Neurological manifestations of Erdheim-Chester disease

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Abstract
Erdheim-Chester disease is a rare sporadic systemic histiocytic disease of unknown aetiology that affects multiple organ systems. The case records of all patients with Erdheim-Chester disease who had been seen at the Mayo Clinic between 1975 and 1996 were reviewed to assess the neurological manifestations of the disease. Two of 10 patients had neurological involvement. A 42 year old woman developed central diabetes insipidus and a progressive cerebellar syndrome. Brain MRI showed a lesion in the left pons with patchy gadolinium enhancement and T2 weighted signal abnormalities extending into both cerebellar peduncles and the medulla. Biopsy of the brainstem mass showed a xanthogranulomatous lesion. The second patient was a 53 year old man with retroperitoneal fibrosis secondary to xanthogranulomatous infiltration. Although he had no neurological symptoms and a normal neurological examination, MRI of the head showed multiple uniformly enhancing extra-axial masses along the dura of both convexities and the falx, and a mass in the left orbital apex. Both patients had the characteristic radiographic and bone scan findings of Erdheim-Chester disease. Review of the literature disclosed a wide variety of neurological manifestations in Erdheim-Chester disease. The most frequent CNS manifestations are diabetes insipidus, cerebellar syndromes, orbital lesions, and extra-axial masses involving the dura.

Keywords: Erdheim-Chester disease, xanthogranuloma, histiocytosis

Erdheim-Chester disease is a rare sporadic systemic histiocytic disease of unknown aetiology. The disease affects multiple organ systems, including musculoskeletal, cardiac, pulmonary, gastrointestinal, and central nervous systems, producing protein manifestations. Using the diagnostic coding system of the medical records database of the Mayo Clinic, Rochester, Minnesota, USA, to ascertain cases, we reviewed the case records of all patients with Erdheim-Chester disease who had been seen between 1975 and 1996. Of the 10 patients who had been diagnosed during this 20 year period, two had neurological involvement.

Report of cases
CASE 1
A 42 year old woman developed central diabetes insipidus. Initial MRI of the head was reported as normal. One year later, the patient noted progressive gait and limb incoordination, with slurring of speech and headache during the 6 months before evaluation. The patient described pain in the left knee region of 2 years duration for which she had received oral and intra-articular corticosteroids. She reported transient symptomatic improvement of her balance during her corticosteroid therapy. She reported no other musculoskeletal symptoms. Family and medical history were non-contributory.

Neurological examination 4 years after the onset of her symptoms disclosed normal cognitive function and a mild ataxic dysarthria. There was chemosis, lid retraction, and slight exophthalmos more prominent on the right side. Extraocular movements showed square wave jerks with horizontal nystagmus at both extremes of lateral gaze without any restriction of extraocular movements. Pupillary responses, fundoscopy, lower cranial nerve function, and tone in all limbs were normal. There was mild, symmetric weakness of the neck, proximal upper extremity, and hip flexor muscles. Deep tendon reflexes, plantar responses, and sensory examination were normal. The gait was wide based and ataxic. Rapid alternating motions of the left limbs were performed with irregular breakdowns in rhythm and range. The left knee seemed normal.

Extensive laboratory investigations were normal. Bilateral conjunctival biopsies were normal with no evidence suggestive of sarcoidosis. Brain MRI showed a lesion in the pons involving the left more than the right side with patchy gadolinium enhancement (figure 1). T2 weighted signal abnormalities extended into the medulla and both cerebellar peduncles. The extent of the abnormality had increased from a scan obtained 2 years previously. Electrophysiological studies performed as a baseline before monitoring during posterior fossa surgery showed bilateral auditory neuropathies and possibly a component of
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slow ing of conduction along brainstem auditory pathways; and bilateral, chronic facial neuropathies. A left suboccipital craniectomy was performed to obtain tissue for diagnostic purposes. The surgeon described a fullness in the brainstem immediately above the seventh and eighth cranial nerves and just below the exiting fifth cranial nerve. A 1.5 to 2 cm firm, fibrous mass which was thought to be indenting but not infiltrating the brainstem was removed after a small amount of milky fluid was drained.

Histological examination of the left cerebellopontine lesion showed a xanthogranulomatous process characterised by a prominent infiltrate of histiocytes with abundant foamy cytoplasm admixed with small numbers of lymphocytes and plasma cells. Subsequently, a technetium bone scan showed markedly increased uptake bilaterally in the metaphyses of the distal tibiae, the proximal and distal femurs, and the distal radii and ulnae, typical of the findings seen in Erdheim-Chester disease. Radiographs of the lower limbs showed a patchy increase in density primarily in the diaphysseal regions of the femur and tibia with some associated cortical thickening.

