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BRIEF REPORT

Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis: A Newly Recognized Inflammatory Brain Disease in Children

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Objective. **Anti–*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a newly recognized antineuronal antibody–mediated inflammatory brain disease that causes severe psychiatric and neurologic deficits in previously healthy children. The present study was undertaken to describe characteristic clinical features and outcomes in children diagnosed as having anti-NMDAR encephalitis.**

Methods. **Consecutive children presenting over a 12-month period with newly acquired psychiatric and/or neurologic deficits consistent with anti-NMDAR encephalitis and evidence of central nervous system (CNS) inflammation were screened. Children were included in the study if they had confirmatory evidence of anti-NMDAR antibodies in the serum and/or cerebrospinal fluid. Features at clinical presentation and results of investigations were recorded. Type and duration of treatment and outcomes at last followup were documented.**

Results. **Seven children were screened, and 3 children with anti-NMDAR encephalitis were identified. All patients presented with neurologic and/or psychiatric abnormalities, seizures, speech disorder, sleep disturbance, and fluctuating level of consciousness. The 2 older patients had more prominent psychiatric features, while the younger child had significant autonomic instability and prominent involuntary movement disorder. None had an underlying tumor. Immunosuppressive therapy resulted in near or complete recovery; however, 2 of the patients had early relapse necessitating re-treatment.**

Conclusion. **Anti-NMDAR encephalitis is an important cause of neuropsychiatric deficits in children, which must be included in the differential diagnosis of CNS vasculitis and other inflammatory brain diseases. Early diagnosis and treatment are essential for neurologic recovery.**

Inflammatory diseases of the central nervous system (CNS) in children present a diagnostic challenge to clinicians. The wide differential diagnosis includes infectious and postinfectious processes, systemic inflammatory conditions such as systemic lupus erythematosus, and primary CNS vasculitis. Recently, newly recognized antineuronal antibody–mediated inflammatory disorders, such as anti–*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, have become an important diagnostic consideration in children presenting with severe, newly acquired neuropsychiatric symptoms (1).

Anti-NMDAR encephalitis was initially described as a paraneoplastic process in women with ovarian teratoma (2). In contrast, in the pediatric population it is most commonly diagnosed in the absence of tumors (3). Children may present with psychosis, seizures, movement disorder, decreased level of consciousness, and/or life-threatening autonomic instability (4). Rapid clinical deterioration may occur. Elevated serum levels of inflammation markers and cerebrospinal fluid (CSF) pleocytosis are commonly found. Findings on brain imaging are often normal or nondiagnostic (5,6). The diagnosis relies on testing for anti-NMDAR antibodies. Rheumatologists' awareness of anti-NMDAR

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Drs. Laxer and Benseler contributed equally to this work.

Dr. Dalmau has a patent for the use of an MAZ autoantibody test, under which he receives royalties, and has filed a patent application for the use of NMDAR as a test. Dr. Laxer has received consulting fees from Novartis (less than $10,000).

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Table 1. Preceding symptoms, clinical features, laboratory characteristics at diagnosis, and associated test results in 3 children at the time of diagnosis of anti-NMDA receptor encephalitis*

	Patient 1 (3-year-old girl)	Patient 2 (16-year-old boy)	Patient 3 (13-year-old girl)
Preceding symptoms			
Systemic	Fever × 2 days	Fever, vomiting, diarrhea × 2 days	None
Neurologic	Ataxia	None	Right facial palsy; dysarthria
Psychiatric	None	Agitation; confusion; emotional lability	None
Clinical findings at diagnosis			
Neurologic			
Seizures	Yes	Yes	Yes
Movement disorder	Choreiform movements; orofacial dyskinesia	None	None
Other neurologic signs	Absence of speech; sleep disturbance; fluctuating LOC	Slowed speech; sleep disturbance; purposeless movements; fluctuating LOC	Dysarthria; aphasia; confusion; sleep disturbance; fluctuating LOC
Psychiatric	Agitation; bizarre behavior	Delusions; echolalia; echopraxia; violent behavior; agitation	Hallucinations; delusions; agitation
Autonomic signs	Fever; tachycardia	Hypertension	Fever
Laboratory results			
ESR, mm/hour (normal 0–10)	97	1	112
CRP, mg/liter (normal 0–8)	3.7	<0.6	29.6
WBC count, × 10^9/liter (normal 4–10)	7.6	13.4	9.5
CSF analysis			
WBC count, × 10^6/liter (normal 0–3)	13	25	80
Protein, gm/liter (normal 0.15–0.4)	0.19	0.52	0.11
Opening pressure, cm H_2O (normal <17)	26	20.5	<17
Oligoclonal bands	Present	Absent	Absent
Anti-NMDAR antibodies†			
Serum titer	1:200	Negative	Negative
CSF titer	1:160	1:160	1:40
Neuroimaging			
Brain MRI	Normal	Swelling and high signal of right hippocampus; subtle diffusion restriction	High signal focus in right frontal lobe; diffuse dural enhancement
Brain MRA	Normal	Normal	Normal
Brain MRV	Normal	Normal	Normal
Other investigations			
EEG	Diffuse slowing; no epileptic activity	Slowing over right frontal–temporal region; electrical seizure	Diffuse slowing with right temporal predominance; no epileptic activity
Brain biopsy	Not done	Mild lymphocytic meningeal infiltrate; no vasculitis	Not done
Malignancy, presence of tumor	No	No	No

