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Mild Encephalitis/Encephalopathy with reversible splenial lesion syndrome: an unusual presentation of anti-GFAP astrocytopathy

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Introduction

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a rare recently-defined antibody-mediated meningo-encephalomyelitis[1]. It usually begins with viral prodrom followed by headaches, meningeal syndrome, alteration of consciousness and neurologic deficit that may include cerebellar and dysautonomia signs. Hyponatremia can be found in half of the adult cases reported in Japan. CSF usually shows lymphocytic pleiocytosis [2] and brain MRI classically demonstrates in 50% of cases, a linear perivascular enhancement extending radially from the ventricles. Clinical outcome is good in most of the cases after immunotherapies and relapses occur in 21% of adult patients[3].

Herein, we present 2 cases of pediatric auto-immune GFAP astrocytopathy and one of them with an unusual MRI characteristic suggestive of Mild Encephalitis/Encephalopathy with reversible splenial lesion syndrome (MERS).

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Case 1

A previously healthy 16 year-old girl was hospitalized after five days of headaches and fever. Initial clinical evaluation revealed lymphocytic meningo-encephalitis (CSF: 700 cells/mm^3, 1.43 g/L proteins). Four days later, a cerebellar syndrome with a nystagmus, dizziness, gait difficulties appeared with dysautonomia and bladder dysfunction. Brain and spinal MRI were normal as well as the thoraco-abdomino-pelvic CT-scan. Infectious investigations (serology and PCR methods) were negative (HSV 1 and 2, CMV, HHV6, EBV, bacterial culture) in sera and CSF. Anti-NMDAR, AMPAR, Lgi1, caspr2 and DPPX autoantibodies were investigated on transfected cells (EuroImmun, Germany) and anti-Hu, Yo, Ri, CV2, amphiphysin, Ma2 and Sox1 autoantibodies were researched on immunodot (PNS9DIV-24, Ravo, Diagnostika GmbH, Germany) in sera and CSF of our patient and were all negative. Anti GFAP pattern was detected on primate cerebellum slices (Inova) and rat hippocampal slices (EuroImmun) in Toulouse immunology laboratory and send for target confirmation to the French reference center of paraneoplastic neurologic syndromes (Pr. Honnorat, Lyon, tested on transfected cells). Auto-antibodies against GFAP were present in serum and CSF. Intravenous steroids, 8 days after the initial hospitalization, allowed a prompt clinical improvement after only 2 days. The patient was able to go back home after 8 days of oral corticotherapy with a progressive decrease. At 3 months, we noted the persistance of cephalalgia, moderate attention disorders and intense asthenia. An oral corticotherapy at 1 mg/kg with progressive decrease over 2 months was conducted, allowing a significant clinical improvement. After a six-month follow-up, complete recovery was observed, cerebral MRI was normal and no neoplasia was highlighted. Anti-GFAP antibodies were still positive after 1 year in sera and CSF.

Case 2

A previously healthy 10 year-old boy, had been vomiting and had headaches with fever for two days. Initial clinical evaluation revealed lymphocytic meningo-encephalitis (CSF: 380 cells/mm^3, 1.33 g/L proteins, oligo-clonal bands negative). Progressively, alteration of consciousness, dysmetria, nystagmus and gait difficulties appeared and a first MRI demonstrated a hypersignal abnormality on T2 and diffusion sequences with increased ADC, suggestive of Mild Encephalitis/Encephalopathy with reversible splenial lesion syndrome (Figure 1. A, B). The EEG electric patterns were in favor of encephalitis. A week later, extra pyramidal syndrome associating dystonic features, abnormal eye movements, bucco-lingual dyskinesia occurred and a new cerebro-spinal MRI showed a complete normalization of the observed lesion while the patient was still symptomatic and no treatment had been started yet (Figure 1. C,D). No infectious agents were found by PCR in CSF (PCR HSV 1 and 2, VZV, enterovirus, CMV, EBV, HHV-6, bacterial culture). In blood all the serological tests were negative (Lyme, mycoplasme, Chlamydia pneumonia) as well as the inflammatory work-up (CRP, ESR) and Quantiferon. The blood ionogram showed hyponatremia at 124 mmol/L which needed sodium supplementation and fluid restriction. All the metabolic screenings and cerebral-thoracic-abdominal-pelvic CT-scan were normal. CSF auto-antibodies panels namely anti-NMDA, CASPR2, Lgi1, AMPAR, GABA were researched on transfected cells (Euroimmun, Germany). Anti-onco-neuronaux were investigated on primate cerebellum slides (Inova, USA) as well as immunodot (Ravo, Diagnostika GmbH, Germany). All antibodies were found negative, except the anti-GFAP antibodies which turned positive in CSF.The GFAP antibodies had been tested in the French reference center of paraneoplastic neurologic syndromes (Pr. Honnorat, Lyon, tested on transfected cells). The child was successfully improved with Ig IV infusion (1g/kg/J) for 2 days. After a 12-month follow-up, he was completely all right.

