Neurological Adverse Effects Associated With Anti-tumor Necrosis Factor Alpha Antibodies in Pediatric Inflammatory Bowel Diseases

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ABSTRACT

Objectives: Neurological adverse effects (NAEs) induced by biotherapies have been reported in the literature mainly in adult patients with inflammatory bowel disease (IBD), rheumatic diseases, or psoriasis. There are scant data in children. Aims of this study are to report and describe noninfective NAE associated with anti-TNFα antibodies in pediatric IBD, and to evaluate their incidence.

Methods: We retrospectively collected all reports of NAE in pediatric IBD treated with anti-TNFα antibodies recorded in the French Pharmacovigilance Database. To estimate the national incidence of NAEs, we extrapolated data from the French regional inception population-based cohort EPIMAD.

Results: Between 2000 and 2018, 231 adverse events in pediatric IBD exposed to anti-TNFα antibodies were reported to this Database. Seventeen NAEs (7.36%) were collected: 8 severe NAE (1 demyelinating neuropathy, 1 optic neuritis, 1 acute transverse myelitis, 1 polyradiculoneuritis, 1 sensorineural hearing loss, 1 seizure, 1 stroke, and 1 glioma), 7 moderate NAE (headaches), and 2 neuropsychic events. The median delay between anti-TNFα start and NAE occurrence was 6 months (range: 13 days to 26 months). In 10 of 17 patients, anti-TNFα antibodies were stopped. Nine of 17 patients had a complete resolution (including 2 severe NAE) and 8 of 17 a partial resolution (including 6 severe NAE). We estimate the incidence of severe NAE in pediatric IBD treated with anti-TNFα antibodies at 1 case for 10,000 patients-year in France.

Conclusions: NAE associated with anti-TNFα antibodies in pediatric IBD are rare. In severe NAE, we recommend to discontinue anti-TNFα therapy and to consider alternative treatment.

Key Words: anti-TNFα antibodies, neurological adverse effects, pediatric inflammatory bowel disease

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What Is Known

- Neurological complications have been described in inflammatory bowel disease, as autoimmune process, but also as adverse effect of medications, including anti-TNFα antibodies, mainly in adult patients.
- Pediatric data are scarce.

What Is New

- We took advantage of the French National Pharmacovigilance database to report and describe neurological complications potentially related to anti-TNFα antibodies in children with inflammatory bowel disease.
- We present first estimations of the incidence of severe neurological adverse effects in pediatric inflammatory bowel disease.

Anti-tumor necrosis factor-alpha (TNFα) antibodies are integral part of the treatment algorithms of inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriasis vulgaris, hidradenitis, and inflammatory bowel disease (IBD). Over the last 20 years, ample experience was gained in treating IBD with

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anti-TNFα antibodies. Several studies and registries indicate that they can be associated with different adverse effects, including hypersensibility/allergic reactions, infections, skin reactions, and other exceptional adverse effects such as congestive heart failure, malignancies, or atypical autoimmune reactions. Reports of neurological complications are quite rare but are reported in patients with IBD or rheumatic disorders (1–7). Of note, before the introduction of anti-TNFα antibodies, neurological complications were described, in retrospective studies and 2 prospective adult IBD cohorts (8–10). They were attributed to autoimmune process or to adverse effects of other medications, with a suggested frequency from 0.25% to 35%, according to the definition (excluding or not headaches or neuropsychiatric disorders).

There is an ongoing discussion of a causal relationship between anti-TNFα antibodies and the occurrence of neurologic symptoms in patients with immune-mediated disorders. First cases of multiple sclerosis (MS) exacerbations were described with the use of lenercept, an experimental anti-TNFα agent developed for the treatment of MS (11). Up to now, more than 800 cases of neurological adverse effects (NAEs) were attributed to anti-TNFα antibodies in patients with immune-mediated disorders (3,4,12–15).

So far, only 8 cases of NAE under anti-TNFα antibodies are reported in children with IBD: 3 cases of posterior reversible encephalopathy, 1 multifocal leukoencephalopathy, 1 ischemic fatal central nervous system (CNS) disease, 1 small fiber neuropathy, 1 meningitis, and 1 medulloblastoma (16–22). Moderate NAE such as headaches are also reported during infusions (23,24). The majority of retrospective or prospective studies in children with IBD (1,25) or rheumatological disorders (2) do not report any NAE, with a follow-up varying between 4 months to 5.5 years. In children with rheumatic diseases treated with anti-TNFα antibodies several severe NAE cases were reported, and neuropsychiatric disorders and headaches (2,5,6,14,26–29).

