ADULT-ONSET (INFRATENTORIAL) LEUKOENCEPHALOPATHY as PRESENTING MANIFESTATION of ERDHEIM-CHESTER DISEASE

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INTRODUCTION

- **Leukoencephalopathies** are diseases characterized by **degeneration of the white matter of the central nervous system** (CNS).

- Most leukoencephalopaties are hereditary diseases of childhood; however, they can also present in **adulthood**, with a **progressive, incurable course, resembling degenerative disorders** of the CNS.

- The **etiology** of adult-onset leukoencephalopaties remains **unknown** in about 30–50 % of cases.

AIMS AND METHODS

- In this study, we report the clinical and radiologic features of 9 adult patients with leukoencephalopaty primarily affecting the cerebellum and brainstem, or ‘infratentorial leukoencephalopathy’ (ITL), and eventually diagnosed with ECD.

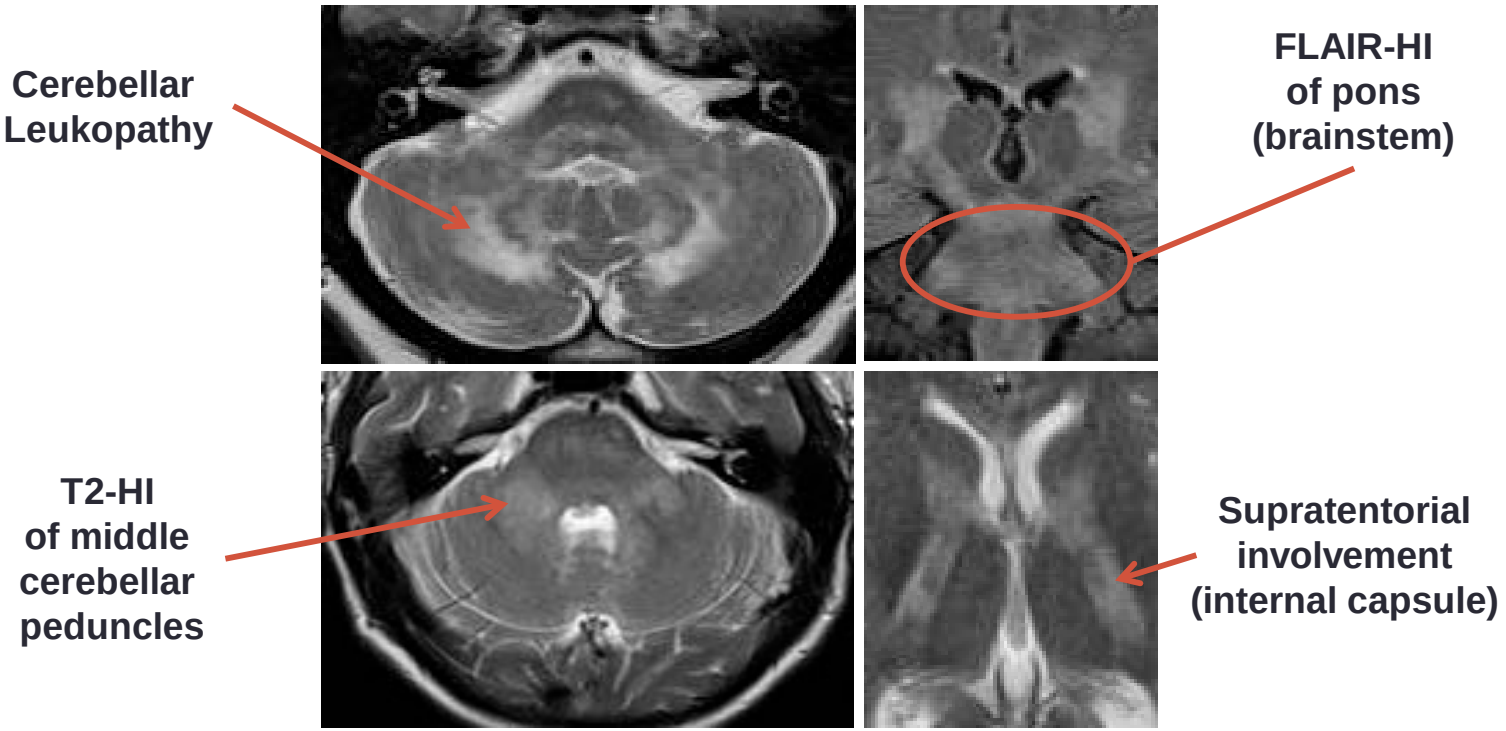
- All patients were initially followed up at a Neurologic Hospital, and were eventually diagnosed with ECD based on typical imaging findings at Tc99m bone scintigraphy and compatible histology.

