Eosinophil-Associated Inflammation and Elaboration of Eosinophil-Derived Proteins in 2 Children With Raccoon Roundworm (*Baylisascaris procyonis)* Encephalitis

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ABSTRACT. *Objective.* **Eosinophil-associated proteins, especially eosinophil-derived neurotoxin, may be important contributors to the neurologic pathology and symptoms caused by *Baylisascaris procyonis* infection.**

Methods. **Two cases of severe *B procyonis* encephalitis with evidence of marked eosinophil degranulation in the central nervous system are presented. Serial cerebrospinal fluid (CSF) specimens were collected from each patient during the course of their illness. Antibodies against *B procyonis* were measured in the patients' serum and CSF. Levels of the eosinophilopoietin interleukin-5 (IL-5) and 2 important eosinophil proteins, eosinophil-derived neurotoxin and major basic protein, were assayed in the CSF.**

Results. **Both patients had rapidly progressive central nervous system disease with evidence of eosinophilic meningoencephalitis. Both tested positive for antibodies to *B procyonis* in serum and CSF and had progressively worsening deep white matter changes on magnetic resonance images of the brain. CSF levels of IL-5, eosinophil-derived neurotoxin, and major basic protein were markedly elevated over controls.**

Conclusions. **This is the first report of the measurement of IL-5, eosinophil-derived neurotoxin, and major basic protein in human CSF. In addition to traumatic damage and necrosis caused by migrating larvae, eosinophil-derived neurotoxin from associated eosinophilic inflammation may be an important contributory factor in the pathogenesis of *B procyonis* encephalitis. *Pediatrics* 2001;108(5). URL: http://www.pediatrics.org/cgi/content/full/108/5/e93; *parasite, eosinophil-derived-neurotoxin, major basic protein, eosinophilia, hypereosinophilia, interleukin-5, encephalitis, child.***

ABBREVIATIONS. CSF, cerebrospinal fluid; CNS, central nervous system; MRI, magnetic resonance imaging; IL-5, interleukin-5; PBS, phosphate-buffered saline.

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Baylisascaris procyonis, the common raccoon ascarid, is a well-known cause of severe neurologic disease (neural larva migrans) in animals, with cases identified in >90 species of mammals and birds in North America.[1,2] Neural larva migrans and eosinophilic meningoencephalitis attributable to *B procyonis* have now been identified in 7 young children, including the 2 reported here.[3–7] We specifically note a novel correlation with elevated cerebrospinal fluid (CSF) levels of major basic protein and the neurotoxic protein eosinophil-derived neurotoxin associated with eosinophilic inflammation in these 2 cases. We hypothesize that the severe neurologic consequences of *Baylisascaris* encephalitis are attributable, in part, to marked eosinophil degranulation and release of these toxic eosinophil proteins in the central nervous system (CNS) of patients with this disease.

CASE REPORTS

Case 1

A 13-month-old boy became irritable 3 weeks before hospital admission, then became progressively irritable, ataxic, and weak. Three days before admission, he was unable to cruise, sit up, or walk, and exhibited dysmetria. He then had an episode of limb twitching followed by rigidity and decreased awareness of his surroundings. On admission, he was crying inconsolably, was hypertonic and hyperreflexic, and did not interact with his family or surroundings. Physical examination of this afebrile child revealed a left corneal abrasion and normal fundi, but no lymphadenopathy, hepatosplenomegaly, nor skin findings. A complete blood count showed 35% eosinophils (absolute eosinophil count: 7035/m^3). A lumbar puncture revealed 6 white blood cells/mm^3 and 1 red blood cell/mm^3, with 54% eosinophils, 23% lymphocytes, 19% monocytes, and 3% basophils, a protein of 21.9 mg/dL, and glucose of 74 mg/dL (Table 1). CSF *Streptococcus pneumoniae* antigen, stains for acid-fast bacilli, and cultures for mycobacteria were negative. Serum protein, electrolytes, renal function, and liver enzymes were normal. Stool was negative for *Giardia*, as well as other ova and parasites. *Toxocara canis* serology was negative. An echocardiogram was normal, and an abdominal ultrasound was negative. A computed tomographic scan of the head was normal, whereas magnetic resonance imaging (MRI) of the head showed iron deposition in the upper pons with minor white matter changes (Fig 1). An electroencephalogram was abnormal, with diffuse slowing of background activity, indicative of central nervous system dysfunction. Bone marrow examination revealed a normocellular marrow with increased eosinophils of normal morphology (20.6% eosinophils, left iliac crest; 26.6% eosinophils, right iliac crest); bone marrow chromosomes were normal. Lumbar puncture 2 days after admission revealed 5 white blood cells/mm^3 and 2 red blood cells/mm^3 with 73% eosinophils.