Because of the sparsity of data in the pediatric field, we took advantage of the French National Pharmacovigilance database to recense and describe neurological complications potentially related to anti-TNFα antibodies in children with IBD.

METHODS

We retrospectively collected and analyzed all reports of NAE involving anti-TNFα antibodies exposure recorded between January 1, 2000 and January 31, 2018 in the French Pharmacovigilance Database, which centralizes all adverse effects reported to the French pharmacovigilance centers network (30). Reports were selected using the medical dictionary for regulatory activities (MedDRA) on System Organ Class ''nervous system disorders'' (excluding infections and hypersensitivity disorders), crossed with ''infliximab (IFX)'' or ''adalimumab (ADA)'' exposure, ''age between 0 and 18 years old,'' and ''Crohn'' or ''Ulcerative colitis'' or ''IBD.'' All children had confirmed diagnosis of IBD, anti-TNFα antibody exposure (at least 1 dose), occurrence of at least 1 neurological complication (demyelinating diseases of CNS, alterations of peripheral nerves, seizures, migraines, headaches, stroke, cancers, posterior reversible encephalopathy syndrome, neuropsychiatric disorders).

For all patients, we recorded anonymously patients' demographic data (age, sex); IBD type; clinical characteristic of the NAE; list of concomitant medications during and before the event; delay between the first anti-TNFα antibody exposure and occurrence of NAE, explorations, or tests results (magnetic resonance imaging, cerebrospinal fluid analysis, electromyography, and nerve conduction studies); and clinical evolution. We classified NAE in 3 categories: neuropsychiatric disorders, moderate NAEs (migraines, headaches), and severe NAE (demyelinating diseases of CNS, alterations of peripheral nerves, seizures, stroke, cancers, posterior reversible encephalopathy syndrome).

TABLE 1. French imputability (I) score

	Semiology		
Chronology	S 1	S 2	S 3
C 0	I 0	I 0	I 0
C 1	I 1	I 1	I 2
C 2	I 1	I 2	I 3
C 3	I 3	I 3	I 4

I 0 = excluded imputability; I 1 = doubtful imputability; I 2 = plausible imputability; I 3 = likely imputability; I 4 = very likely imputability.

To evaluate a potential causal relationship between drug exposure and the occurrence of an AE, the French National Pharmacovigilance database uses a score defined in the 1985 version of the French method (31), which is based on the evaluation of 8 criteria divided into 3 groups: chronology, semiology, and bibliographic data. Once combined, the chronological (C) and semiological (S) scores yield the ''intrinsic'' causality score ranging from 0 (unlikely) to 4 (very likely) (Table 1), allocated on the sole basis of the case considered. The eighth criterions derive an ''extrinsic'' or bibliographic score (B) for the reaction from a categorization of the scientific literature available.

To estimate the national incidence of NAE in pediatric IBD in France, we used the French hospital discharge database and the EPIMAD data for extrapolation. EPIMAD is an exhaustive prospective study recording all incident IBD cases in Northern France since 1988, representing 9.3% of the whole French population (32). From 2000 to 2015, EPIMAD records 1519 incident cases of IBD in children younger than 18 years, corresponding to approximately 100 new cases per year. From 1988 to 2004, this database reported a cumulative probability for receiving anti-TNFα antibodies of 24% 10 years after the IBD diagnosis. Geographical distribution of this registry is quite similar to the prevalence rate given by the French hospital discharge database: IBD prevalence is estimated to be approximately 210,000 to 240,000 cases in France (33,34). Approximately 9% of this population is younger than 17 years, representing approximately 20,000 children with IBD in France.

