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

Ettore Salsano
Luisa Chiapparini
Mario Savoiardo
IRCCS CARLO BESTA NEUROLOGIC HOSPITAL

Lorenzo Dagna
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