The child was treated with intravenous methylprednisolone (20 mg/kg/d) and subsequently with vincristine (0.6 mg/kg intravenously), 6-thioguanine (40 mg/m^2 by mouth), and prednisone (2

TABLE 1. Laboratory Values in Patient 1 With *Baylisascaris* Encephalitis

Illness day	21	50	58	125
CBC				
Hemoglobin (g/dL) Normals: 11.5–13.5	12.4	11.3	12.3	12.5
WBC (per mm³) Normals: 6,000–17,000	20 100	7 100	5 700	11 100
Platelets (per mm³) Normals: 150,000–450,000	466 000	520 000	464 000	670 000
Absolute eosinophil count (per mm³) Normals: 180–510	7 035	0	798	1 332
CSF				
White cells (per mm³) Normals: 0–5	6	2	3	1
Red cells (per mm³) Normals: 0–10	1	222	1	0
Eosinophils (%) Normal: 0	54	4	6	0
IL-5 (pg/mL) Control values: undetectable	281	27	36	<8
MBP (ng/mL) Control values: <8 ng/mL	50	<8	<8	16
EDN (ng/mL) Control values: ≤5 ng/mL	53	27	36	159

WBC indicates white blood cells; MBP, major basic protein; EDN, eosinophil-derived protein.

mg/kg/d by mouth). A prednisone taper was attempted, but when the eosinophil count began to increase, the taper was discontinued (Fig 2). The CSF interleukin-5 (IL-5), eosinophil-derived neurotoxin, and major basic protein were monitored (Table 1). His neurologic status did not significantly improve, and he developed opisthotonic decerebrate posturing. An MRI examination conducted 4 weeks after admission revealed severe cortical atrophic changes and severe diffuse white matter degeneration with abnormal basal ganglia and brainstem iron deposition (Fig 1). He continued to have an unremitting downward neurologic course. He remained in a chronic vegetative state and died 57 months after the onset of his initial symptoms. No autopsy was conducted.

Case 2

A 19-month-old boy with a history of developmental delay suffered the sudden onset of severe ataxia after 1 week of mild unsteadiness and a single emesis. His neurologic status declined rapidly despite therapy with empiric antibiotics, acyclovir and high-dose methylprednisolone. He became progressively more hypertonic and unresponsive over the next 8 weeks. Physical examination revealed an afebrile child with normal fundi, no lymphadenopathy, hepatosplenomegaly, or skin findings. A complete blood count revealed significant eosinophilia (absolute eosinophil count: 2232/m³; Table 2, Fig 2). A lumbar puncture revealed 121 white cells/mm³ and 8000 red cells/mm³ with 4% eosinophils, a protein of 50 mg/dL, and glucose of 52 mg/dL. CSF and blood bacterial and viral cultures were negative. Stool was negative for ova and parasites. Serologies for *Toxocara canis*, toxoplasmosis, and *Mycoplasma* were negative. The initial MRI of the head revealed minor white matter changes. Peripheral blood lymphocyte chromosome analysis revealed an XXXY (Klinefelter variant) genotype.

On day 60 of his illness, he exhibited severe diffuse hypotonia, cortical thumb positioning of the upper extremities, and rarely tracked with his eyes. The peripheral blood absolute eosinophil count was 2068/mm³. CSF analysis revealed 20 white cells/mm³ and 2 red cells/mm³, with 13% eosinophils. A computed tomographic scan of the chest and abdomen was normal. Bone marrow examination revealed a hypocellular marrow with 13% eosinophils. Immunosuppressive therapy was instituted with vincristine, 6-thioguanine, and prednisone, but no clinical improvement was noted. Serial MRIs of the head revealed ongoing severe white matter loss and cortical atrophy. The patient died of aspiration pneumonia 15 months after the onset of illness. An autopsy was declined.