RESULTS

During the study period, a total of 231 AE were reported to the French National Pharmacovigilance database, in children with IBD exposed to anti-TNFα antibodies. Seventeen of them presented NAEs (7.36%), the first NAE report dates from 2009, and the others date from 2010 to 2017. Among the 17 NAE potentially related to anti-TNFα antibodies exposure, we found 8 severe NAE, 7 moderate NAE, and 2 neuropsychological events. Severe NAE occurred in 8 children, including 1 demyelinating neuropathy, 1 optic neuritis (ON), 1 acute transverse myelitis (ATM), 1 polyradiculoneuritis, 1 sensorineural hearing loss, 1 seizure, 1 stroke, and 1 glioma during anti-TNFα antibody therapy (Table 2). The 7 moderate NAE concerned 1 report of migraines and 6 reports of headaches. Two patients with IBD developed a depression during anti-TNFα antibody medication. For comparison, during the same study period an additional 27 NAE were reported for children with IBD not exposed to anti-TNFα antibodies: n = 9 receiving azathioprine, n = 4 on corticosteroid medication, n = 3 on metronidazole, n = 4 under methotrexate therapy, n = 2 on cyclosporine medication, n = 5 on mesalazine (severe NAE occurred in 7 children, including

TABLE 2. Pediatric inflammatory bowel disease case reports of severe neurological adverse effects with anti-TNFα antibodies reported to the French National Pharmacovigilance database

Year of declaration Patient number	Neurological adverse effects	Age, y/sex IBD (active/ remission)	Type of anti-TNFα (concomitant drugs)	Time to onset of NAE after introduction of anti-TNFα	Diagnosis tests	NAE's treatments	Anti-TNFα discontinuation	Resolution (duration of follow-up)	Causality assessment Score
2014 Patient 1	Retrobulbar optic neuritis	15/F CD (r)	IFX	26 mo	Cerebral MRI (normal CSF analyses)	Corticosteroids IV then PO	Yes	Complete (1 year)	C1S1B3 I1
2015 Patient 2	Acute transverse myelitis	14/F CD (NA)	ADA (MTX)	4 mo (and 4 mo after MTX)	Medullar MRI (normal cerebral MRI)	Corticosteroids	Yes (switch UST)	Partial (NA)	C1S1 I1
2012 Patient 3	Polyradiculoneuritis	16/M CD (a)	IFX	13 days	EMG/NC	IVIg 5 days	Yes (but switch ADA)	Partial (NA, return from default)	C3S1B3 I3
2017 Patient 4	Demyelinating neuropathy	16/F UC (r)	IFX	9 mo	EMG/NC (normal CSF analyses and cerebral MRI)	IVIg 5 days	Yes	Partial (1 y)	C2S1B3 I1
2009 Patient 5	Unilateral sensorineural hearing loss	17/M CD (r)	IFX (MTX)	6 mo	Auditive tests	/	No	Partial (NA, return from default)	C1S1B1 I1
2016 Patient 6	Visual and auditory hallucinations, epilepsia	11/F/CD (NA)	ADA	1 mo	EEG: slow posterior spike-wave pointes (normal cerebral MRI)	Corticosteroids 6 days IV	Yes	Complete (4 mo)	C1S1B1 I1
2016 Patient 7	Arterial stroke on carotid aneurism	17/M CD (r)	IFX	4 mo	Cerebral MRI cerebral arteriography	Neurosurgery	No	Partial (NA)	C1S1B3 I1
2017 Patient 8	Generalized convulsions, low grade cerebellar glioma	18/M UC (a)	IFX biosimilar (vedolizumab, MTX, mesalazine)	12 mo (12 mo after MTX, 2 days after vedolizumab)	Cerebral MRI DOPA-PET	Neurosurgery steroids anti-epileptic drugs	Yes	Partial (1.5 y)	C2S1B2 I1

ADA = adalimumab; a/r = active/remission; CD = Crohn disease; CSF = cerebrospinal fluid; EEG = electroencephalogram; EMG/NCS = electromyography and nerve conduction studies; F = female; IC = indeterminate colitis; IFX = infliximab; IVIg = intravenous immunoglobulins; M = male; MRI = magnetic resonance imaging; MTX = methotrexate; NA = not available; NAE = neurological adverse effects; PET = positron emission tomography; UC = ulcerative colitis; UST = ustekinumab.

3 venous cerebral thrombosis and 1 seizures in patients treated with an association of azathioprine and corticosteroids, 1 encephalitis in a patient treated with an association of azathioprine and cyclosporine, and 2 peripheral neuropathies occurred in patients treated with metronidazole).

The demographic data of the IBD population with NAE potentially related to anti-TNFα antibodies exposure show 9 girls and 8 boys, with a mean age of 14.7 years (range 6–18 years). Eleven patients had Crohn disease, 5 ulcerative colitis, and 1 IBD unclassified. Eight patients with IBD were in remission when they developed an NAE, whereas 4 had an active disease. In 5 patients no data on disease activity were available.

