Fig. 1). Bone marrow biopsy showed focal infiltration by histiocytes. CD68 stain was strongly positive, and S-100, CD1a, and reticulin stains were negative. This staining pattern is consistent with a diagnosis of ECD. The skin biopsy specimen showed chronic inflammation with a minor component of histiocytes. The histiocytes were negative for CD68 but weakly positive for S-100 and strongly positive for CD1a. These findings suggested Langerhans cell histiocytosis. However, on electron microscopy, no Birbeck granules were identified. The overall presentation was thought to support the diagnosis of ECD.

Case 2

A 75-year-old man with chronic low back pain and myofascial pains presented with a 1- to 2-year history of progressively worsening gait imbalance. He had intermittent tremors and changes in cognition, including agitation, abnormalities in long bones,

dyspnea, double vision, and abdominal pain. He also had a history of loculated pericardial effusion. On neurologic examination, his Mini-Mental State Examination score was 23 of 31 correct responses, and he had orthostatic hypotension and mild reduction in pain, temperature, and joint sensation in a stocking distribution. His gait was wobbly and shaky, and he could not walk without assistance.

Electroencephalography demonstrated intermittent slowing diffusely. MRI showed mild atrophy and nonspecific changes in the periventricular and subcortical white matter and in the pons. A biopsy specimen from the left tibia showed findings consistent with a diagnosis of ECD. The patient was treated with vinblastine with some improvement in symptoms for 8 months before his condition started to worsen.

Results

Sixty-five articles were included in our review with a total of 108 published patients plus 2 patients from Mayo Clinic in Jacksonville for a total of 110 patients

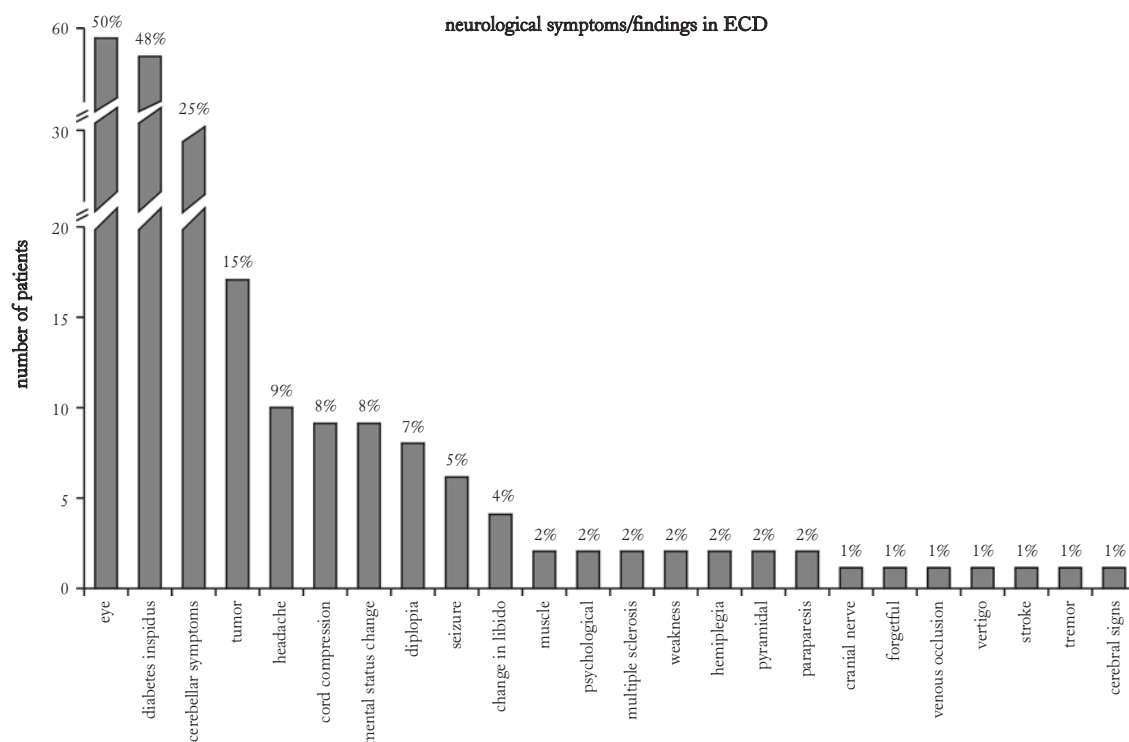


Fig. 2. The neurologic symptoms or findings seen in the 110 patients with Erdheim-Chester disease. The number at the top of each column indicates the number of patients affected; each patient may have had more than 1 symptom or finding