METHODS

Informed consent was obtained from the patients' parents/guardians for diagnostic testing and therapy. Serum and CSF were tested for antibodies against *B procyonis* by indirect immunofluorescence assay using cryostat-sectioned third-stage larvae as antigen. Patient sera were tested in fourfold dilutions (from 1:16–1:4096) in phosphate-buffered saline (PBS), and CSF from undiluted to 1:1024. Sections were blocked with 1:10 normal goat serum, and reacted first with patient serum or CSF, and then with 1:200 fluorescein isothiocyanate-conjugated affinity-purified goat anti-human immunoglobulin G (IgG; H+L) with minimal cross-reactivity to bovine, horse, and mouse serum proteins (Jackson ImmunoResearch, Inc, Westgrove, PA). All washes were done with PBS and rinses with deionized water. Sections were examined using a Nikon Labophot-2 (Nikon Inc, Melville, NY) or Olympus BX-60 fluorescent microscope (Olympus America Inc, Melville, NY). Each batch included known positive and negative control sera and a PBS reagent (sample negative) control. Reactions were also compared with those of other positive and negative individuals, including 2 confirmed positive by brain biopsy.

Patient sera tested were from illness day 18 (patient 1) and day 39 (patient 2). Also tested were 5 sequentially-collected CSF samples from each patient, from illness day 21 to 125 (patient 1) and illness day 39 to 109 (patient 2). These were compared with remaining CSF samples from 12 children who had undergone diagnostic lumbar puncture in the course of evaluation for other disorders, including neuropathy, CNS vasculitis, headaches, growth retardation, Ebstein's anomaly, Burkitt lymphoma, and acute lymphoblastic leukemia. None of these controls had peripheral blood or CSF eosinophilia. Major basic protein was assayed by a 2-site radioimmunoassay [8]; eosinophil-derived neurotoxin was assayed by a double antibody radioimmunoassay.[9] IL-5 was measured by a 2-site radioimmunoassay according to the manufacturer's instructions (R&D Systems, Minneapolis, MN).

RESULTS

Serum and CSF from both patients were strongly positive for antibodies to *B procyonis* tissue, including cuticular structures, muscle, and intestine. Serum

