GFAPα IgG-associated encephalitis upon daclizumab treatment of MS

Felix Luessi, MD,* Sinah Engel,* Annette Spreer, MD, Stefan Bittner, MD, and Frauke Zipp, MD

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Abstract

Objective
To describe a case of glial fibrillary acidic protein (GFAP)α immunoglobulin G (IgG)-associated encephalitis in a patient referred to us with MS on daclizumab treatment and to summarize characteristics of 5 additional recent German MS cases of serious encephalitis along with a previously published American case of CNS vasculitis associated with daclizumab.

Methods
Evaluation of cause, clinical symptoms, and treatment response.

Results
The 6 patients included 4 women and 2 men. The median age at onset was 38 years (range 32–51 years). Clinical presentation was marked by progressing neuropsychologic and/or neurologic deficits. Additional drug rash with eosinophilia was seen in 3 patients, whereas 2 patients showed a highly active demyelinating process. Examination of CSF samples detected pleocytosis, elevated total protein levels, and GFAPα IgG antibodies, which were not found in serum. In our case, we discovered autoimmune GFAP astrocytopathy associated with encephalitis as secondary autoimmunity, which was steroid responsive. Clinical outcome of other cases was marked by partial recovery in 4 patients and persistent foster care in 1 patient.

Conclusions
Our case of GFAPα IgG-associated encephalitis along with 12 other cases of serious inflammatory brain disorders following daclizumab treatment so far indicates that interfering with NK cells and Tregs by anti-CD25 antibody therapy can result in severe secondary CNS autoimmunity in man.
The antibody daclizumab (Zinbryta; Biogen, Cambridge, MA) inhibits the interleukin 2 (IL-2) signaling pathway by blocking the IL-2 receptor α (CD25). In clinical trials, daclizumab had proven to be an effective therapy for patients with relapsing-remitting MS (RRMS). However, recently, the use of daclizumab in MS was overshadowed by safety concerns associated with secondary autoimmunity. We here report the occurrence of steroid-responsive glial fibrillary acidic protein (GFAP)-mediated encephalitis in a patient with MS receiving daclizumab together with a series of other severe autoimmune CNS adverse events.

Case report

We describe a 32-year-old Caucasian man with the first onset of RRMS in 2013 presenting with sensory spinal syndrome below thoracic vertebra (Th) 7. MRI scans showed disseminated cerebral and spinal lesions including 2 asymptomatic contrast-enhancing left parietal lesions. Analysis of CSF showed pleocytosis with 14 white blood cells (WBCs)/μL (100% mononuclear cells) and the presence of oligoclonal bands. Differential diagnoses were tested for and thus ruled out. The diagnosis of RRMS was therefore made according to McDonald Criteria 2010. Treatment with interferon β-1a (Avonex; Biogen, Cambridge, MA) was initiated. Because of clinical and paraclinical disease activity, therapy was escalated to dimethyl fumarate (Tecfidera; Biogen, Cambridge, MA) in September 2016 (figure 1A). Because of gastrointestinal side effects under dimethyl fumarate, daclizumab therapy was started in December 2016. The recommended blood examinations were uneventful.

In August 2017, the patient demonstrated aggressive behavior and occasionally expressed suicidal thoughts. Because of fluctuating dysarthria, progressive memory loss, fatigue, and depression, the patient was admitted to our hospital in December 2017. On initial examination, the patient was afebrile and demonstrated perceptive impairment, confusion, incoherent thoughts, and delusions. Neurologic examination revealed ataxia and nystagmus. His blood tests and differential blood count were normal. Lymphocyte subset analysis revealed values within the range of untreated patients with RRMS. The MRI scan showed a new juxtacortical right frontal lesion and a new focal gliosis at Th 3/4 (figure 1B), both without contrast enhancement. Electrocorticography showed moderately severe encephalopathy with generalized theta activity. A lumbar puncture revealed 74 WBC/μL (100% mononuclear cells), a CSF protein level of 61.5 mg/dL, and a CSF lactate level of 2.7 mmol/L. Oligoclonal bands and intrathecal immunoglobulin A (IgA) synthesis were present (figure 2A). Diagnostic tests (detailed in Supplement, links.lww.com/NXI/A60) did not disclose any infectious agent. Immunostaining of rat hippocampal tissue exhibited GFAP immunoglobulin G (IgG) antibodies in CSF (figure 2B, diagnostic laboratory of Euroimmun AG; Lübeck, Germany). GFAP antibodies could not be detected in serum (figure 2C). Antigen specificity was further confirmed by GFAPα-transfected HEK293 cell-based assay. Patient GFAP-IgGs reacted with GFAPα isoform (figure 2D), whereas no reaction was observed on control-transfected cells (figure 2E).

Magnetic resonance (MR) angiography did not show vascular abnormalities, but it demonstrated a slight brain edema as volume increase in comparison to pre-MRI from 2016 (figure 1B). An additional 18F-Fluorodeoxyglucose (FDG)-PET scan revealed no evidence of tumors. Chest CT findings were normal.