Treatments used were IFX and ADA in 11 and 6 patients, respectively. The median delay between anti-TNFα antibodies start and NAE occurrence was 6 months (range: 13 days–26 months). In 10 of 17 patients, anti-TNFα antibody therapy was discontinued (6/8 severe NAE, 4/7 moderate NAE, 0/2 neuropsychic NAE), and the follow-up was available for 11 of 17 patients. For severe NAE, neuropathies worsened after each infusion in the case anti-TNFα antibody therapy was not immediately stopped (patients 3 and 4): after discontinuation, there was an improvement for all patients (partial improvement in 6/8, complete improvement 2/8), but a relatively long follow-up period (1 year) was only available for 3 of 8 patients. For moderate NAE (headaches), all patients had a complete symptoms resolution, and the 2 patients with depression had a partial resolution, but duration of follow-up was not available.

Twelve patients received anti-TNFα antibodies as monotherapy and 5 patients received a concomitant therapy: methotrexate (n = 3), azathioprine (n = 1), ursodesoxycholic acid (n = 1). In patients receiving a combo therapy with methotrexate, a possible relationship of MTX to the occurrence of an NAE cannot be excluded and it was stopped (patients 2, 5, and 8). Patient 8 had severe ulcerative colitis treated first with mesalazine, followed by methotrexate and IFX biosimilar (6 perfusions), 1 month later vedolizumab was started due to nonresponse to IFX medication. He presented generalized convulsions, and cerebral MRI revealed a cerebellar glioma. All of these medications were stopped for this patient.

According to the French causality assessment, the French imputability score established by the French National Pharmacovigilans database (ranging from I1 to I4), was scored in 14 patients I1 (=doubtful imputability), in 2 patients I3 (=likely imputability), and in 1 patient I4 (=very likely imputability) for patients exposed to anti-TNFα antibodies. For patients who received also methotrexate, the imputability score for this drug was I1.

For comparison, during the same study period, 11 NAE were reported in children with a rheumatic disease exposed to anti-TNFα antibodies. Five NAE with ADA (3 headaches during injection, 1 reduced visual acuity, 1 anxiety attack), and 6 cases with etanercept (ETA) (1 ON, 1 facial palsy, 1 convulsion, 1 headache, 1 trembling, 1 infectious myelitis), with imputability French score I1.

The data of the French hospital discharge database and the EPIMAD registry allowed to estimate the national incidence of NAE in pediatric IBD in France: during the study interval 2000 and 2018, about 20,000 children had a diagnosis of IBD, and about 5000 were exposed to anti-TNFα antibodies. Based on these data the incidence of severe NAEs in children with IBD receiving anti-TNFα antibodies can be estimated to 0.16% between 2000 and 2018 in France, which represents about 1 case for 10,000 patients-year.

DISCUSSION

Previous meta-analyses of postmarketing studies and randomized trials in IBD or rheumatic diseases found a prevalence of NAE induce by anti-TNFα antibodies between 0.05% and 0.2% (7,35–37), and an incidence comparable to our data with 2 to 10 cases for 10,000 patients-year (38). Our data may, however, be under-estimating the real incidence, because drug adverse events could be under-reported: the cases recorded by the French National Pharmacovigilance database are based on voluntary reports from physicians; thus, there may be a strong bias, with physicians being more likely to report more severe events. For this reason, we estimated the incidence only for severe NAE. In a similar way, Fernandez-Espartero et al (36) described a major difference between their biologic registry and their pharmacovigilance system. No NAE was reported before 2009, probably due to the rather restricted use of anti-TNFα antibodies. Nevertheless, in all large retrospective or prospective adult cohorts studies with IBD or rheumatic diseases, NAE with anti-TNFα antibodies are very rare, with a median follow-up varying from 6 to 58 months (3,4,12,13,35). Table 3 summarizes the available data for children in literature.

Of note, the incidence of neurological diseases in general pediatric population is very low: ON in children is evaluated to be 0.2 per 100,000 patients-year (39), idiopathic ATM is rare in adults and children (8.6 per 1 million) (40), chronic inflammatory demyelinating polyneuropathy occurs mainly in adults rarely in children (0.33 per 100,000 patients-years) (41), as compared to our data for each of these disease (1 per 100,000 patients-year). In the literature, an increased incidence of NAE under anti-TNFα antibody therapy has been mainly observed for MS, whereas some randomized controlled trials, post-marketing programs, and retrospective long-term safety studies revealed no increased incidence (4,7,36). In the present study, we did not detect a single case of MS, in keeping with the notion that MS occurs mainly in adults (only 3%–10% pediatric cases) and incidence is estimated at 7.6 and 8.8 per 10,000 (42).

