




RESEARCH ARTICLE

Neurological manifestations of Erdheim–Chester Disease

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Introduction

Erdheim–Chester disease (ECD) is a treatable histiocytic neoplasm frequently involving the brain. It is characterized by infiltration and accumulation of inflammatory foamy macrophages in multiple tissues leading to end-organ dysfunction and failure through mass effect, tissue restriction, organ encasement, and by local and systemic inflammatory cytokines.^{1–3} The most commonly involved organs are bone, retroperitoneum, kidneys, brain, heart, skin, and lungs. The biopsy of affected tissue reveals foamy to epithelioid histiocytes that are CD1a–, CD68+, CD163+, factor XIIIa+, and S100±.⁴ Notably, this molecular signature is not specific to ECD, as it is also found in the macrophages of inflammatory

Abstract

Objective: To characterize the spectrum of neurologic involvement in Erdheim–Chester Disease (ECD), a treatable inflammatory neoplasm of histiocytes. **Methods:** Sixty-two patients with ECD were prospectively enrolled in a natural history study that facilitated collection of clinical, imaging, laboratory, neurophysiologic, and pathologic data. **Results:** Ninety-four percent of the patients had neurologic abnormalities on examination or imaging, and 22% had neurologic symptoms as the initial presentation of ECD. The most common neurologic findings were cognitive impairment, peripheral neuropathy, pyramidal tract signs, cranial nerve involvement, and cerebellar ataxia. Imaging revealed atrophy and demyelination along with focal lesions that were located throughout the nervous system, dura, and extra-axial structures. The *BRAF* V600E variant correlated with cerebral atrophy. Brain pathology revealed lipid-laden, phagocytic macrophages (histiocytes) accompanied by demyelination and axonal degeneration. **Interpretation:** In patients with ECD, neurologic morbidity is common and contributes significantly to disability. Since neurologic symptoms can be the presenting feature of ECD and, given the mean delay in ECD diagnosis is 4.2 years, it is critical that neurologists consider of ECD and other histiocytosis in patients with inflammatory, infectious, or neoplastic-appearing white matter. Furthermore, given the broad spectrum of neurologic involvement, neurologists have an important role in a team of specialists treating ECD patients.

conditions such as multiple sclerosis, sarcoid, and IgG4 disease. The treatment of ECD involves anti-inflammatory or antineoplastic agents⁴ and vemurafenib is FDA-approved for the treatment of ECD.⁵

To date, the neurologic features of ECD have been described in small series and retrospective studies.^{6–10} A meta-analysis showed that approximately half of ECD patients have neurologic involvement, and these patients carry a poorer prognosis and may be refractory to first-line treatments.^{11,12} Given the therapeutic and prognostic implications, it is paramount to recognize ECD in neurologic patients, distinguish it from other inflammatory and oncologic disorders, and provide for timely diagnosis and treatment.

The goal of this study was to systematically characterize the spectrum of neurologic disease in ECD in a large cohort of patients enrolled in a longitudinal observational study.³

Methods

Standard protocol approvals, registrations, and patient consents

Patients were prospectively enrolled in the “Clinical and Basic Investigations into Erdheim-Chester Disease” study (Protocol 11-HG-0207, clinicaltrials.gov identifier NCT01417520) at the National Human Genome Research Institute (NHGRI)⁸ and provided written informed consent. The NHGRI Institutional Review Board approved the study. Recruitment was primarily via physician referral or through the ECD Global Alliance. Inclusion required diagnosis of ECD based on clinical evaluation with histological confirmation. Seventy-nine ECD patients were enrolled, and 62 patients were admitted for the first time to the NIH Clinical Center between October 2011 and September 2016. Seventeen patients were unable to travel to the NIH and were excluded from this analysis. ECD diagnosis was confirmed at the NIH using consensus criteria.⁴ Given the rarity of ECD, pre-enrollment power calculations were not employed (the ECD Global Alliance estimates 359 patients worldwide, of which 191 are in the USA).¹³

Protocol 11-HG-0207 provides for the collection of tissue from confirmed ECD patients in the absence of clinical evaluation. Neurologic postmortem tissue was obtained from one additional patient.

Clinical evaluation

A multidisciplinary team focused on ECD composed of neurologists, ophthalmologists, geneticists, and endocrinologists performed a comprehensive evaluation.³ All patients were screened for neurologic comorbidities in a standardized manner. This included trauma, concussions, meningitis, encephalitis, surgery, vestibular disorders, other brain tumors (metastatic and primary), seizures, migraines, cerebrovascular ischemia, spinal injuries, toxic environmental exposure, and nerve entrapment syndromes. A complete general physical and neurologic examination – including assessment of mental status by a mini-mental status examination (MMSE), cranial nerves, motor, sensory, coordination, reflexes, and gait – were performed on all participants.

Electrophysiologic investigation of the peripheral nervous system included nerve conduction studies of peroneal, tibial, and median nerves and limited EMGs of

the lower extremities on 34 patients (selection limited by consent).