With a diagnosis of autoimmune GFAPα astrocytopathy, we started treatment with 1,000 mg methylprednisolone/d, followed by 5 courses of plasma exchange every other day. The patient gradually improved while methylprednisolone was continued with 100 mg/d orally and tapered over time. Neuropsychologic examination thereafter demonstrated ongoing impairment in all cognitive domains including attention span, attention selectivity, information processing, short-term memory, verbal and figural long-term memory, and executive functions. However, there were no incoherent thoughts or noticeable behavioral disturbances, no signs of depression, and no ataxia.

Despite the clinical improvement, the follow-up MRI in March 2018 showed, apart from a reduction in swelling, progressive non–contrast-enhancing white matter lesions with a prominent radial pattern, which resembles a previously published patient with GFAP meningoencephalitis. Follow-up CSF analysis revealed 39 WBC/μL, persistent intrathecal synthesis of IgA, but normal CSF protein and lactate levels.

In the context of MRI results and persistent CSF pleocytosis under continuous steroid therapy, treatment with rituximab (MabThera; Roche, Basel, BS) was added. This led to a stabilization of the clinical status. Although neuropsychologic testing in general still showed significant deficits, the performance in some cognitive domains had improved. Currently,

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**Glossary**

- **EMA** = European Medicines Agency
- **FDG** = 18F-Fluorodeoxyglucose
- **FLAIR** = fluid attenuation inversion recovery
- **GFAP** = glial fibrillary acidic protein
- **IgA** = immunoglobulin A
- **IgG** = immunoglobulin G
- **IL-2** = interleukin 2
- **NK** = natural killer
- **NMO** = neuromyelitis optica
- **MR** = magnetic resonance
- **RRMS** = relapsing-remitting MS
- **Th** = thoracic vertebra
- **WBC** = white blood cell

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2 Neurology Neuroimmunology & Neuroinflammation | Volume 5, Number 5 | September 2018

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the patient is capable of participating in daily life activities again. Anonymized data will be shared on request from any qualified investigator.

**Discussion**

This report of a patient with encephalitis extends the spectrum of secondary autoimmune complications of daclizumab treatment by GFAP autoimmunity.\(^3\) GFAP-IgG autoantibodies are rarely found in CSF in healthy controls or patients with other diseases. A recent study using GFAP\(\alpha\) isoform–transfected cells reported GFAP antibodies in 0 of 20 CSF specimens of MS patients.\(^3\) When detected in CSF, GFAP-IgG autoantibodies have been identified as a biomarker for a distinct spectrum of immunotherapy-responsive autoimmune CNS disorders.\(^5\) Anti–GFAP-IgG may occur alone or in the setting of other diagnoses, for example, anti-NMDA-receptor encephalitis or CNS vasculitis. Because one-third of cases with GFAP-IgG are paraneoplastic, neoplasia was ruled out in our case by FDG-PET. Because MS is ultimately a diagnosis of exclusion, there is a slight possibility that the primary pathology in this patient was a neuroinflammatory disorder other than MS. However, taking into account the relapsing-remitting disease course, the appearance of lesions typical in MS, the CSF findings in 2012, and the absence of anti-GFAP autoantibodies in MS CSF,\(^3\) it is most likely that the induction of GFAP autoimmunity is causally linked to daclizumab treatment. A limitation of our report is the lack of GFAP antibody investigation before deterioration on daclizumab treatment.
Meanwhile, the European Medicines Agency (EMA) has received notifications of 12 other patients having severe encephalopathy syndromes following daclizumab therapy, 4 of those with fatal outcome. Among 5 German cases, 3 were suspected of drug rash with eosinophilia and systemic symptoms syndrome with CNS manifestation and 2 with highly active demyelinating process (data retrieved from Paul Ehrlich Institute, Federal Institute for Vaccines and Biomedicines, Germany). One American patient had CNS vasculitis (table).

Underlying mechanisms like inhibition of Tregs without concomitant expansion of immunoregulatory CD56<sup>bright</sup> natural killer (NK) cells or general immune suppression by depletion of activated effector CD25<sup>+</sup> T cells on daclizumab can currently merely be speculated. Autoimmune encephalitis in our patient may have been induced by GFAP-IgG in combination with enhancement of NK cells on daclizumab therapy, eventually resulting in antibody-dependent cellular cytotoxicity. Such a mechanism has previously been described for neuromyelitis optica (NMO) lesions.

Cases of suspected secondary autoimmunity under daclizumab treatment have been previously reported including 2 deaths of study patients. In both cases (autoimmune hepatitis and psoas abscess), daclizumab treatment could not be excluded as a contributing factor. In 2017, the indication of the drug had to be restricted because of another death by liver injury that was most likely caused by autoimmune hepatitis. Moreover, the rare occurrence of autoimmune hemolytic anemia under daclizumab treatment has been reported in an extension study. After the recent EMA decision to urgently review daclizumab, in March 2018, marketing authorizations of daclizumab were withdrawn following twelve cases of serious inflammatory brain disorders, 4 of them with fatal outcome. In the 13th patient, who was referred to us, we discovered anti-GFAP encephalitis, which was steroid responsive.