REPRESENTATIVE CLINICAL CASE

Middle-aged adult male

Ataxia ± other neurological symptoms (spasticity, cranial nerve dysfunction, cognitive decline, neurogenic bladder, diabetes insipidus)

Gradual onset



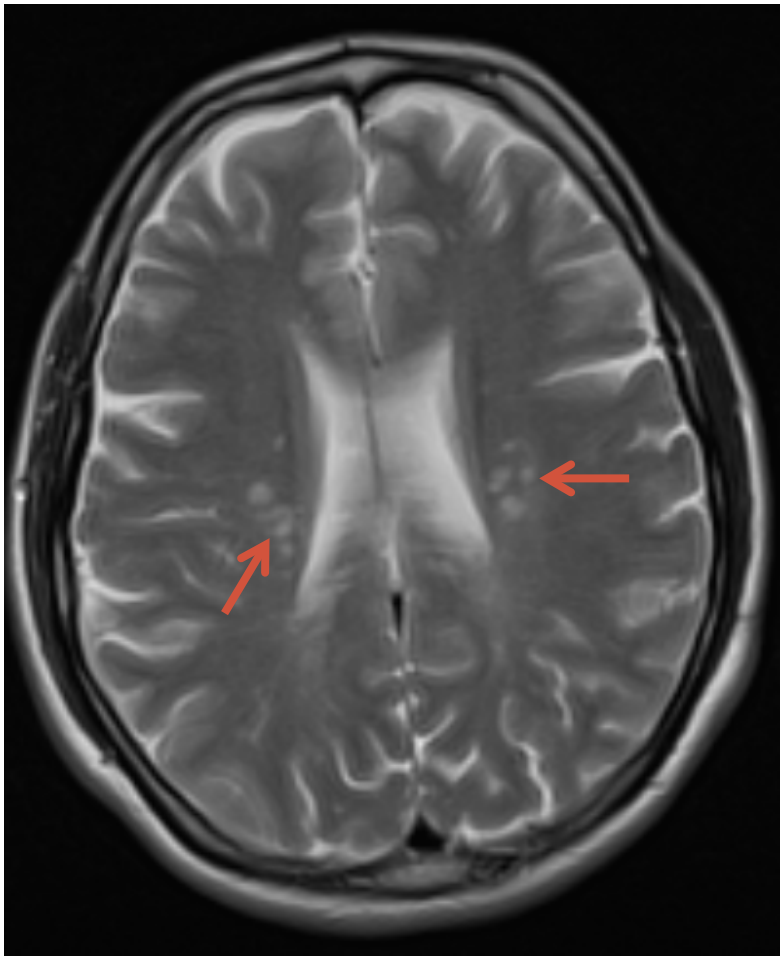
LEUKOENCEPHALOPATHY with
PROMINENT INFRATENTORIAL INVOLVEMENT

LEUKOENCEPHALOPATHIES with PROMINENT INFRATENTORIAL INVOLVEMENT: DIFFERENTIAL DIAGNOSIS

MULTIPLE SCLEROSIS
LBSL (Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation)
FXTAS
Cerebrotendineous xanthomatosis (CTX)
Adult autosomal-dominant leukodystrophy (*LMNB1*)
Alexander Disease
Mitochondrial defects
***CLCN2*-related leukodystrophy**

ISOLATED CASE
NO EVIDENCE OF AUTOIMMUNE or HEREDITARY DISEASES
UNREMARKABLE CSF EXAMINATION

HISTIOCYTOSIS ?