Formal neuropsychologic testing was obtained in 14 patients (limited by consent and availability of testing). A standardized battery was used to assess overall intelligence (Wechsler Reading and Wechsler Abbreviated Scale of Intelligence II), memory (Wechsler Memory test, digit span, Hopkins Verbal Learning Test), visuospatial functioning (Brief Visuospatial Memory Test, Rey Complex Figure), language function (Controlled Oral Word Association Test, Boston Naming Test), executive functioning (Symbol Digit Modality Test, Wisconsin Card Sorting Test, Paced Auditory Serial Addition Test), and mood (Frontal Systems Scale of Behavior, Beck Depression Inventory).

Imaging

MRIs of the brain, orbits, and pituitary (sellar and suprasellar regions) with and without gadolinium were obtained using a 1.5- or 3-Tesla scanner ($n = 58$). Spinal imaging with gadolinium was obtained ($n = 2$). Three patients were unable to tolerate MRI or had contraindications to MRI imaging. Multiplanar T1-weighted, T2-weighted, and diffusion sequences were obtained using an MRI protocol developed for this study, and images were interpreted by one of three neuroradiologists experienced in ECD. The radiologists were provided clinical history and ECD diagnosis to facilitate interpretation within the context of this observational study. The written reports were used to generate frequencies of the imaging findings.

Subjects were considered to have atrophy if the report reflected generalized or lobar atrophy or ventricular enlargement. Intracranial tumors were defined as either measurable lesions or patchy, confluent, and large lesions. Punctate changes (even if potentially related to ECD) were not considered tumor-like.

Quantitative brain volumes were obtained in 15 patients and 15 age-matched healthy controls using an unbiased voxel-wise morphometric (VBM) approach using FSL (v5.0.11).^{14–16} Also, 3-Tesla diffusion tensor imaging was obtained in 15 ECD patients and 15 age-matched healthy controls, and voxel-wise maps were created for fractional anisotropy, mean diffusivity, axial, and radial diffusivity using the TORTOISE and TBSS software packages.¹⁷ As these methods require a specific protocol for capturing and processing images, they could not be performed on the entire cohort.

Molecular studies and histology

DNA from CNS and non-CNS biopsy tissues of 58 subjects was sequenced to evaluate for the presence of the *BRAF V600E* variant.³ Paraffin-embedded sections

prepared by referring institutions were evaluated by a hematopathologist experienced in histiocytic disorders.³ Unstained CNS tissue blocks were obtained from referring centers, and immunohistochemistry was performed at NIH ($n = 5$).

Statistical analysis

Clinical, imaging, and molecular data were analyzed using descriptive statistics, and *BRAF* versus atrophy comparisons were performed using a one-tailed Fisher's exact test. A one-tailed test was used because the *BRAF V600E* variant is likely pathogenic and correlates with worse organ-specific disease in untreated patients.^{2,18–20} Diffusion tensor imaging and volumetric data were compared using the FSL Randomise tool (v5.0.11, 5000 permutations) – which conducts pairwise, permutation-based inference on *t*-statistic maps^{21,22} – was used to identify clusters of voxels that differed between the healthy controls and patient group. The threshold for significance was $P < 0.05$, after correcting for multiple comparisons across space (FSL TFCE tool).^{14,23–25}

Results

Patient characteristics and therapy

We evaluated 62 patients (47 males and 15 females), all of whom met consensus criteria for a diagnosis of ECD.⁴ Mean age at enrollment was 54 years (range 22–74 years), mean age of symptom onset was 46 years (range 16–74 years), and the mean time to diagnosis was 4.2 years (range 0–24 years). Fifty-four percent were positive for the targetable *BRAFV600E* variant.

Ninety-four per cent of the patients had objective neurologic findings: abnormalities on examination or neuroimaging. Twenty-two percent (14/62) of patients had an initial ECD presentation that was neurologic in nature, including cerebellar ataxia, focal weakness, gait imbalance, seizures, and Horner's syndrome (Table S1). Bone pain (17%) and diabetes insipidus (25%) were the most common initial systemic presenting findings.³ Prior to reaching a conclusive ECD diagnosis, other considerations included autoimmune disease (27%), sarcoid (18%), IgG4 disease (17%), multiple sclerosis/neuromyelitis optica (15%), CNS malignancy (10%), and vasculitis (22%). Additionally, one patient had comorbid myasthenia gravis, and another had comorbid CNS lymphoma. One patient, initially considered to be CNS-isolated ECD, had minimal asymptomatic perinephric fibrosis that facilitated the diagnosis.