(electronic Table 1). The mean age was 49 ± 14 years (range, 7-76 years). Sixty (54.5%) were male (mean age 49 ± 14 years), and 50 (45.5%) were female (mean age 48 ± 11 years). Clinical neurologic signs, including eye involvement and DI, are summarized in Figure 2. Eye involvement includes proptosis, visual loss, exophthalmos, infiltrating mass, motility problems, choroidal and retinal folds, and optic nerve swelling. Cerebellar symptoms included dysarthria, nystagmus, dysmetria and ataxic gait. Cord compression was from extradural, epidural and paraspinal mass. Psychological symptoms included depression, psychosis or personality change. Muscle involvement was from infiltrating cells. The most common nonneurologic symptoms or involvement in patients with neurologic manifestations of ECD are summarized in Figure 3. Retroperitoneal findings included renal failure, infiltration, renal artery stenosis, obstructive uropathy, and abdominal pain. Lung findings included dyspnea, infiltrates, mediastinal mass, pleural thickening, and pleural effusion. Pericardial thickening and pericardial effusion were seen with heart involvement. Eighteen patients had no other symptoms. Sclerotic bone changes were seen in 81 patients (74%), and lytic changes were reported in 5 patients (5%). Only 2 patients had no other symptoms and no radiologic findings.

Imaging

The range of MRI findings was wide. MRIs were reviewed in 57 patients. No MRIs were reported as

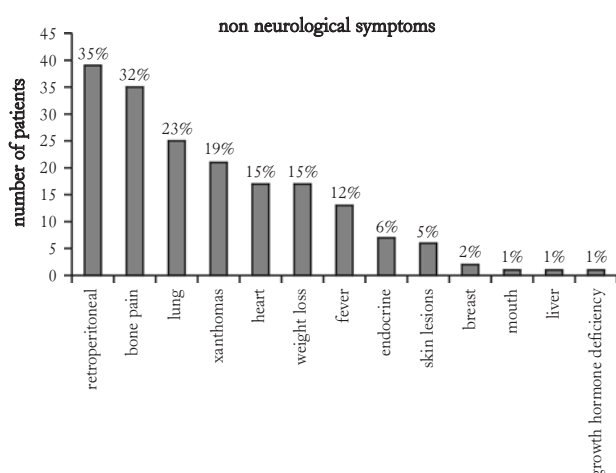


Fig. 3. Nonneurologic symptoms seen in the 110 patients with neurologic manifestations of Erdheim-Chester disease

normal, although some had nonspecific findings such as cortical atrophy. Enhancement was seen in 28 patients with 5 reports of prolonged enhancement (6-30 days) [4,6,15,31,55].

In the 53 patients with DI, only 14 had abnormalities (on MRI or computed tomographic scan) along the pituitary-hypothalamic axis. The abnormalities seen included enhancement of the pituitary-hypothalamic axis, an infiltrating lesion of the pituitary stalk, or thickening of the infundibulum [2,9,15,22,30,34,39,47,57,58,62]. Two patients had abnormalities without symptoms of DI [6,31]. Twenty-five patients had abnormalities in the brainstem, cerebellum, or both. These abnormalities were usually hyperintense lesions on T2-weighted and fluid-attenuated inversion-recovery images and were usually seen in the pons and cerebral peduncles and around the dentate nuclei [6,12,17,26,31,41,44,47-49,54,56,59,61,65]. Isointense lesions were also seen in 3 cases [15,55,57]. Some of the hyperintense and isointense lesions also enhanced. Of the 27 patients with cerebellar symptoms, 16 had abnormalities reported on their MRI in the cerebellum [2,17,30,34,44,47-49,54,56,57,59,61,65]. One patient with paraparesis had abnormalities in multiple areas in the brainstem and cortex [55]. Seven patients with abnormalities in the brainstem, cerebellum, or both, had no clear symptoms relating to abnormalities [6,12,15,26,31,41,57]. Of patients with eye involvement where imaging was reported, only 1 patient had a reported normal CT of the head [28]. Findings consisted of enhancement of the optic nerve and/or retrobulbar or orbital masses that were hypointense or hyperintense on T2-weighted imaging. Abnormal enhancement of the dura was seen in 6 patients [17,18,22,41,44,51,58]. Cortical lesions were seen in 8 patients, most commonly in the hippocampus [6,15,47,55,59,65]. Lesions in the basal ganglia were seen in 2 patients [41,56]. Twelve patients had masslike lesions that usually were hypointense or isointense with enhancement [1,7,10,14,32,33,35,51,57,58,63]. Hypervascularity with edema was seen in 1 patient [12], only cortical atrophy in 2 [16,51], and surplus of tissue in 1 [45]. Spine involvement consisting of epidural, dural, and paraspinal masses typically was seen in the thoracic region [14,25,28,55,58].