* LOC = level of consciousness; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; WBC = white blood cell; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; MRA = magnetic resonance angiography; MRV = magnetic resonance venography; EEG = electroencephalography.

† Titers were measured by immunocytochemistry analysis of HEK 293 cells recombinantly expressing *N*-methyl-D-aspartate receptor (NMDAR). Titers are defined as the maximal dilution after which antibody reactivity was no longer visible (starting point of dilution at 1:40). Methods of transfection and immunocytochemistry are reported in ref. 6.

encephalitis is limited, with no reports published in the rheumatology literature to date. However, early recognition is crucial since the condition is treatable and prompt treatment likely leads to improved outcomes (4). Herein we describe the presenting clinical features, test results, treatment, and outcomes in consecutive children

diagnosed as having this recently recognized inflammatory brain disease.

PATIENTS AND METHODS

Patients. A single-center prospective cohort study of children age <18 years who were diagnosed as having anti-NMDAR encephalitis between July 1, 2009 and June 30, 2010 was conducted. Children were screened for inclusion if they had 1) evidence of a newly acquired neuropsychiatric deficit compatible with anti-NMDAR encephalitis, such as psychosis, seizures, movement disorder, and/or autonomic dysfunction; and 2) supportive evidence of inflammation from blood or CSF testing or neuroimaging. Children were included in the study if confirmatory evidence of anti-NMDAR antibodies in the serum and/or CSF was obtained. Children with primary CNS vasculitis and those with underlying systemic conditions such as rheumatic diseases or infections were excluded from the study. Approval was obtained from the Research Ethics Board (REB no. #1000019862).

Clinical data. Demographic information, preceding systemic and neurologic symptoms, earlier medical history, current illness, and results of detailed neurologic, psychiatric, and rheumatologic examinations were recorded. Neurologic status was determined by standardized assessment using the previously validated Pediatric Stroke Outcome Measure (7).

Laboratory data. Complete blood cell count (CBC) including white blood cell (WBC) differential count, erythrocyte sedimentation rate (ESR), and levels of C-reactive protein (CRP), complement C3 and C4, and von Willebrand factor antigen were recorded. CSF was analyzed for cell count, protein level, oligoclonal bands, and opening pressure. Autoantibody testing included studies for antinuclear antibody, rheumatoid factor, anti–double-stranded DNA, anti-Ro, anti-La, anti-Sm, anti-RNP, antineutrophil cytoplasmic antibodies, and anticardiolipin antibodies. Viral and bacterial cultures, serologic studies, and viral polymerase chain reaction studies were performed in both peripheral blood and CSF, according to the standardized institutional evaluation for encephalitis (8).

Anti-NMDAR antibodies. Serum and CSF were tested for anti-NMDAR antibodies at the Laboratory of Neuro-Oncology and Paraneoplastic Disorders, University of Pennsylvania, as previously reported (2,6).

Neuroimaging and additional testing. All patients underwent standardized magnetic resonance imaging (MRI) including T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging, and post-gadolinium sequences, at diagnosis and subsequently when indicated. MR angiography (MRA), MR venography (MRV), and conventional angiography were also performed as indicated. Patients tested for anti-NMDAR antibodies were screened for malignancies by abdominal/pelvic and/or testicular ultrasound. All patients underwent electroencephalography (EEG). Brain biopsies were performed when indicated. Ascertainment and review of biopsy specimens were performed according to the previously reported institutional protocol (9).