Therapy prior to, or at, enrollment commonly included interferon $\alpha 2b$, anakinra, vemurafenib, imatinib,

methotrexate, and cladribine (Table S1). Isolated cases were treated with natalizumab, cyclophosphamide, daclizumab, tocilizumab, dasatinib, 6-mercaptopturine with vincristine, vinblastine, or dabrafenib with trametinib. Clinical and radiologic neurologic improvement were seen with cladribine in a patient who had a brainstem lesion. The correlation of clinical improvement with specific therapies was limited since several subjects were receiving multiple agents for variable periods of time, sometimes prescribed for alternative diagnoses. Recent case reports suggest that MEK inhibitors may show promise for neurologic disease.²⁶

Clinical features

We found involvement throughout the nervous system. The most common findings were subjective or objective cognitive difficulty (52%), cerebellar ataxia (46%), cranial neuropathy (61%), peripheral neuropathy (56%), pyramidal tract involvement (30%), and seizures (8%). Dysmetria was observed in 33% and dysidiadochokinesia in 26%. 44% of our cohort had oculomotor abnormalities resulting from lesions affecting the cerebellar peduncles, nuclei, nerve fibers, or extraocular muscles. Two patients had a myelopathy (confirmed on spinal imaging).

To assess peripheral nerve involvement, neurophysiologic testing was obtained in 34 patients. Fifty-six percent of those patients have peripheral neuropathies. Electromyography revealed axonal neuropathy in all patients – peripheral demyelination was not seen. Deficits were equally distributed amongst polyneuropathies (15% sensorimotor; 6% isolated sensory), isolated mononeuropathies (12% peroneal; 12% median; 9% ulnar), and polyradiculopathies (9%). Contributing comorbidities included toxicity from therapies such as immunomodulators, chemotherapy and glucocorticoids (69%; 43/62), diabetes mellitus (14%), vitamin D deficiency (29%), and hypothyroidism (both central and primary, 28%). Symptomatically, subjects commonly complained of pain that reflected both tumor infiltration into bone marrow and neuropathic pain. In summary, neuropathies are common in ECD, but the etiologies may be multifactorial.

Elevated inflammatory markers were noted in some patients (ESR in 47%, CRP in 43% and borderline ANA in 23%; $n = 62$), but none of these patients met ACR diagnostic criteria for connective tissue disease or autoimmune thyroiditis seen. These results likely reflect the inflammatory nature of ECD.

Cognition

Cognitive impairment was unexpectedly common in our entire cohort. Fifty-two percent of the subjects

complained of disabling cognitive difficulties and 11% had an abnormal mini-mental status examination. Neuropsychologic testing identified cognitive deficits in 64% (9 of 14) of studied subjects (see Table 1). One patient had dementia and eight had mild cognitive impairment. The most frequently affected domains were verbal fluency (COWAT; 6 patients), psychomotor slowing (FRSBE; 5 patients), executive dysfunction (SDMT, PASAT, WCST or Rey; 5 patients), and memory (WMS-3, HVL, VSMT; 5 patients). Two patients exhibited mood disorders (pseudobulbar affect and anxiety).

This cognitive dysfunction reflects the fact that ECD patients have reduced brain volumes compared to healthy controls as determined by quantitative brain volumetric analysis ($n = 15$ per group), with the ECD group being 2.7 mL smaller than the control group. The gray matter volume loss involved specific regions within the right frontal and parietal cortices (Fig. 3b). Congruently, analysis of brain MRI reports revealed that 28% of the entire cohort had age-inappropriate atrophy (Fig. 1). The *BRAF* V600E variant correlated with the presence of atrophy on imaging ($p = 0.047$; odds ratio 3.5). Overall, symptomatic neurodegeneration is frequent in ECD.

MRI lesions

Radiologic abnormalities involving the brain, orbits, or pituitary were noted in 75% of the cohort. Brain parenchyma (50%; 20/61), meninges (6%, 4/61), orbits (38%), and pituitary (26%) were most common (Fig. 2).

Parenchymal lesions were distributed throughout the brain: most frequently locations were the periventricular region (31%), pons (20%), and midbrain (16%) but lesions were seen in the frontal lobe, temporal lobe, occipital lobe, basal ganglia, and cerebellum. Enhancement was infrequent (18%) and typically heterogenous when present. Most of the lesions were tumor-like (67%; 20/31) but punctate abnormalities unexplained by age or vascular disease were also seen (potentially ECD-related). The tumor-like lesions were frequently ill-defined or patchy (55%) and not always discrete or measurable. Lesion-associated edema was seen in only one patient. These findings suggest that neuro-ECD is a multifocal disease.

To better understand parenchymal disease, quantitative diffusion tractography was performed in 15 patients and 15 age-matched healthy controls. Compared to controls, ECD patients exhibited increased radial diffusion of water molecules (Fig. 3). These results indicate disruption of myelin integrity, and suggest ECD may involve CNS demyelination (see pathology section).²⁷

Orbital lesions were common (38%) and caused proptosis in 22% of patients. The most frequent location was intraconal (22%) but 5% of the patients had tumor infiltration of the extraocular musculature and 9% had extraconal lesions. Five percent of patients had optic nerve encasement or infiltration but chiasmal compression was not seen. Pituitary involvement typically manifest as nodules, stalk thickening (20%) or empty sella (6%). Meningeal disease was dural in location (no leptomeningeal disease was seen), rarely enhancing, and did not compress the brain parenchyma.