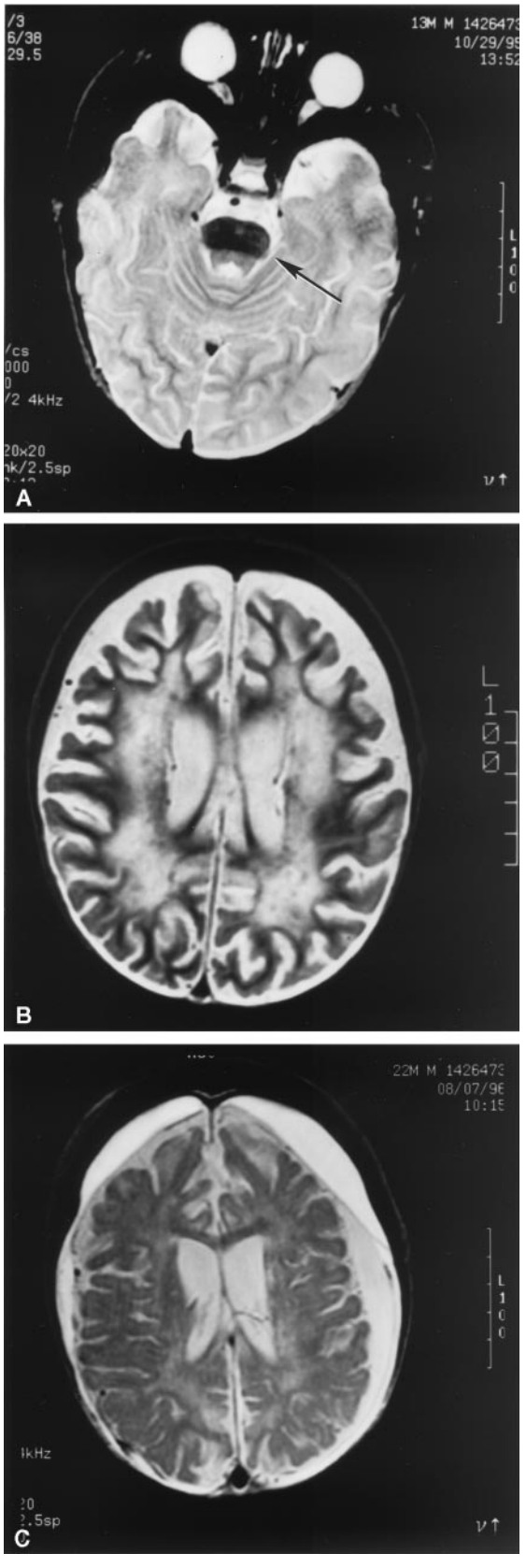

Fig 1. Sequential MRIs of brain of patient 1. A, Magnetic resonance T2 spin echo image at diagnosis: Iron deposition in the upper pons (arrow) and early white matter changes. B, MRI 4 weeks after diagnosis: Progressive T2 abnormalities with severe diffuse white matter degeneration; cortical surfaces collapsed onto each other. C, MRI 9 months after diagnosis: Additional evolution, showing nearly complete loss of cerebral white matter and development of bilateral subdural hematomas.

gave brilliant 5+ overall staining at 1:16, 4–5+ at 1:64, and 2–3+ at 1:256, with crisp cuticular staining and excellent differential staining of the intestine, the latter evident to >1:1024. With increasing serum or CSF dilution, overall staining quality and intensity decreased to negative (brownish), especially in cuticular structures and muscles, whereas differential staining of the intestine became increasingly evident and was titratable further. Based on this differential staining, both patients were judged positive (patient 1 between 1:1024 and 1:4096; patient 2–1:4096). Serum (1:64) from the positive control was 4+ positive, with excellent differential staining of the intestine (patient previously titered to 1:4096 and matching other known positives). Serum from the negative control was negative, the reaction being weak, dull, and uniform at 1:16 and negative (brown) at 1:64, matching other known negatives. The reagent control was also negative.

All CSF samples from both patients were positive for *B procyonis* antibodies, and increased in intensity and titer over time (samples 1–5). Patient 2 gave stronger reactions than patient 1, with intense 4 to 5+ reactions on undiluted CSF samples (Fig 3), as compared with 2 to 3+ for patient 1. Excellent differential staining of the intestine was noted (Fig 3). Patient 1 was judged positive to 1:16 in early CSF samples and 1:64 in later samples, whereas patient 2 was positive to 1:64 in all CSF specimens and weakly positive at 1:256 in later samples. CSF samples from the 12 control patients were negative.

Both patients had CSF levels of eosinophil-derived neurotoxin and major basic protein markedly elevated above control values (Tables 1 and 2). During treatment, the levels of both eosinophil-derived neurotoxin and major basic protein in the CSF fell, usually to normal, then rose again. IL-5 was detectable in all 4 CSF samples examined from each patient (Tables 1 and 2; Fig 2).

DISCUSSION

The diagnosis of *B procyonis* encephalitis in these cases is well-established. Both patients exhibited the typical clinical syndrome of *B procyonis* larval infection, both had peripheral and CSF eosinophilia, and both had strong serologic evidence of infection on indirect immunofluorescence testing of serum and CSF. Neither patient was seropositive for *Toxocara canis* or lived in or had traveled to areas where other causes of eosinophilic meningoencephalitis would be suspect.[6] Feral raccoons were common in the domestic environment in both situations. The families of both patients were able to document, in retrospect, a history of raccoon exposure. In addition to incidental exposure to feral raccoons, patient 1 was directly exposed to a pet raccoon kept in the home. Patient 2 had exposure to wood chips and soil in his yard, probably contaminated with eggs, similar to the patient described by Fox et al[4] For both patients, it is likely that ingestion of infective *B procyonis* eggs took place, through pica, geophagia, or other hand-to-mouth transfer, from areas or articles contaminated with raccoon feces.

