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 as a baseline before monitoring 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.

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slow ing of conduc tion along brainstem audi-
tory 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 indent-
 but not infiltrating the brainstem was
removed after a small amount of milky fluid
was drained.

Histological examination of the left cerebel-
lopatine lesion showed a xanthogranuloma-
tous 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 in-
 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 dia-
 physeal 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 essen-
tially 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 abnor-
mality in the pons had decreased in size and the
overall amount of patchy gadolinium enhance-
ment 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, nys-
tagmus 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 symp-
toms were unchanged. Neurological examina-
tion 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 direc-
tions 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 cer-
ebellar peduncles were more prominent. The
patient is currently being followed up to see if
her recent deterioration is due to radiation tox-
icity 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 uncer-
tain cause (this patient has previously been
reported on by Chiang et al.). Fine needle aspi-
ration of the retroperitoneal lesion showed
mature histiocytes with abundant foamy cyto-
plasm consistent with a xanthogranulomatous
process. Technetium bone scan showed in-
creased uptake in the tibias and proximal
femurs bilaterally. Radiographs showed an
abnormal increase in density involving the
shafts of the femurs, tibias, and fibulas bilat-arily. These findings were characteristic of
Erdheim-Chester disease.

The patient had no neurological symptoms
and a normal neurological examination. A pre-
viously 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 dis-
ease, and bilateral retrograde ureteral stents
were placed. The patient did not return for
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Caparros-Lefebvre4 showed extra-axial masses of the three patients reported by consistent with Erdheim-Chester disease. Two of our second patient is unknown, the findings are the cause of the neuroimaging abnormalities in similar to those of our first patient. Although and extra-axial brainstem lesions that are very involvement of the CNS, including intra-axial apex of the left orbit in our second patient cal orbital contents and the 1 cm mass near the asymmetry of the xanthogranulomatous nature of one of the patients having pathological confir-

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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May extend further forward than the left.10 However, several patients have shown no response to radiation therapy.10 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 Cunningham1 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 planum temporale is much larger than the right, but the right frontal lobe is wider and may extend further forward than the left.10

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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