Table 1. Summary of neuropsychologic testing results.

| # | WMS3 | HVL | VSMT | COWAT | BNT | Peg | TMT | SDMT | WCST | FrBSE | Other |
|----|---|-----|------|-------|-----|----------------|-----|------|------|-------|-------|
| 1 | | | | X | | | | X | | | |
| 5 | | | | | | | | | | | |
| 7 | | X | | X | | | | | | | |
| 8 | | | X | | | | | X | X | X | REY |
| 12 | | X | | X | | | | X | | X | |
| 13 | | | | X | | | | | X | | |
| 16 | | | | | | | | | | X | |
| 17 | | X | | | | | | X | X | | |
| 20 | X | X | X | X | | X | | | | X | |
| 34 | | | | | | | | | | | |
| 36 | | | | | | | | | | | |
| 41 | | X | X | X | X | | | | | X | PASAT |
| 47 | | | | | | X ¹ | | | | | |
| 60 | Significant dementia, MOCA 10/30, cannot complete battery | | | | | | | | | | |

x, more than 2 SD abnormal on any aspect of given test or one of its subsets.

BNT, Boston Naming Test; COWAT, Controlled Oral Word Association test; FrBSE, Frontal System Scale of Behavior Family-rating Form; HVL, Hopkins Verbal Learning Test; MOCA, Montreal Cognitive Assessment; PASAT, Paced Auditory Serial Addition Test (>2SD abnormal in indicated patient); Peg, Grooved Pegboard; Rey, Rey Complex Figure Task (abnormal in indicated patient); SDMT, Symbol Digit Modality Test; TMT, Trail Making Tests A & B; VSMT, Brief Visuospatial Memory Test; WCST, Wisconsin Card Sorting Test; WMS-3, Wechsler Memory Scale, third edition.

¹Note: for patient #47, the abnormality was attributed to motor dysfunction rather than cognitive abnormality.