HISTIOCYTOSIS-RELATED WHITE MATTER CHANGES

HISTIOCYTOSES AND CNS

ABNORMALLY PROLIFERATING HISTIOCYTES

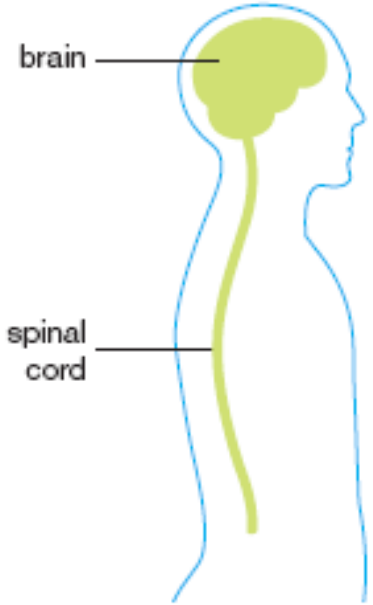
ECD ($CD68^+/CD1a^-$)

Langerhans ($CD68^+/CD1a^+$)

Mixed forms

INVASION

INTRACRANIAL MASS-FORMING LESIONS

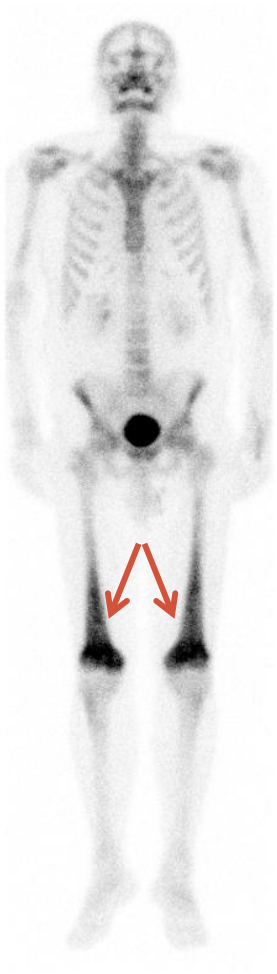


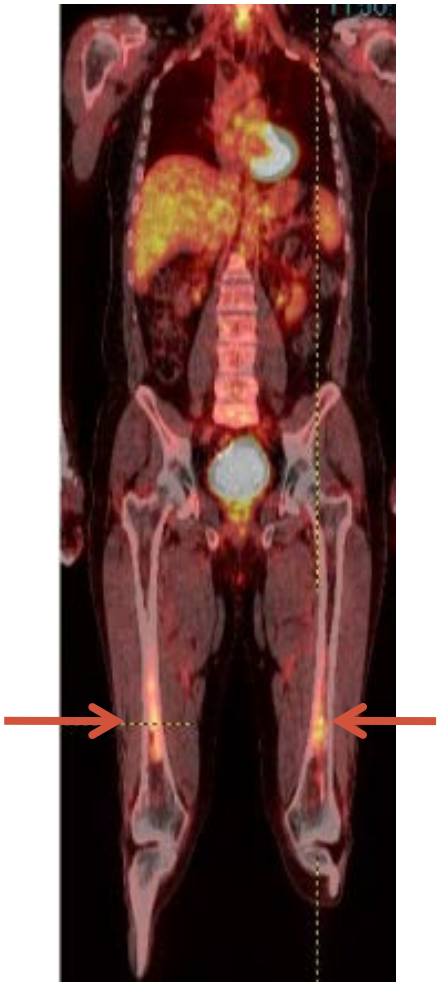
PARANEOPLASTIC

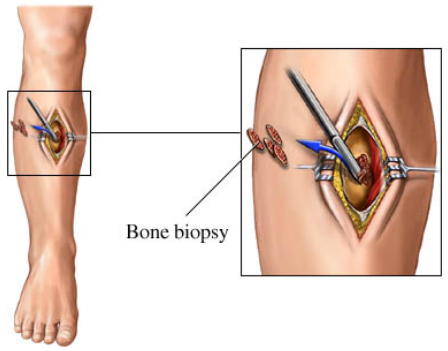
INFRATENTORIAL LEUKOENCEPHALOPATHY

INFRATENTORIAL LEUKOENCEPHALOPATHY RELATED TO HISTIOCYTOSIS: DIAGNOSIS

^{99m}Tc BONE SCAN	Total Body FDG-PET	BONE BIOPSY







Sex, age	Neurologic Manifestations	Systemic Manifestations	Biopsy	Brain MRI				Spine MRI
				Infratentorial Abnormalities (T2 HI)	Supratentorial Abnormalities (T2 HI)	Hypothalamic pituitary axis	Meninges	Spine and spinal cord
M, 70	Gait disturbances, Ataxia, Spasticity, DI	Retroperitoneal Pericardiall Aorta	Perinephric BRAF^{V600E}	Cerebellar peduncles (enhanced), Brainstem (enlarged pons)	No	Loss of T1-HI in neurohypophysis	Yes	No
F, 68	Gait disturbances, Ataxia, Spasticity, Neurogenic bladder, DI	No	Bone	Cerebellum (dentate nuclei), Cerebellar peduncles, Brainstem (pons and midbrain)	Internal capsules, Basal ganglia, Subcortical white matter	Loss of T1-HI in neurohypophysis	No	T2-HI in lateral columns (cervical)
M, 59	Gait disturbances Ataxia, Diplopia, Dysarthria, DI	Pulmonary	Bone	Cerebellum (dentate nuclei), Cerebellar peduncles, Brainstem (enlarged pons) T1-HI in dentate nucleus	T1-HI in caudate nuclei	Loss of T1-HI in neurohypophysis	No	T2-HI in lateral columns (thoracic and lumbar)
M, 50	Gait disturbances, Ataxia, Spasticity, Neurogenic bladder, DI	Fever Weight loss	Basicranium	Cerebellum (dentate nuclei, enhanced) Cerebellar peduncles	Internal capsules, Subcortical white matter, Corona radiata; T1-HI in internal capsules	T2-HI of infundibular stalk (enhanced)	No	T2-HI in lateral columns (cervical)