Discussion:

Anti-GFAP astrocytopathy is a rare condition in adults and children and specific MRI lesions have been suggested[4]. Herein, we describe two distinct pediatric anti-GFAP astrocytopathies, one with normal brain and spinal MRI while the other had MRI characteristics suggestive of MERS.

Clinical phenotypes of both our patients were concordant with anti-GFAP positive astrocytopathy. Brain and spinal MRI of the first patient was normal. In a previous adult and pediatric study, 50% (5/10) of the children had a normal MRI [2] while only 16 % of the adults (7/38 available MRI of 107 adult patients) were unremarkable[3], which may suggest that in children normal MRI might be a frequent finding.

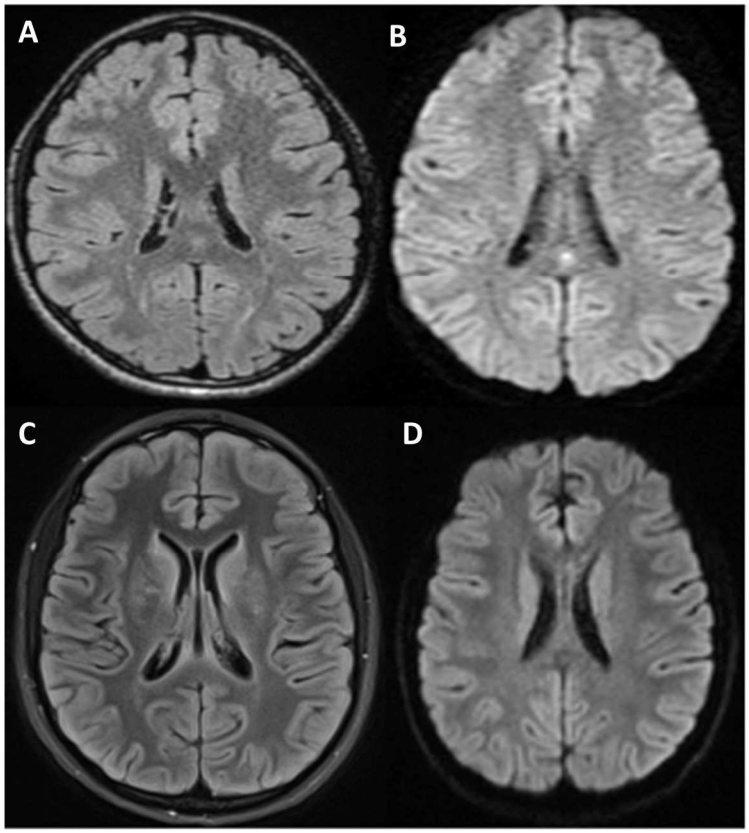
In our second patient, MRI lesions and their evolution were unusual. Focal lesions in the corpus callosum had already been described but in L.M. Theroux case report[4], lesions persisted during the evolution while in our case they disappeared even though the patient was still symptomatic. Initial diagnosis for this child, following clinical description and the MRI lesion was Mild Encephalitis/Encephalopathy MERS which is most frequently a post infectious disease. Indeed, the patient had prodromal symptoms of viral infection, meningo-encephalomyelitis and hyponatremia which was reported in 31% of patients [5]. In our case, the MRI normalized in 3 weeks as expected although the patient was still symptomatic but clinical resolution of MERS can take up to one month in some series with or without treatment. While most of these presentations are post infectious, the etiology of 40% of MERS patients remain unknown and no association with auto-antibodies has been described to our knowledge yet. The association of clinical symptoms (dystonia, bucco-lingual dyskinesia…) of neuro-autoimmune disease prompted us to look for NMDAR antibodies and related diseases and we only found anti-GFAP antibodies. As in MERS, most anti-GFAP astrocytopathies are post infectious diseases and in 25% of cases a paraneoplasic condition, which was negative in both of our patients.