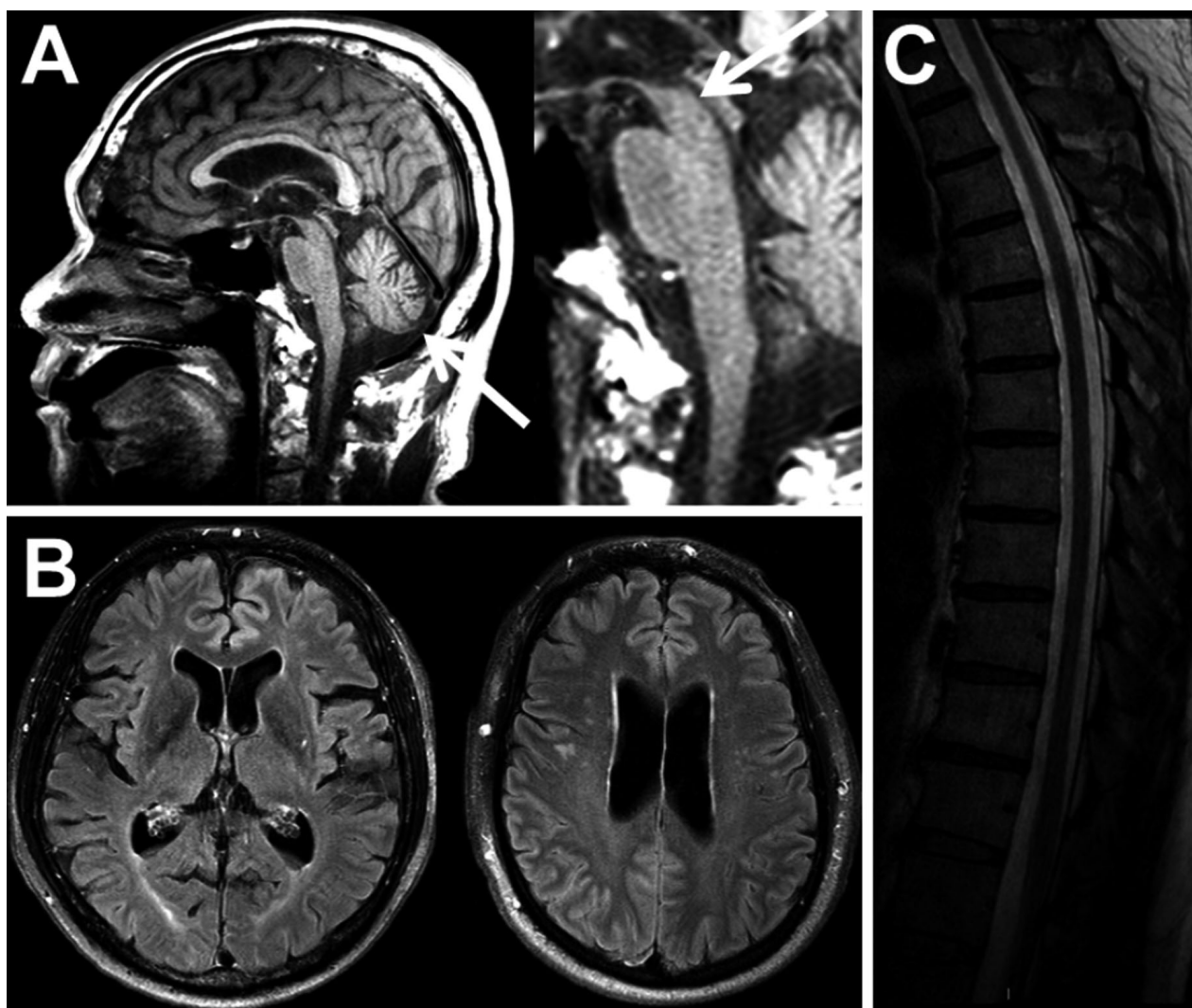


Figure 1. CNS neurodegeneration in Erdheim–Chester Disease. (A) Cerebellar and midbrain atrophy seen on FLAIR imaging. (B) Cerebral atrophy (FLAIR imaging). (C) Spinal cord atrophy (T2-weighted image).

Pathology

Biopsy tissue of CNS lesions revealed lipid-laden (foamy) macrophages (Fig. 4) positive for CD68 (100%, 5/5) and negative for CD1a (100%), accompanied by gliosis (80%) and Touton giant cell formation (100%). Cells were variably positive for CD163 (60%) and S100 (40%). The ECD histiocytes were surrounded by demyelination (Fig. 4D) and scant axonal loss on neurofilament staining, consistent with the tractography findings. It should be noted that these findings may not be specific for ECD (see Discussion).

Additionally, two patients with confirmed ECD had brain pathology suggesting comorbid disease including B-cell lymphoma and Langerhans cell histiocytosis (CD68+,

CD1a+, S100+). Autopsy tissue was available from a patient whose brain contained multiple well-circumscribed, but not encapsulated, fibrohistiocytic infiltrates involving the parenchyma, dural venous sinuses and the neurohypophysis.

Discussion

Erdheim–Chester disease is a rare, life-threatening disorder characterized by macrophage (histiocyte) infiltration in multiple organs including the brain.^{4,28,29} Since these histiocytes can be clonal³⁰ and contain disease-causing variants in proliferative signaling pathways,^{31,32} the World Health Organization classifies ECD as an inflammatory neoplasm.³³