Treatments

A number of different treatments have been used: corticosteroids, methotrexate, vinblastine, CHOP

chemotherapy (a combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone), cladribine, cyclophosphamide, vincristine, interferon, immunoglobulin, azathioprine, etoposide, a combination of intrathecal cytarabine and methotrexate, cyclosporine, cytarabine, stem cell transplantation, surgery, and radiotherapy. Combined treatment with corticosteroids, radiotherapy, and surgery was used most frequently. In most cases, follow-up, if provided, was less than 1 year. Overall, the various treatments appeared to provide little or no improvement. A few patients' condition improved with corticosteroids [3,5,31,37,40,42,45,48,58], radiotherapy [65], interferon [35,58], etoposide, surgery [10], a combination of vinblastine and prednisone [46], CHOP chemotherapy [18,58], and a combination of intrathecal cytarabine and methotrexate [41].

Discussion

ECD is a rare non-Langerhans histiocytosis. Symmetric long-bone osteosclerosis of the diaphyses and metaphyses is a typical feature of ECD with clinical features of retroperitoneal fibrosis, pulmonary fibrosis, and orbital infiltration. Retroperitoneal involvement is secondary to infiltration of the fat and surrounding structures by histiocytes. The typical pulmonary symptom is dyspnea with interstitial prominence and pleural thickening. Sclerotic bone changes were seen in 81 out of 110 patients. Although sclerotic changes are typical of ECD and lytic changes are seen with Langerhans histiocytosis, 5 out of 110 patients with ECD in this study had lytic changes.

DI and eye involvement were the most common symptoms seen in patients with ECD. Although the DI and eye involvement accompanying ECD may not be clear neurologic symptoms and the diagnosis of ECD may involve other specialists, patients with MRI findings that suggest ECD may lead to neurologic consultation, and a wide range of neurologic symptoms occur in patients with ECD. DI also may present years before any other symptom of ECD. Cerebellar symptoms, as seen in our 2 patients, were the third most common neurologic symptom seen. Despite the wide range of neurologic symptoms seen in patients with ECD, only 2 of the 110 patients reviewed had only neurologic symptoms. All other patients had long bone findings and other nonneurologic symptoms. The nonneurologic findings were most often related to retroperitoneal infiltration followed by bone pain. Xanthomas, weight loss, fever, skin lesions, endocrine

abnormalities, and involvement of the lungs, heart, liver, breast, and mouth were also seen.

As with neurologic symptoms, MRI findings also were variable. However, overall, masslike lesions and eye involvement tended to be more isodense or hypodense and enhanced more than brainstem and cerebellar lesions, which were hyperdense on T2-weighted images. The cerebellar and brainstem lesions may be considered nonspecific white matter disease. In fact, the MRI findings in our first case could have been overlooked as white matter changes secondary to small vessel disease. So often neurologists overlook white matter changes on the MRI; however, it is important to correlate MRI findings with the patient's clinical presentation. In the first case, her findings were more important in the posterior circulation, which correlated with her symptoms.

Evaluation of treatment is difficult given variable follow-up, variable treatment, and the rarity of the disease. Corticosteroids and chemotherapy, radiotherapy, and surgery have been used to treat patients with ECD with neurologic symptoms. Overall, the responses reported are poor, with no or minimal improvement.

Histologic findings of ECD demonstrate infiltration of non-Langerhans cell histiocytes that stain positively for CD68 and negatively for S-100 protein and CD1a and demonstrate no Birbeck granules on electron microscopy. Langerhans histiocytosis cells test positively for S-100 and have Birbeck granules. In our first case, the bone marrow tested positive for CD68 and negative for S-100 and CD1a and had no Birbeck granules. However, the skin biopsy specimen demonstrated inflammation with minor component of histiocytes. The histiocytes were CD68 negative, weakly S-100 positive, and strongly positive for CD1a. These findings suggest Langerhans histiocytosis more than ECD, but there were no Birbeck granules. The histologic findings in this case were not definitive. However, overall the clinical picture was that of ECD. This is not the first case of conflicting histology; cases of a non-Langerhans histiocytosis along with Langerhans histiocytosis have been reported [11,16,56]. These findings support a closer association of ECD with Langerhans histiocytosis than has been traditionally thought. Clinical features of Langerhans histiocytosis are typically exophthalmos, lytic bone defects involving axial skeleton, and DI, and they also can occur in children and young adults.

In conclusion, ECD can have a range of neurologic symptoms and is therefore important for a clinician to

be aware of. This disease is rare, and only 1.8% of patients with neurologic symptoms had no other symptoms or bone changes. Therefore, a detailed history and an awareness of the disease would prompt a clinician to conduct further testing for ECD. In the setting of only neurologic symptoms, we recommend a bone survey if a previous work-up did not reveal the cause of the symptoms.

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