To evaluate the causal relationship between medications and clinical symptoms, pharmacovigilance databases use scoring tools such as the Naranjo score in USA, WHO score, or French score. Deepak et al (14) described 772 NAE reported to the Food Drug Adverse Event Reporting System (FDAERS) over a 10-year period: by using the Naranjo score they estimated that the majority of reports were of possible causality (71.4%) with anti-TNFα antibodies. In our study, NAEs were associated with a doubtful, likely, or very likely imputability French score. It was not detailed in the files, but all were also suspected with the WHO score. In practice, it is difficult to give a real imputability score for a drug, because it is rarely possible to re-expose the patient to the same drug, especially when a severe AE occurred. In IBD, neurological symptoms can be due to various immune processes, potential vitamin deficiencies, or non-TNFα medications (as summarized in Table 4). Thus, several factors contribute to decrease the imputability score. The pathophysiology of NAE under anti-TNFα antibody therapy is not well understood. It has been suggested as a potential autoimmune process induced by the underlying disease itself, but NAEs have been reported in patients treated with anti-TNFα antibodies without underlying autoimmune disease (12). TNF is a cytokine that signals through 2 receptors, TNFR1 (proinflammatory) and TNFR2 (immunoregulation, including remyelination). In the first stages of MS, TNF would be involved in demyelination, whereas in later stages it seems to be fundamental for remyelination by the activation of TNFR2. It is hypothesized that chronic TNF inhibition may disturb the equilibrium of these 2 signaling pathways (43). In neuropathies, nerve biopsies sometimes do not show cellular infiltration, which suggested a primary humoral attack against peripheral nerve myelin. A vasculitis-induced nerve ischemia has also been suggested in mononeuropathies multiplex, and inhibition of signaling support in axonal neuropathies (37,44).

TABLE 3. Pediatric case reports of neurological adverse effects with tumor necrosis factorα- antibodies in literature

Reference type of study	N patients disease	NAEs	Age, y/sex	Type of anti-TNFα	Time to onset of NAE after introduction of anti-TNFα	Diagnosis tests	NAE's treatment	Anti-TNFα discontinuation	Resolution (duration of follow-up)
IBD									
Zamvar, 2010 (16) Case report	1 UC	1 Posterior reversible encephalopathy (generalized tonic-clonic seizures)	15/F	IFX	2 wk	MRI	No	NA	Total recovery (NA)
Zamvar, 2009 (17) Case report	1 CD	1 Posterior reversible encephalopathy (generalized tonic-clonic seizures, visual disturbances)	14/M	IFX	5 days	MRI	No	Y	Total recovery (NA)
Haddock, 2011 (18) Case report	1 CD	1 Posterior reversible encephalopathy (headaches, seizures, visual disturbance, altered mental status)	8/F	IFX	2 wk	Computer tomography, MRI	Intracranial hypertension drugs	Y	Total recovery (NA)
Kolho, 2007 (19) Retrospective cohort study	23 CD	1 Multifocal leukoencephalopathy	16 /M	IFX	3 mo	MRI	NA	Y	Total recovery (6 mo)
Baumer, 2016 (20) Case report	1 UC	1 Ischemic fatal CNS disease	7/M	IFX	6 h after first injection	MRI	Empirically treatment for anaphylactic shock	Y	Death, no autopsia
Breton, 2018 (21) Case report	1 UC	1 Small fiber neuropathy	17/F	IFX + ADA	1.5 y	Positive antiGM2 ganglioside IgM nerve biopsy	IVIg	Y	No resolution (5 mo)
Dziechciarz, 2016 Meta-analysis (22)	500 CD	1 Meningitis 1 medulloblastoma	NA	ADA	NA	NA	NA	NA	NA
Cameron, 2015 (23) Retrospective cohort study	132 IBD	1 Headaches (in 1 CD)	8/M	ADA	NA	NA	NA	N	NA
Lamireau, 2004 (24) Retrospective cohort study	88 CD	3 Headaches	NA	IFX	During the perfusion	NA	NA	1/3	NA
Rheumatic diseases									
Pastore, 2017 (2) Retrospective cohort study	78 JIA	2 Anxiety (ETA)	NA	ETA IFX ADA	8 and 12 mo	NA	NA	Y	Total recovery (NA)
Kunzmann, 2005 (29) Case report	1 JIA	Cerebral demyelination and aseptic meningitis	5/ F	ETA	1 y	MRI, CSF	NA	NA	NA
Tarkiainen, 2015 (5) Retrospective cohort study	348 JIA	1 Infectious encephalitis 36 headaches, 11 migraines 11 depression 4 serious mental illness	NA	ETA IFX ADA	NA	NA	NA	NA	NA (median 51 mo)
Horneff, 2004 (28) Prospective cohort study	322 JIA	1 CNS demyelination	NA	ETA	NA	MRI, CSF	NA	Y	No resolution (6 mo)
Verazza, 2016 (6) Retrospective cohort study	1038 JIA	21 Neuropsychiatric disorders (3.1%)	NA	ETA	NA	NA	NA	NA	NA
Gerloni, 2008 (27) Prospective cohort study	163 JIA	53 Neuropsychiatric disorders (12.3%)	NA	ETA IFX	NA	NA	NA	Y or dose reduction	Total recovery (median 23 mo)
Tauber, 2005 (26) Case reports	2 JIA	2 Optic neuritis	12/F 17/F	ETA	2.5 and 8 mo	Visual evoked potentials, fundoscopy	Steroids	Y	Total recovery (NA)
Deepak, 2013 (14) Retrospective cohort study	26 JIA	NA	NA/	ETA, IFX ADA	Mean time 21 mo	NA	NA	NA	NA