Treatment and outcome. The use of immunosuppressive medication, including intravenous immunoglobulin (IVIG), IV methylprednisolone, oral corticosteroids, and IV rituximab was documented. Dose and duration were recorded. Adverse events were noted. Treatment was given at the discretion of the treating rheumatologist and/or neurologist. Neurologic status at last followup and relapses during the observation period were recorded.

RESULTS

Patients with clinical features compatible with anti-NMDAR encephalitis. During the study period, a total of 7 children presented with clinical features compatible with anti-NMDAR encephalitis, including psychiatric manifestations, seizures, and/or movement disorders. Three children (43%) were found to be positive for anti-NMDAR antibodies and were diagnosed as having anti-NMDAR encephalitis. These included 1 boy and 2 girls, with a median age of 13 years (range 3–16). The remaining 4 children were subsequently diagnosed as having postinfectious inflammatory brain disease (2 patients), channelopathy (CACNA1A calcium-channel gene mutation) (1 patient), or other inflammatory brain disease (choreiform movements and weakness of right leg of unknown etiology) (1 patient).

Demographic characteristics, preceding symptoms, clinical features at presentation, and results of investigations in the 3 children with anti-NMDAR encephalitis are shown in Table 1, and treatment and outcomes are described in Table 2. Each patient's course is described in detail below.

Case reports. *Patient 1.* Patient 1, a previously healthy 3-year-old girl, presented with a 2-week history of progressive ataxia along with pain and weakness of her left leg. She had had a transient low-grade fever 2 weeks prior to the onset of neurologic symptoms. Neurologic examination revealed a circumductive, high-stepping gait and mild weakness of the left leg. She subsequently developed choreiform movements involving the left leg. Other results on initial tests, including CBC, ESR, toxicology screening, and MRI of the brain and spine, were normal.

She returned 10 days later with increasing choreiform movements of the left leg and involvement of the right foot and left arm. In addition, she had developed sleep disruption, confusion, and slowed speech. Carbamazepine treatment was started, and her movements improved. Lumbar puncture was performed, revealing an elevated CSF WBC count (13×10^6/liter), with 91% lymphocytes. CSF protein, lactate, and amino acid levels and results of testing for infection were normal.

Over the next 2 weeks, she developed continuous choreiform movements of all extremities, as well as dyskinesia of the orolingual and extraocular muscles.

Table 2. Treatment and outcome in the 3 patients with anti–*N*-methyl-D-aspartate receptor encephalitis*

	Patient 1	Patient 2	Patient 3
Initial therapy			
IVIG	Yes	Yes	Yes
IV methylprednisolone pulse	Yes	Yes	No
Oral prednisone	Yes	No	No
IV rituximab	Yes	No	No
Duration of therapy	7 months	7 months	3 months
Course			
Relapse	No	Yes	Yes
Time to relapse	NA	13 months	3 months
Re-treatment	No	IVIG × 6 months	Rituximab plus IVIG × 6 months
Outcomes			
Time at last followup	12 months	14 months	4 months
Neurologic deficits at last followup	None	Seizures; speech difficulties; memory impairment	Seizures

* IVIG = intravenous immunoglobulin; NA = not applicable.

She had severe agitation, complete loss of speech, and was only minimally responsive. Subsequently, she had recurrent seizures and autonomic changes including fever and tachycardia, and oxygen treatment was required. She was treated with phenobarbital for seizure control and trihexyphenidyl for abnormal movements. Repeat blood testing revealed an elevated ESR (97 mm/hour) and a normal CRP level. She received empiric treatment with acyclovir and antibiotics, although results of repeated testing for infection and metabolic abnormalities remained negative. Results of all autoantibody tests were negative. Repeat lumbar puncture demonstrated an elevated opening pressure (26 cm H_2O), mild pleocytosis, and positive oligoclonal banding. Repeat brain MRI/MRA/MRV consistently yielded normal results. EEG demonstrated diffuse slow background activity and no epileptiform discharges. For suspected inflammatory brain disease, the child was treated with intravenous immunoglobulin (IVIG; 2 gm/kg) and a 5-day course of pulse methylprednisolone (20 mg/kg/dose), followed by oral prednisone (2 mg/kg, tapered and discontinued over 6 months).