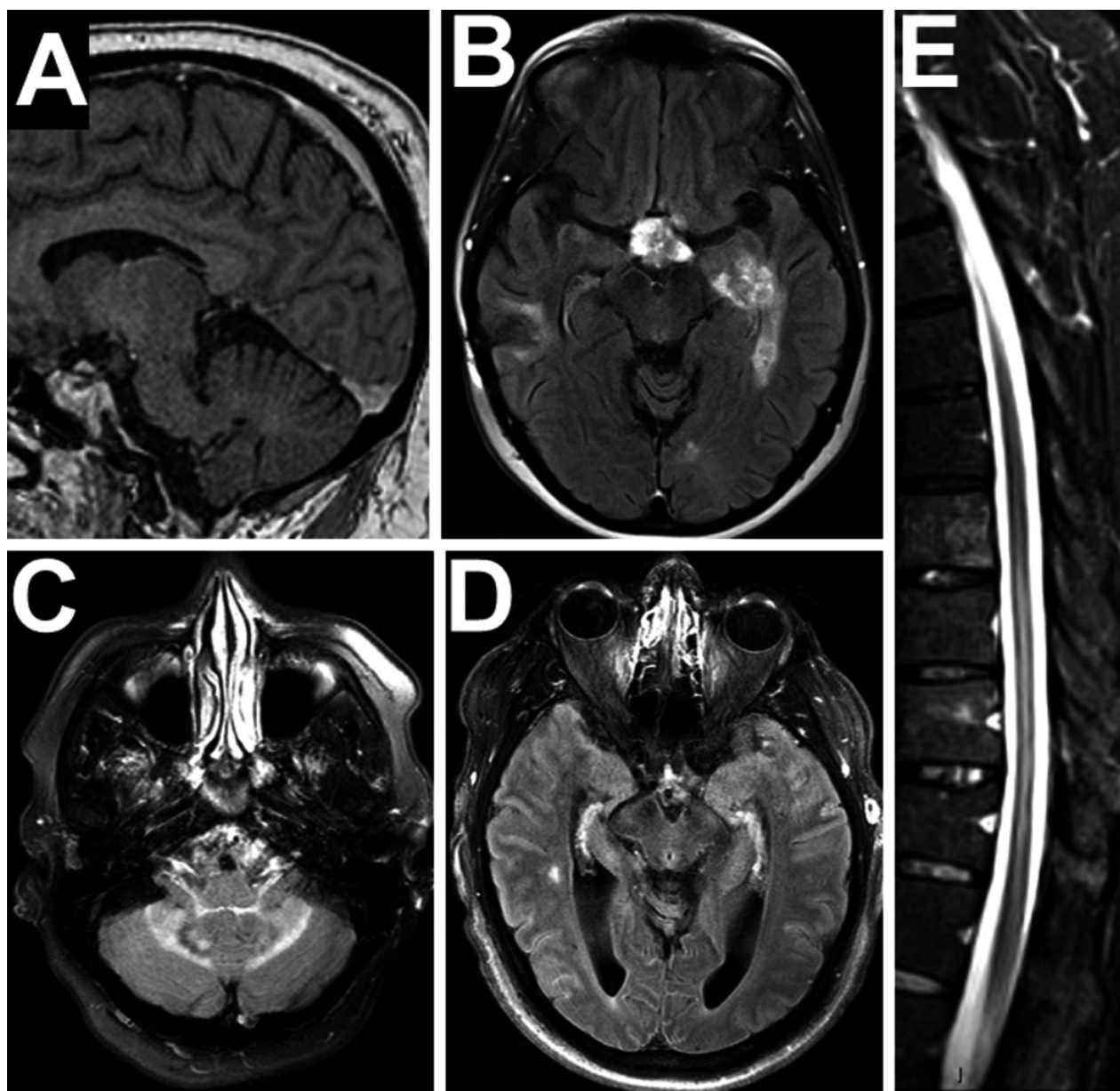


Figure 2. Examples of CNS parenchymal lesions in ECD. (A) Dural enhancing lesion on gadolinium-enhanced T1 image. (B) Gadolinium-enhanced FLAIR image revealing patchy enhancement within the left temporal lesion (right temporal resection is also seen) (C) Non-enhancing cerebellar and peduncular lesion (D) Subtle bilateral temporal FLAIR lesions with cerebral atrophy. (E) Longitudinal spinal lesion and cord atrophy on short tau inversion recovery (STIR) imaging.

Our results derive from a large observational cohort study on ECD and therapeutic decisions were made by referring physicians (ethical considerations preclude studying treatment-naïve ECD). This study design does not permit conclusions regarding therapeutic efficacy or disease mechanisms, and we cannot exclude the potential impact of treatment on our findings.

Our data suggest that neurologic disease is more prevalent than previously reported, likely a consequence of our

prospective study design. Also, in contrast to initial reports suggesting that intracranial ECD is posterior-fossa predominant, we found broad neurologic involvement throughout the brain, spinal cord, meninges, orbits, and pituitary. Extra-axial mass effects can cause significant neurologic morbidity in this population. Examples include tumor infiltration in orbital vault and musculature causing visual symptoms or carotid bulb lesions resulting in dysautonomia.

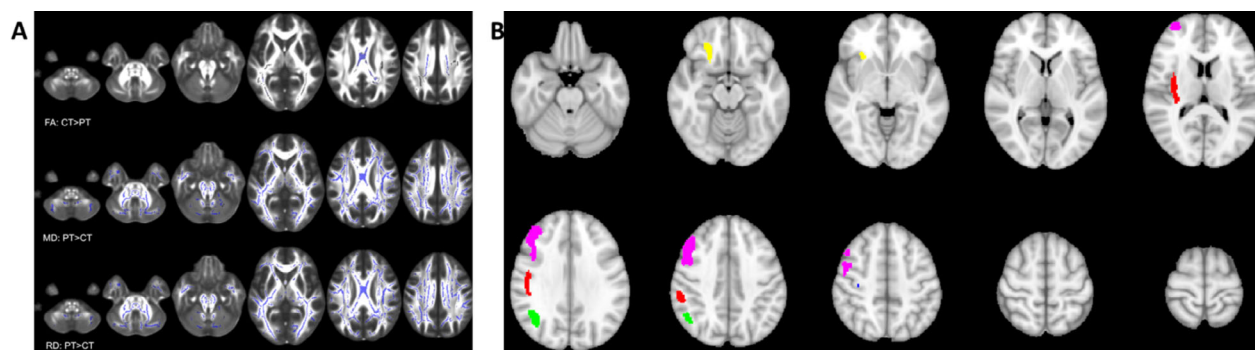


Figure 3. Quantitative MRI reveals demyelination and atrophy in ECD. (A) Purple demarcates white matter regions where fractional anisotropy (FA), mean diffusivity (MD), or radial diffusivity values were significantly different between patients (PT) and controls (CT) ($P < 0.05$). (B) Brain images were averaged for 15 ECD patients and 15 healthy controls, generating two image maps that were statistically compared on a voxel-by-voxel basis. Five clusters of gray matter volume loss were found in ECD patients compared to controls ($P < 0.05$) and are demarcated in various colors. These clusters are all located on the right hemisphere, within the middle frontal gyrus (1.356 mL/pink), insula and perirolandic cortex (0.699 mL/red), posterior-parietal cortex (0.411 mL/green), orbitofrontal cortex (0.254 mL/yellow), and perirolandic cortex (0.004 mL/blue).