F, 54	Ataxia, Spasticity, Neurogenic bladder, DI	No	Dorsal vertebral pedicle	Cerebellum (dentate nuclei), Cerebelllar peduncles, Brainstem, Trigeminal nerves; T1-HI in dentate nuclei (enhanced)	Internal capsules, Subcortical white matter, Corona radiata; T1-HI in internal capsules (enhanced)	Loss of T1-HI in neurohypophysis	No	T2-HI in lateral columns (thoracic)
M, 52	Gait disturbances, Ataxia, Dysarthria, Dysphagia, Behavioral changes, DI	No	Bone BRAF^{V600E}	Cerebellum (dentate nuclei), Cerebellar peduncles Brainstem	Subcortical white matter	Loss of T1-HI in neurohypophysis	No	No
M, 44	Gait disturbances, Ataxia, Diplopia, Dysarthria, DI	No	Bone BRAF^{V600E}	Cerebellum (dentate nuclei), Cerebellar peduncles, Brainstem, Trigeminal nerves; T1-HI in dentate nuclei	Internal capsules Corona radiata; Optic chiasm (enlarged, enhanced)	Loss of T1-HI in neurohypophysis T2-HI of infundibular stalk (enhanced)	No	T2-HI in lateral columns (cervical, thoracic, lumbar)
M, 65	DI	No	Not performed	Cerebellum (deep white matter), Brainstem, Cerebellar peduncles, Trigeminal nerves	Optic chiasm (enlarged)	Loss of T1-HI in neurohypophysis T2-HI of infundibular stalk (enhanced)	No	No
F, 60	Gait disturbances, Ataxia, Neurogenic bladder, DI	Pericardial Aorta Exophthalmos	Orbit	Cerebellum, Brainstem, Cerebellar peduncles, Trigeminal nerves; T1-HI in dentate nuclei	Internal capsules, Subcortical white matter, Corona radiata; T1-HI in internal capsules (enhanced)	Loss of T1-HI in neurohypophysis	No	T2-HI in lateral columns (cervical)

CONCLUSIONS

- **ECD** emerges as a **cause of adult-onset ITL**, a finding with relevant diagnostic and therapeutic implications.
- Brain involvement causing **ITL may predate the clinical onset of systemic manifestations of ECD**.
- Investigations aimed at unveiling ECD are indicated in all patients with ITL, even in the absence of typical ECD manifestations.
- **Diagnosing ECD enables therapeutic strategies** in patients with adult-onset leukoencephalopathy, an otherwise untreatable, chronically degenerative condition.

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