The patient's CSF and serum were both strongly positive for anti-NMDAR antibodies. No associated malignancy was found on abdominal imaging. Due to severe symptoms, she received additional therapy with rituximab (500 mg/m^2; 2 doses, 14 days apart). She required gastrostomy tube insertion for feeding purposes and received intensive neurocognitive rehabilitation therapy. At the 12-month followup examination, she had made a complete neurologic recovery.

Patient 2. Patient 2, a 16-year-old boy, developed emotional lability, confusion, agitation, and slowed speech following a 2-day history of low-grade fever, vomiting, and diarrhea. Two weeks later he developed generalized tonic-clonic seizures. He had previously used cannabis for 2 years. Neurologic examination revealed brisk reflexes and clonus bilaterally. Mental status examination revealed flat affect, delusional and disorganized thoughts, and poor eye contact. Laboratory testing demonstrated a slightly elevated WBC count and a normal ESR, CRP level, and autoantibody profile. Results of toxicology screening, including testing for cannabis, were negative. Initial lumbar puncture showed a CSF WBC count of 25×10^6/liter (94% lymphocytes) and elevated CSF protein (0.52 gm/liter). Initial brain MRI results were normal. He was started on a regimen of acyclovir and antibiotics, although results of tests for infection and metabolic abnormalities were negative. Video EEG showed complex partial seizures and a slowing pattern over the right frontal–temporal region.

Approximately 1 week after presentation he developed echolalia, echopraxia, catatonic posturing, and purposeless movements, as well as several episodes of agitation and violent behavior. Repeat MRI/MRA/MRV findings were normal, as were the results of conventional cerebral angiography. A nonlesional brain biopsy performed 2 weeks after presentation showed scattered lymphocytes in the meninges only, and no evidence of vasculitis. He was treated with pulse methylprednisolone (1,000 mg/dose), followed by IV methylprednisolone (60 mg/day) for 5 days for presumed inflammatory brain disease. In addition, he required multiple medications to control his agitation and behavioral abnormalities, valproic acid for seizure control, and amlodipine for transient hypertension. He slowly

became less agitated without violent episodes and responded to commands.

Five weeks after presentation, repeat brain MRI revealed high signal and swelling of the right hippocampus, consistent with limbic encephalitis. Repeat lumbar puncture showed high opening pressure, with normal findings on CSF studies. Serum and CSF tested positive for anti-NMDAR antibodies. No associated malignancy was found.

Given the confirmed diagnosis of anti-NMDAR encephalitis, IVIG treatment was instituted (70 gm/dose). The patient also received intensive rehabilitation, occupational therapy, and physiotherapy for 2 months. At followup 11 months after diagnosis he was calm with no agitation or confusion, but had mild memory impairment and slow speech. At last followup at 14 months he presented with recurrence of seizures and began a second course of IVIG.

Patient 3. Patient 3, a previously healthy 13-year-old girl, presented with a right facial palsy and dysarthria. She was treated with a short course of prednisone for presumed Bell's palsy. One week later she developed agitation, sleep disturbance, and seizures. Assessment showed a right upper motor neuron facial palsy without other neurologic deficits. The CBC was normal, and lumbar puncture demonstrated CSF pleocytosis (WBC count 80×10^6/liter [94% lymphocytes]). Findings on brain MRI were normal, and EEG revealed background slowing over the right temporal region. She received phenytoin for seizure control and acyclovir for possible viral encephalitis.

During her admission, the patient exhibited expressive and receptive dysphasia, confusion, auditory hallucinations, and a fluctuating level of consciousness. Further investigations demonstrated an increased ESR and CRP level. Results of autoantibody testing, toxicology screening, and evaluation for infection were negative. An MRI/MRA/MRV was repeated at 3 weeks after symptom onset and showed a nonspecific focus of high FLAIR signal in the right frontal lobe (Figure 1) and diffuse dural, but no leptomeningeal, enhancement. Repeat lumbar puncture demonstrated normal opening pressure, a CSF WBC count of 11×10^6/liter, and a CSF protein level of 0.11 gm/liter (normal 0.15–0.4). During her admission, she developed febrile neutropenia and transaminitis, thought to be secondary to medication effects. Anti-NMDAR antibodies were detected in the CSF. There was no evidence of malignancy.