We found cognitive impairment (and sometimes dementia) was common in ECD patients. Cognitive difficulty was assessed both clinically and by neuropsychologic testing, suggesting impairment in 50–60% of the cohort. Moreover, the *BRAF* V600E variant – which may be pathogenic and is an emerging risk factor for aggressive ECD^{2,18–20} – statistically correlates with poor cognitive outcomes. This concurs with 28% of the cohort exhibiting cerebral atrophy on MRI interpretation. Since the interpreting radiologist was not blinded and clinical judgment may confound the results, we also assessed brain volumes using a fully automated method to quantify regional brain volumes. The statistical approach used directly compares two cohorts (ECD vs. age-matched healthy controls) to each other but does not yield individual-level data or prevalence information. ECD brain volumes were smaller than age-matched healthy controls by 2.7 mL, and the volume loss was concentrated within the right frontal and parietal cortices. The regional selectivity and *BRAF* variant association data raise the hypothesis that impaired cognition might be pathophysiologically related to ECD. Proving this hypothesis would require identifying mechanisms underlying neurodegeneration in ECD, a subject for further investigation.

Electrophysiologic studies revealed neuropathies in half of our patients, which was purely axonal in nature. The lack of demyelination and rheumatologic comorbidity argues against an inflammatory etiology. Although direct perineural ECD tumor invasion is possible, complications of ECD² (e.g., hypothyroidism or pituitary abnormalities), treatment (e.g., glucocorticoid, immunosuppressant, or antineoplastic therapies), or diabetes (which, in some cases, may have been induced by corticosteroid therapy) likely contribute to the neuropathy. Nonetheless, it

behooves the practicing clinician to remain vigilant for possible comorbid neuropathy while treating ECD patients.

Neuro-ECD is frequently mistaken for diseases such as progressive multiple sclerosis, neurosarcoid, CNS vasculitis, IgG4 disease, or adrenoleukodystrophy. It typically affects middle-aged adults (rarely children) and has a progressive course. Transient improvement can sometimes be seen with glucocorticoids. ECD should be a consideration in patients who respond poorly to lymphocyte-directed immunotherapy (such as natalizumab, cyclophosphamide, rituximab, or ocrelizumab). Also, since the systemic manifestations of ECD may be asymptomatic or otherwise not readily apparent,³ a thorough search for extra-neurologic involvement (including recurrent evaluations over time) can facilitate diagnosis.

Radiologically, ECD lesions can mimic sarcoid, lymphoma, atypical multiple sclerosis, astrocytoma, and leukoencephalopathy. ECD lesions are multifocal, variably sized and demarcated, infrequently enhancing, and rarely cause significant mass effect or elicit surrounding edema. Dural, orbital, pituitary, or osteosclerotic lesions, when present, should be biopsied to facilitate the identification of ECD.

The brain pathology of ECD mimics inflammatory CNS disorders with the presence of lipid-laden macrophages, demyelination, and relative axonal preservation. Although histologic staining helps differentiate ECD from other histiocytic disorders,^{2,4} these markers are identical between ECD histiocytes and the reactive macrophages found in MS or sarcoid. Giant cells are not specific to ECD and can be a feature of sarcoid. Thus, routine clinical histologic analysis does not differentiate ECD from inflammatory disorders such as multiple sclerosis, sarcoid,

