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CORRESPONDENCE

Rasmussen's encephalitis: a histological perspective in a 1-year-old child

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Dear Editor

As we work in a paediatric institution that also deals with epilepsy surgery, we read the article by Doherty et al. entitled "MRI and pathology comparisons in Rasmussen's encephalitis: a multi-institutional examination of hemispherotomy outcomes relative to imaging and histological severity" with great interest.

Doherty et al. discuss Rasmussen's encephalitis (RE) in detail, with particular reference to the role of radiology and pathological staging in predicting seizure outcome after epilepsy surgery, but without finding statistically significant correlations [1].

RE is a rare chronic inflammatory neurological disorder that predominantly affects children. It manifests as progressive neurological deterioration, focal seizures and hemiparesis. Histologically, RE is characterised by several distinctive features [5]. The most prominent feature is usually the presence of perivascular lymphocytic infiltrates. These infiltrates consist mainly of T-cells (CD3 +). The inflammatory cells are typically found around blood vessels in both grey and white matter, indicating widespread inflammation. Another significant histological finding in RE is neuronal loss in the affected regions, particularly in the cortex, accompanied by gliosis, a reactive process involving the proliferation of glial cells in response to injury. Gliosis contributes to the structural changes in the brain, exacerbating the functional decline. Additionally, microglial nodules, small clusters of activated microglia, are frequently observed. These nodules are indicative of an ongoing immune response and are often found in conjunction with the lymphocytic infiltrates. Microglial activation plays a critical role in the disease's progression by perpetuating inflammation and neuronal damage. Astrocytic changes are also seen in RE. Reactive astrocytes, characterised by enlarged cell bodies and prominent processes, proliferate in response to neuronal injury. This astrogliosis further disrupts neural networks, contributing to the neurodegenerative process and, clinically, to seizures.

And it is precisely from a histological point of view that we would like to comment on the above-mentioned article, as after several years of experience in the histopathology of epilepsies, we believe that the microscopic aspects are not as rigid as the staging system of Pardo et al. adopted by Doherty et al. would like to imply [3]. Pardo et al.'s histopathological staging system, an implementation of Robitaille's [4], includes five stages (0 to 4). Each of these stages takes into account the state of the cerebral cortex (whether it is inflamed and/or gliotic), neuronal loss, astrogliosis, microglial activation and inflammatory T-cell infiltration.

However, although this staging system is valid, it is rather rigid because it requires that the histological parameters at each stage always have a fixed ratio between them, which in our experience is not always the case. To simplify Pardo et al.'s staging as much as possible (without diminishing it), it is as if he were telling us that: no change in the cortex always corresponds to no change in the other parameters (stage 0) or that mild/focal inflammation and gliosis of the cortex always correspond to minimal changes in the other parameters (stage 1) and so on.

The histopathological reality of REs seems to us to be less categorisable, and to support our argument, we present the histological case of a 1-year-old child who underwent neurosurgery for drug-resistant epilepsy.

Microscopy revealed the following histopathological features characteristic of RE: cortical panlaminar degeneration, moderate/severe multifocal (non-panlaminar)

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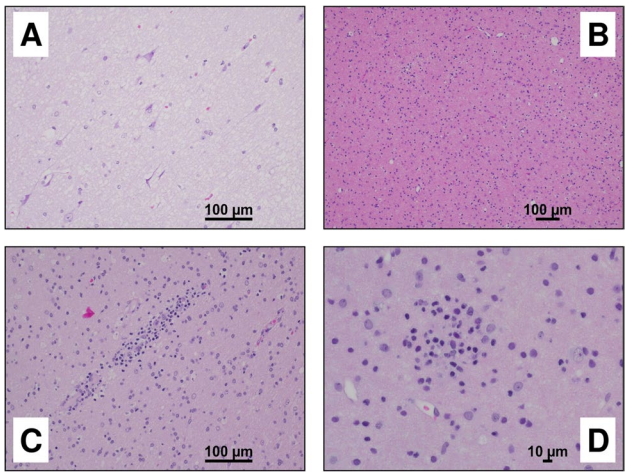

Fig. 1 Photomicrograph showing features of Rasmussen's encephalitis: **A** marked neuronal loss (EE, × 20); **B** mild astrogliosis (EE, × 10); **C** perivascular lymphocyte capsules (EE, × 20), later shown by immunohistochemistry to be CD3 + ; **D** microglial nodule (EE, × 40)

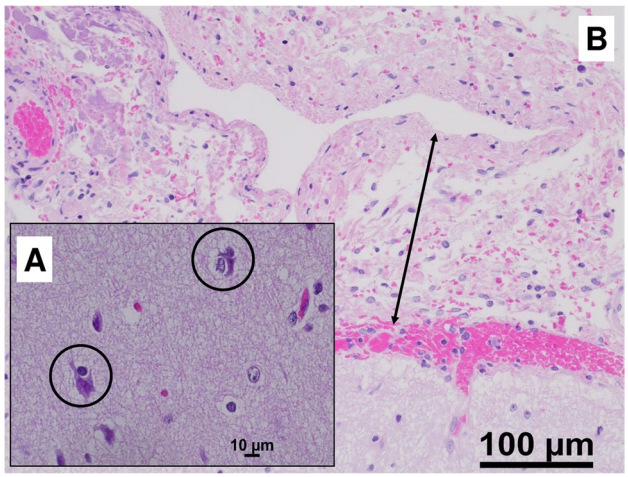

Fig. 2 Photomicrograph showing two other aspects: **A** the presence of neuronophagia (circles, EE, × 40); **B** a leptomeningeal thickening that was multifocal in the material examined, without a relevant inflammatory infiltrate (EE, × 20)

neuronal loss, mild/moderate and focal astrogliosis, mild and focal microglial activation and mild T-cell lymphocytic infiltrate (CD3 +) with the presence of perivascular cuffs (Fig. 1). In addition, foci of neuronophagia and diffuse leptomeningeal thickening were observed (Fig. 2).

The case described seems to be clearly unclassifiable according to Pardo et al.'s classification criteria:

- The condition of the cortex with panlaminar degeneration would fit with Pardo et al.'s stage 3.
- Moderate/severe multifocal (non-panlaminar) neuronal loss would fit with stage 2.
- Mild/moderate and focal astrogliosis would fit with stage 1.
- Mild and focal microglial activation would fit with stage 1 or stage 3 or stage 4.
- Mild T-cell lymphocytic infiltrate would fit with stage 1 or 3, but the presence of perivascular cuffs would only fit with stage 1.
- Neuronophagia would fit with stage 1.
- Leptomeningeal thickening would not be consistent with any stage (histological parameter not included in Pardo et al.'s staging).

The question then arises: what if the multi-institutional cohort analysed by Doherty were examined in relation to the single histological lesions found, rather than in relation to Pardo et al.'s staging, which groups such lesions together in a rather rigid and obligatory manner?

We are aware that a better understanding of REs will come from the ever-expanding molecular knowledge of the role of T lymphocytes and more generally of the inflammatory microenvironment in such pathology [2, 5], but we are equally hopeful that the "old" microscopic examination may still hold some positive "surprises," not only in the diagnostic understanding of the disease but also in the identification of individual cyto-/histological parameters of prognostic and/or predictive significance.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Declaration of animal and human protection The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

Informed consent Obtained.

Competing interest The authors declare no competing interests.

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