It has to be assumed that in man, disturbing the NK cell/Treg balance appears to be detrimental, even if the upregulated NK cells are considered as regulatory.

**Author contributions**
F. Luessi and S. Engel: study concept and design, acquisition of data, and analysis and interpretation. A. Spreer: analysis and interpretation and critical revision of the manuscript for important intellectual content. S. Bittner and F. Zipp: critical revision of the manuscript for important intellectual content.

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| Sex/Age at onset (y) | Diagnosis                                                                 | Presenting symptoms                                                                 | MRI findings                                                                                                           | CSF                                                                                  | Histologic findings                                                                 | Therapy                                                                                       | Outcome                        |
|----------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------|
| 1 M/51/ Germany      | Highly active MS disease and ADEM                                         | Severe dysphagia, dysarthria, increased fatigue, paresis of the right leg, and vigilance reduction | Multiple (>50) contrast-enhancing lesions with perifocal edema, significant increase in lesion load with development of central necrotization in follow-up MRI | Pleocytosis and elevated total protein levels                                             | No information available.                                                                | High-dose steroid therapy and immune absorption                                          | Recovered with sequelae          |
| 2 F/43/ Germany      | Suspicion of DRESS syndrome with CNS manifestation                        | Fever, skin eruption, and MS exacerbation with tetraparesis                         | Prominent lesion progression                                                                                       | Pleocytosis                                                                              | Inflammatory demyelinating CNS process and eosinophilic infiltration                    | High-dose steroid therapy, plasmapheresis, cyclophosphamide, and rituximab                 | Severe disability resulting in foster care         |
| 3 F/30/ Germany      | Inflammatory demyelinating CNS process, NMDA receptor–associated encephalitis and DRESS syndrome with CNS manifestation | Severe MS relapse, fever, rash, facial edema, paresthesia, severe hair loss, memory disturbance, personality change, and tonic-clonic seizure | Distinct progression in the size of preexisting MS lesions and multiple, partially contrast-enhancing, new lesions | Positive presence of NMDA receptor antibodies                                             | Inflammatory demyelinating CNS process, signs of cerebral vasculitis, and eosinophilic infiltration | High-dose steroid therapy and plasmapheresis                                          | Partial recovery                 |
| 4 F/33/ Germany      | Suspicion of DRESS syndrome with CNS manifestation                        | MS relapses, fatigue, cough, fever, joint pain, muscle tension, nuchal pain, holocerebral headache, and nausea | Disseminated contrast-enhancing lesions with perifocal edema. Signs of cerebellar swelling.                         | Pleocytosis and elevated total protein and elevated lactate levels                         | Inflammatory demyelinating CNS process, signs of cerebral vasculitis, lymphoplasmacellular meningoencephalitis, and eosinophilic infiltration | High-dose steroid therapy, plasmapheresis, and craniectomy (because of cerebellar swelling) | Tetrasyndrome and partial recovery |
| 5 F/38/ Germany      | Inflammatory demyelinating CNS process                                    | Fever, facial edema, epileptic seizures, fulminant MS relapse with progressive paraparesis, and vigilance reduction | No information available                                                                                           | No information available                                                                  | Inflammatory demyelinating CNS process                                                   | High-dose steroid therapy and plasmapheresis                                          | Recovered with sequelae          |
| 6 F/42/ United States (reported in Ref. 5) | CNS vasculitis                                                            | Headaches, fever, weight loss, arthralgia, ataxia, and gait difficulty               | Numerous cerebral T2-weighted lesions and striking linear contrast enhancement in the deep medullary veins; diffuse intramedullary cord abnormalities with cord swelling, edema, and numerous petechial foci of contrast-enhancement | Pleocytosis and elevated total protein levels                                             | Cerebral vasculitis and no evidence of demyelination                                        | High-dose steroid therapy and cyclophosphamide                                           | Partial recovery                 |
| 7 M/32/ Germany (case presented here) | Steroid-responsive GFAPα IgG-mediated encephalitis                       | Perceptive impairment, confusion, incoherent thoughts, delusions, slight ataxia, and nystagmus | New juxtacortical lesion in the right gyrus frontalis medius and a new focal gliosis in the spinal cord at level Th3/4 | Pleocytosis and elevated total protein levels and positive presence of GFAPα IgG antibodies | No information available.                                                                | High-dose steroid therapy, plasmapheresis, and rituximab                                   | Partial recovery                 |

Abbreviations: ADEM = acute disseminated encephalomyelitis; DRESS = Drug rash with eosinophilia and systemic symptoms; GFAPα IgG = glial fibrillary acidic protein (GFAP) α immunoglobulin G (Ig); Th = thoracic vertebra.
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