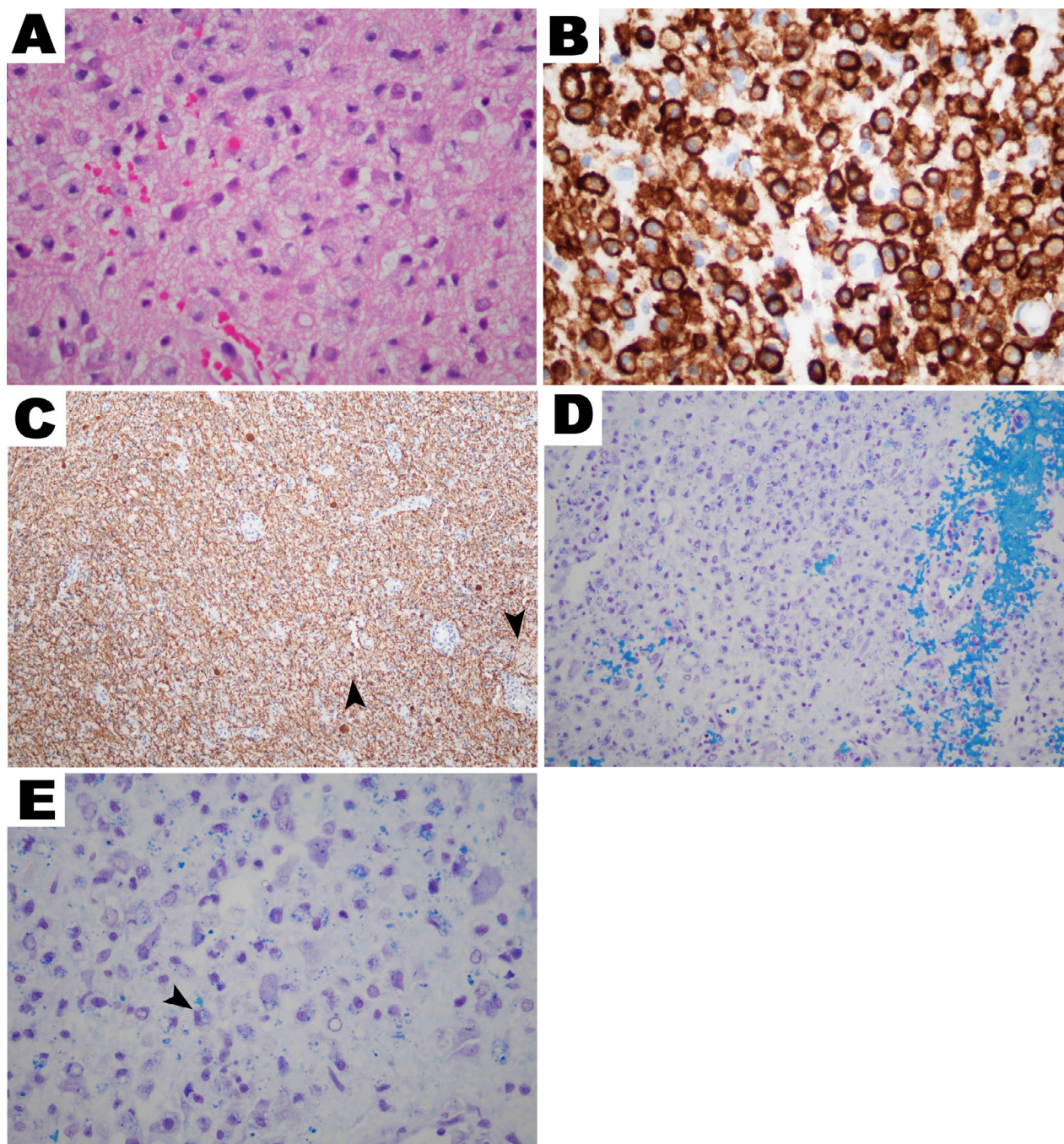


Figure 4. Histology of ECD brain lesions. Brain biopsy of an ECD lesions revealing (A) lipid-laden histiocytes on H&E stain. (B) CD163 + reactivity on histiocytes (brown). (C) Neurofilament staining (brown) demonstrating axonal neurodegeneration in the vicinity of cerebral ECD histiocytes (arrowhead is an example). (D) Area of demyelination surrounding histiocytes (myelin is stained blue). (E) ECD macrophage phagocytosing PAS + myelin fragments (arrowhead for examination).

vasculitis, or IgG4 disease. The assessment of clonality and identification of *BRAF* and MAP-kinase pathway variants have the potential to distinguish the neoplastic histiocytes in ECD from reactive macrophages in multiple sclerosis.^{3,30}

BRAF and MEK inhibitors are effective in treating systemic ECD, and investigations are underway to assess the efficacy of these agents in modulating CNS disease (see also clinicaltrials.gov).^{5,34} While vemurafenib is FDA approved for patients bearing the *BRAF V600E* variant,

cobimetinib may be effective in *BRAF*-negative patients who have other MAP kinase pathway variants.³⁵ Such studies promise a changing landscape in our understanding and treatment of ECD, and patients are best served at specialized referral centers. A list is maintained by the ECD Global Alliance at erdheim-chester.org.

In conclusion, neurologists play a critical role in identifying and monitoring ECD and other histiocytic disorders, because patients may present with neurologic symptoms, isolated neurologic disease occurs, and neurologic involvement portends a poorer prognosis.^{36–38} Furthermore, identification of ECD can spare patients morbidity associated with immunotherapies directed toward other diseases and ineffective therapies.^{39,40} Ultimately, it is important for neurologists to understand histiocytic diseases because the associated dysfunction might respond to appropriate treatment.^{26,41}

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Conflict of Interest

All authors report no conflicts of interest relevant to this work.

Author Contributions

LCB analyzed the data and wrote the manuscript; KOB, WG, JIEV, and RHD designed the study, analyzed the data and wrote the manuscript; NO, TL, BG, FHS, AN, and CT analyzed the data and wrote the manuscript; AM analyzed the data.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient Characteristics