ADA = adalimumab; CD = Crohn disease; CNS = central nervous system; CSF = cerebrospinal fluid; ETA = etanercept; F = female; IBD = inflammatory bowel diseases; IFX = infliximab; IVIg = intravenous immunoglobulins; JIA = juvenile idiopathic arthritis; M = male; MRI = magnetic resonance imaging; NA = not available; NAEs = neurological adverse events; TNF = tumor necrosis factor; UC = ulcerative colitis.

TABLE 4. Anti-tumor necrosis factorα antibodies related and non–anti-tumor necrosis factorα antibodies related neurologic symptoms in inflammatory bowel disease, described in literature

Neurologic symptoms in IBD without treatments	Neurologic adverse effects in IBD with non–anti-TNFα treatment	Neurologic adverse effects in IBD with anti-TNFα antibodies
Peripheral neuropathies (polyradiculoneuritis, chronic inflammatory demyelinating polyneuropathy, mononeuropathy or multifocal neuropathy)	Azathioprine: Infections (spinal epidural abscess, myelo-radiculitis) Multifocal leukoencephalopathy,	Multiple sclerosis Acute transverse myelitis Optic neuritis Peripheral neuropathies (polyradiculoneuritis, chronic inflammatory demyelinating polyneuropathy, axonal sensory-motor neuropathies, mononeuropathy multiplex, multifocal motor neuropathy with conduction block)
Multiple sclerosis	Corticosteroids Psychotic condition, confusion, excitation, insomnia	
Optic neuritis	Convulsions	
Sensorineural hearing loss	Infections	
Cranial nerve palsy		
Myopathy	Metronidazole	
Myelopathy	Peripheral demyelinating or axonal neuropathies	
Acute myelitis transverse	Headaches, dizziness, confusion, convulsions, encephalopathy, cerebellar ataxia, aseptic meningitis	
Strokes		
Autonomic neuropathy	5-Aminosalicylic acid (5-ASA) preparations	
Cerebral tumor	Peripheral neuropathy, multiple sclerosis	
Myasthenia	Depression, anosmia, dizziness, paresthesia, headaches	
Seizures		
Parkinson-like syndrome,	Cyclosporine	
Cerebellar syndrome	Tremors, headaches, psychosis, seizures, paresthesia, ataxias, motor neuropathies, visual hallucinations, optic neuropathy, cerebellar atrophy, migraine, benign intracranial hypertension, confusion, agitation, insomnia, coma, posterior reversible encephalopathy syndrome	
Vestibular disorders		
Sleep disturbances,		
Restless legs syndrome,		
Wernicke encephalopathy,		
Migraines and headaches		
Neuropsychiatric disorders (anxiety, depression, chronic fatigue syndrome).	Methotrexate Posterior reversible encephalopathy syndrome cognitive and mood disorders, paresthesia, myelopathy, encephalopathy, coma, seizures, confusion, ataxia, paraplegia, dyskinesia.	