The patient was treated with IVIG (70 gm/dose) and subsequently exhibited gradual improvement in cognitive function and psychiatric and neurologic symptoms. At 6 weeks she had mild dysarthria and aphasia. At 3 months, she presented with recurrence of seizures and received IV rituximab and re-treatment with IVIG.

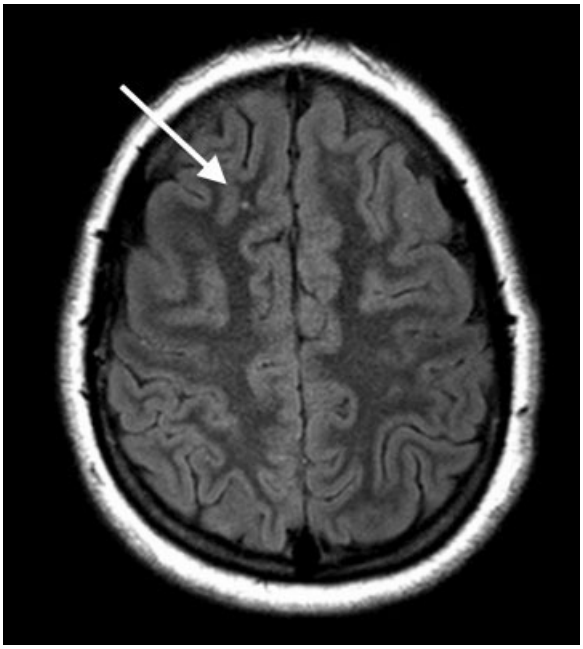

Figure 1. Fluid-attenuated inversion recovery magnetic resonance imaging, conducted 3 weeks after symptom onset in patient 3, a 13-year-old girl with anti–*N*-methyl-D-aspartate receptor encephalitis. A small, nonspecific focus of increased signal in the right frontal lobe is seen (**arrow**).

DISCUSSION

Anti-NMDAR encephalitis is a recently recognized antineuronal antibody–mediated disease in the spectrum of childhood inflammatory brain diseases. The children with anti-NMDAR encephalitis described herein presented with characteristic progressive neuropsychiatric symptoms and nonspecific evidence of CNS inflammation. Targeted testing for antibodies against NMDAR NR1/NR2 heteromers confirmed the diagnosis. Disease recognition and appropriate management led to improvement in symptoms.

Our patients presented with a flu-like prodrome followed by psychiatric features and neurologic abnormalities including seizures and movement disorder, consistent with patients described in other reports (3,5,10–13). The course of anti-NMDAR encephalitis has been proposed to represent a severity continuum starting with bizarre behavior and psychotic symptoms with subsequent progression to seizures, movement abnormalities,

decreased consciousness, and autonomic dysfunction (4). A significant proportion of patients require intensive care unit admission and intubation (3,6). Increasing clinical disease severity is thought to correlate with gradually decreasing availability of NMDAR function. Anti-NMDAR antibodies in increasing titers crosslink NMDARs, resulting in internalization and alteration of synaptic function. This reduction in surface NMDARs is reversible after antibody removal (14). Patient age may be a confounding factor, as younger children are often unable to describe hallucinations or paranoid thoughts. Reports of previous case studies have described abnormal movement as the initial presenting feature in young children with anti-NMDAR encephalitis (10,12,13). In contrast, in case series of adolescents and young adults, initial psychiatric symptoms are commonly reported (6,11,15).

All 3 of our patients had evidence of CNS inflammation. Correspondingly, CSF pleocytosis has been described in nearly all cases reported in the literature, with or without elevated CSF protein and/or oligoclonal bands (3,6,10). Measures of systemic inflammation appear to be less consistent. MRI findings in anti-NMDAR encephalitis are variable. Some patients exhibit radiologic evidence of limbic involvement, as did one of our patients, although the clinical picture usually corresponds to a diffuse encephalopathy rather than a focal limbic dysfunction (6). Nonspecific FLAIR signal abnormalities can be found. Most importantly, however, neuroimaging findings are normal in the majority of patients (3,10).