Five months postoperatively, the patient reported that her speech had improved slightly. Her balance and gait problems had remained stable. Neurological examination was essentially unchanged. The patient was treated with 60 mg oral prednisone/day. One month later, she reported that her balance and speech were slightly better. Neurological examination was unchanged apart from some reduction in gait ataxia. Repeat MRI of the head showed that the extent of the patchy T2 weighted signal abnormality in the pons had decreased in size and the overall amount of patchy gadolinium enhancement had also decreased. The dosage of oral prednisone was slowly decreased to 60 mg on even days and none on odd days because of appreciable side effects of corticosteroids.

Six weeks later her gait, balance, left arm coordination, and vision in the left eye had deteriorated. She was experiencing further severe side effects due to corticosteroids. Neurological examination disclosed increased gait ataxia, arm dysmetria, and dysnergia, nystagmus on lateral gaze, and a slight decrease in visual acuity in the left eye. A repeat MRI of the head showed no significant change. The patient received 1600 cGy of whole brain radiation in eight fractions over 2 weeks. At the end of the radiotherapy, the patient reported that she thought that her balance and gait had improved and that the coordination of her arms may have been slightly better. The other symptoms were unchanged. Neurological examination disclosed slight improvement in her gait ataxia.

The patient's symptoms were stable for 3 months; she then experienced progressive gait ataxia, such that she was unable to walk unaided. Her speech was slightly more ataxic, and she developed horizontal diplopia. On examination she had nystagmus in all directions of gaze and a left sixth nerve palsy. Her ataxic dysarthria had worsened and she had left facial weakness. She had marked limb and truncal ataxia. Brain MRI showed that the enhancing lesions in the brainstem and cerebellar peduncles were more prominent. The patient is currently being followed up to see if her recent deterioration is due to radiation toxicity or to progression of her underlying xanthogranulomatous disease.

CASE 2

A 53 year old man was evaluated because of a 20 year history of hypertension and renal impairment, due to bilateral hydronephrosis secondary to retroperitoneal fibrosis of uncertain cause (this patient has previously been reported on by Chiang et al.). Fine needle aspiration of the retroperitoneal lesion showed mature histiocytes with abundant foamy cytoplasm consistent with a xanthogranulomatous process. Technetium bone scan showed increased uptake in the tibias and proximal femurs bilaterally. Radiographs showed an abnormal increase in density involving the shafts of the femurs, tibias, and fibulas bilaterally. These findings were characteristic of Erdheim-Chester disease.

The patient had no neurological symptoms and a normal neurological examination. A previously obtained brain MRI showed multiple uniformly enhancing extra-axial masses along the dura of both convexities and the falx. The largest measuring about 4 cm in its greatest dimension. There was some localised mass effect, but no appreciable oedema or midline shift. The lesions were thought to be either xanthogranulomas or meningiomas (figure 2). There was also asymmetry of the orbital contents near the apex with a 1 cm mass near the left orbital apex. After careful consideration of the patient's general medical condition and lack of symptoms or signs related to the lesions noted on the MRI, no treatment of the cerebral lesions was recommended. Treatment with corticosteroids was begun for his systemic disease, and bilateral retrograde ureteral stents were placed. The patient did not return for
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subsequent follow up at our institution. He died of progressive renal failure in 1994 without any neurological problems. No further information was available.

Discussion

Two of the 10 patients who had Erdheim-Chester disease diagnosed had neurological involvement. Most of these 10 patients presented with musculoskeletal symptoms such as bone pain, but our patient 1 presented with neurological symptoms and our patient 2 presented for investigation of hypertension and renal impairment. The current patients' clinical histories and findings are consistent with a diagnosis of Erdheim-Chester disease. Other authors have reported cases with widespread involvement of the CNS, including intra-axial and extra-axial brainstem lesions that are very similar to those of our first patient. Although the cause of the neuroimaging abnormalities in our second patient is unknown, the findings are consistent with Erdheim-Chester disease. Two of the three patients reported by Caparros-Lefebvre showed extra-axial masses in the frontal region and along the falx, with one of the patients having pathological confirmation of the xanthogranulomatous nature of the cerebral lesions. The asymmetry of the apical orbital contents and the 1 cm mass near the apex of the left orbit in our second patient would also be consistent with lesions previously reported in Erdheim-Chester disease.