CNS = central nervous system; IBD = inflammatory bowel disease; TNF = tumor necrosis factor.

As in our study, most of the NAE in IBD reported in the literature occurred in patients treated with IFX, probably because this was the first anti-TNFα antibody approved for IBD. NAEs are mainly reported in adult patients as isolated case reports, collected in reviews (7,12,44), or from postmarketing database (7,13–15), and biologic registries (15,36). *Demyelinating diseases of CNS and peripheral neuropathies*, the more frequently reported severe NAE, appear often <2 years after the initiation of anti-TNFα therapy: >200 cases of MS have been reported, about 150 cases of ON and about 30 cases of ATM (8,14,15,29,36). Here, we describe the first child developing ATM. More than 400 cases of peripheral neuropathies have been reported: polyradiculoneuritis (13), chronic inflammatory demyelinating polyneuropathy (12,14,15,44), axonal sensorimotor neuropathies, mononeuropathy multiplex, and multifocal motor neuropathy with conduction block (12,45). Most of the authors recommend withdrawal of anti-TNFα antibodies. Specific neurologic additional drugs are generally used (immunosuppressants, intravenous immunoglobulin, corticosteroids, plasmapheresis), although spontaneously resolutive cases have been described. The prognosis appears generally favorable mainly in neuropathies. From the FDAERS, Deepak et al (14) described a majority of peripheral neuropathy (38.3%), followed by CNS and/or spinal demyelination (19.8%), with an average full recovery of 33% but the follow-up duration was not specified. In 2010, from the Spanish biologic registry BIOGEAS, Ramos-Casal et al (15) reported 175 demyelinating diseases and 44 peripheral neuropathies, with a better NAE resolution rate of 70% in ON and MS, and 89% in peripheral neuropathies (median follow-up of 10 months). Others NAEs include *seizures* in posterior reversible encephalopathy syndrome (as described in patient 6), which improved after anti-TNFα antibody discontinuation (8,16–18), progressive multifocal leukoencephalopathy, CNS infections, and vasculitis with CNS involvement (5,8). *Strokes* have been described after the first IFX infusion (20), but the FDAERS has not found a statistically increased risk (14), and in meta-analysis risk of stroke is modestly increased in IBD: for patient 7, the association of aneurism, IBD, and IFX has probably favorized the development of cerebral thrombosis (46). In addition, our study describes the first case of *sensorineural hearing loss* under anti-TNFα-antibodies in a child with IBD, but it has already been reported as extraintestinal manifestation of IBD (47). *Cerebral tumors* occur extremely rarely in patients with IBD (22): Guo et al (48) have recensed in 2016, 202 cases of glioblastomas under IFX or ADA medication (FDAERS and WHO database), but causality is difficult to establish: for patient 8, it is not known if the lesion was pre-existing before initiation of IFX therapy, but it cannot be excluded that IFX increased the tumor growth. *Neuropsychiatric disorders* are mainly reported as isolated cases reports (49), with some pediatric cohorts reported occurrence of neuropsychiatric disorders between 3% and 12% of cases (5,6,27), once more with a difficult causality link (50).

Migraines and headaches have a high prevalence in IBD, independent of medication (51), but they are also reported with ADA, ETA, IFX (during perfusion, or as serum sickness-like reaction) (1,5,23,24,27), or with aseptic meningoencephalitis (29,52).

In conclusion, NAE with anti-TNFα antibodies are rare, but gastroenterologists and pediatricians have to be aware of this possibility and should recognize first symptoms to limit complications. A multidisciplinary staff with a neurologist could be necessary to definite diagnosis and discuss appropriate therapeutic options. As IBD can be associated with neurological symptoms independent of the medication, a collegial discussion is necessary to evaluate the relationship between symptoms and anti-TNFα antibodies. We recommend to discontinue anti-TNFα antibody therapy when a severe NAE is detected and consider alternative treatments. Anti-TNFα antibodies should not be administrated in patients with history of MS, and patients with a history of peripheral neuropathy should be carefully evaluated before starting anti-TNFα antibodies. Prospective cohorts are necessary to identify subjects at risk for NAE with anti-TNFα antibodies and others recent biotherapies.

Supplemental Content: Appendix (Supplemental Digital Content, *http://links.lww.com/MPG/B787*): members of the GETAID pédiatrique and participating centres.

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