There is no established treatment protocol for the management of anti-NMDAR encephalitis. Treatment of our patients was administered in a stepwise manner. All patients received a 6-month course of IVIG. Two were treated with steroids. Additionally, rituximab, an anti-CD20 monoclonal antibody, was administered to 2 of the children, in one case at diagnosis and in the other at the time of early recurrence of symptoms. In the literature, good responses have been described with steroid and IVIG combination therapy, and more severely affected patients have been treated with rituximab, cyclophosphamide, or plasmapheresis (2,3,6). Of interest, there have been adult cases in which clinical recovery has occurred without specific treatment (11,15).

An estimated 75% of anti-NMDAR encephalitis patients have a substantial or full recovery (3,10). All 3 of our patients improved over time. However, early relapses were documented in 2 of the children. The reported time to clinical recovery is variable, ranging from 2 weeks to 24 months (3,6,10). Intensive rehabilitation is frequently required following the acute illness. Large clinical series indicate that patients without tumors, as is the case in many children, often require second-line immunotherapies such as rituximab or cyclophosphamide, due to limited response to corticosteroids, IVIG, or plasma exchange (16). Patients who do not have tumors also experience more relapses than those who have tumors (16).

Characteristic neuropsychiatric features should alert clinicians to consider the diagnosis of anti-NMDAR encephalitis. A high index of suspicion is required when assessing children who present with a combination of psychosis, seizures, movement disorder, and/or autonomic instability. Testing for anti-NMDAR antibodies in children with CNS inflammation should be initiated prior to more invasive strategies such as brain biopsy. Early recognition and treatment may reverse the deficits and prevent permanent brain injury.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Benseler had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Luca, Daengsuwan, Dalmau, Laxer, Benseler.

Acquisition of data. Luca, Daengsuwan, deVeber, Laxer, Benseler.

Analysis and interpretation of data. Luca, Dalmau, Jones, Kobayashi, Laxer, Benseler.

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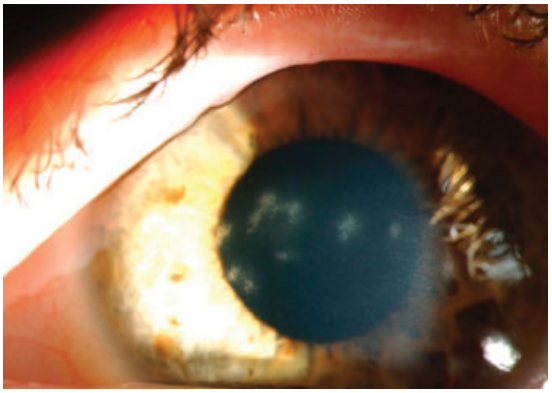
Clinical Image: Keratitis in reactive arthritis



The patient, a 24-year-old man, presented to the ophthalmology cornea clinic with a 10-day history of pain and severe photophobia in his left eye. Examination revealed bilateral anterior stromal keratitis with multiple subepithelial infiltrates and epithelial breakdown; infiltration and breakdown were more extensive in the left eye, as seen in this slit lamp photograph. There was relatively little conjunctival injection, and the best corrected visual acuity was slightly reduced in the left eye (at 20/25). He had been referred from the ophthalmology emergency department, where he had presented 7 days previously and had been treated empirically with topical chloramphenicol, which produced no improvement. Results of polymerase chain reaction analysis of a conjunctival swab obtained at that time were negative for herpes simplex virus. Two months earlier, he had had culture-proven *Salmonella* gastroenteritis, which had been followed 10 days later by conjunctivitis and polyarticular arthritis affecting the knees, ankles, and left elbow. At that time, his erythrocyte sedimentation rate was 84 mm/hour and antinuclear antibody, rheumatoid factor, and anti–citrullinated protein antibodies were absent. He was diagnosed as having salmonella-related reactive arthritis (ReA). At presentation to our clinic he was taking oral prednisolone (20 mg/day), as prescribed by his rheumatologist. ReA occurs in $\leq$4% of patients $\sim$1 month after an occurrence of gastroenteritis caused by *Shigella*, *Salmonella*, or *Campylobacter*. While the triad of ReA includes conjunctivitis, numerous other ocular manifestations have been described, including episcleritis, scleritis, and uveitis. Keratitis is a rarely reported manifestation of ReA. In this case, treatment with prednisolone acetate 1% drops led to complete resolution of the ocular symptoms within days, and disappearance of the clinical signs within 3 weeks. After 1 year, the keratitis has not recurred.

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