Erdheim-Chester disease is a non-Langerhans form of histiocytosis with distinctive radiological and pathological features. The disease produces protean clinical manifestations as a result of involvement of multiple organ systems. In many cases detailed descriptions of the neurological manifestations are lacking, which makes detailed analysis of the neurological symptoms, signs, and imaging abnormalities difficult. Our review of 80 cases (70 from the literature and our 10 from the Mayo Clinic records) disclosed neurological involvement in at least 29 patients (not counting an additional 27 of these 80 cases with diabetes insipidus). The incidence of neurological involvement in Erdheim-Chester disease is unknown as there is probably a bias towards reporting cases with unusual manifestations. However, the most frequent symptoms and signs indicating involvement of the CNS are those of central diabetes insipidus which occurred in at least 27 cases which we reviewed. Diabetes insipidus has been associated with the presence of orbital involvement in several cases. It is has been suggested that there may be extension of the process from the orbit along the optic nerves and chiasm to the hypothalamic-pituitary axis. Next in reported frequency are cerebellar symptoms and signs, with ataxia, usually of gait. The multifocal nature of involvement in Erdheim-Chester disease can produce a wide variety of clinical signs and has led to a possible diagnosis of multiple sclerosis. Spinal epidural and extradural masses have also been reported.

The temporal profile of the evolution of the neurological symptoms and signs, although variable, is usually slowly progressive. The neurological problems may arise in isolation or in association with symptoms and signs of systemic disease. Analysis of CSF is usually normal or shows small increases of protein. The characteristic radiographic findings consist of bilateral, symmetric, patchy, sclerotic lesions of the metaphyses and diaphyses of long tubular bones, with epiphyseal sparing. Radionuclide bone scans typically disclose increased tracer uptake in the areas that are abnormal on routine radiographs.

Computed tomography is most useful in showing the orbital, dural, and retroperitoneal lesions; MRI is probably more sensitive than CT in Erdheim-Chester disease, disclosing both intra-axial and extra-axial lesions. There is often intense gadolinium enhancement, which may persist for a prolonged period. As in our patient 2 there may be multiple extra-axial lesions involving the dura over the convexities or along the falx. As in our patient 1 intra-axial lesions often involve the cerebellum and pons. Imaging evidence of lesions in the hypothalamus or pituitary gland that might explain diabetes insipidus are rarely found. Occasional cases have shown enhancement or abnormal signal intensity of the pituitary gland.

The clinical manifestations of Erdheim-Chester disease vary from asymptomatic or minimally symptomatic bone lesions to a severe multisystem disease which significantly shortens a patient’s lifespan. This heterogeneity along with the relative rarity of the disease and the relatively few cases reported with long term follow up, make the assessment of the efficacy of various therapeutic modalities difficult. Reported treatments for patients with significant multisystem disease usually involve single case reports. Various therapies have been tried including corticosteroids, chemotherapy, radiation therapy, interferon, and cyclosporin. Improvements in patient’s symptoms have been reported after corticosteroids and whole brain radiation. It would seem from our literature review and our experience with one patient that corticosteroids result in only transient improvement. Radiation therapy seems to have a beneficial effect on bone lesions and some patients have had a beneficial effect on soft tis-
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Some patients have shown benefit after whole brain radiotherapy, however, several patients have shown no response to radiation therapy. Chemotherapy with various agents has resulted in inconsistent and meagre beneficial results. The eventual outcome of the cases reported in the literature was often not mentioned. Of those with significant systemic disease in whom it was detailed, most showed gradual progression, and many died as a result of their disease. Sustained improvement seems unusual.

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Handedness was another example of lateralised hemispheric function which attracted Broca and other French physicians in the 1860s. DJ Cunningham had noticed that the Sylvian fissure was higher on the right side than the left. Much later, Norman Geschwind and colleagues observed in right handers that the left hemisphere was appreciated over the lesser non-dominant one, until the degree of crossing of the pyramidal tracts, stimuli and to evoked potentials were to follow.

Anatomical variants of the ventricular size, the degree of crossing of the pyramidal tracts, and later asymmetries in response to visual stimuli and to evoked potentials were to follow. It was understood that the dual brain was marked by one dominant hemisphere which, through the vital corpus callosum, held sway over the lesser non-dominant one, until the importance of non-verbal functions of the right hemisphere was appreciated.

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