The pathogenicity of these antibodies is far from being demonstrated. The uniformity of clinical presentations at the beginning and the good and rapid evolution under corticosteroid therapy could suggest a pathogenicity of the antibodies[1]. However, with the significant increase of case reports and a more global investigation of anti-GFAP antibodies, many variety of clinical presentation have been described [6,7], as well as cases associated with other antibodies or even regressing spontaneously[3,7,8]. This may suggest that for all or some of these patients, these antibodies are "reactive" of other autoimmune process allowing the access to this intracellular antigen.

Our two cases illustrate that anti-GFAP antibodies should be sought in children presenting meningo-encephalitis with a normal and/or MERS suggestive MRI, as treatment strategies may differ.

1. Fang B., McKeon A., Hinson SR., Kryzer TJ., Pittock SJ., Aksamit AJ., et al. Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy: A Novel Meningoencephalomyelitis. *JAMA Neurology* 2016;**73**(11):1297. Doi: 10.1001/jamaneurol.2016.2549.
2. Dubey D., Hinson SR., Jolliffe EA., Zekeridou A., Flanagan EP., Pittock SJ., et al. Autoimmune GFAP astrocytopathy: Prospective evaluation of 90 patients in 1 year. *Journal of Neuroimmunology* 2018;**321**:157–63. Doi: 10.1016/j.jneuroim.2018.04.016.

3. Flanagan EP., Hinson SR., Lennon VA., Fang B., Aksamit AJ., Morris PP., et al. Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: Analysis of 102 patients: Autoimmune GFAP Astrocytopathy. *Annals of Neurology* 2017;**81**(2):298–309. Doi: 10.1002/ana.24881.
4. Theroux LM., Goodkin HP., Heinan KC., Quigg M., Brenton JN. Extreme delta brush and distinctive imaging in a pediatric patient with autoimmune GFAP astrocytopathy. *Multiple Sclerosis and Related Disorders* 2018;**26**:121–3. Doi: 10.1016/j.msard.2018.09.015.
5. Tada H., Takanashi J., Barkovich AJ., Oba H., Maeda M., Tsukahara H., et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. *Neurology* 2004;**63**(10):1854–8.
6. Shan F., Long Y., Qiu W. Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy: A Review of the Literature. *Front Immunol* 2018;**9**:2802. Doi: 10.3389/fimmu.2018.02802.
7. Kimura A., Takekoshi A., Yoshikura N., Hayashi Y., Shimohata T. Clinical characteristics of autoimmune GFAP astrocytopathy. *J Neuroimmunol* 2019;**332**:91–8. Doi: 10.1016/j.jneuroim.2019.04.004.
8. Francisco C., Meddles K., Waubant E. Pediatric glial fibrillary acidic protein meningoencephalomyelitis: A case report and review of the literature. *Mult Scler Relat Disord* 2019;**29**:148–52. Doi: 10.1016/j.msard.2018.12.008.



MRI at onset : (A) Axial Flair image showing a splenial corpus callosum lesion visible also in diffusion sequence (B).

MRI two weeks after the onset : Same sequence in axial Flair (C) and diffusion sequence (D) showing a complete normalisation of the MRI while the child was still symptomatic.