Effective therapy for *B procyonis* encephalitis is yet

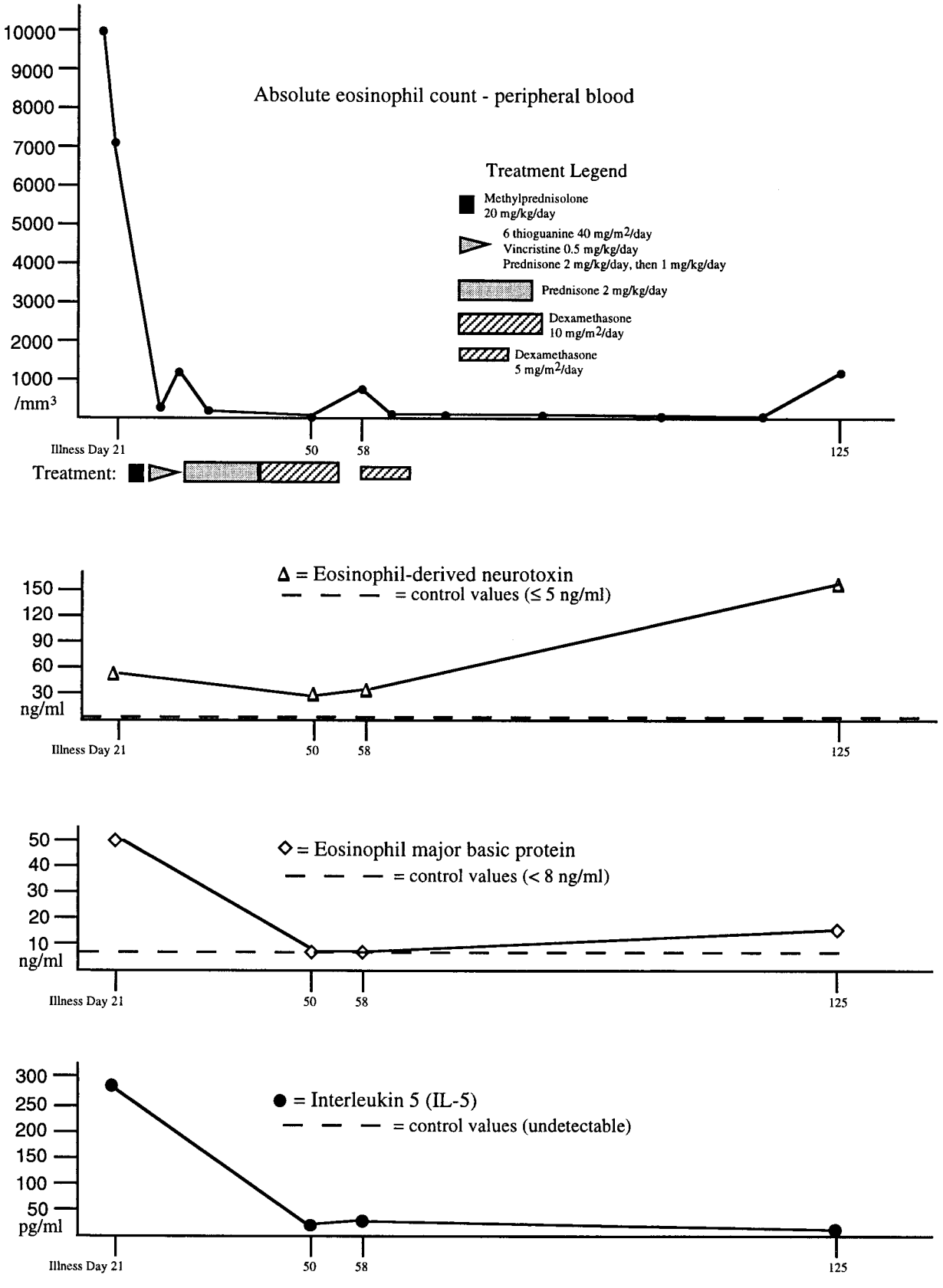

Fig 2. Laboratory values and treatment regimen for patient 1.

to be established, and *B procyonis* neural larva migrans carries a guarded to poor prognosis.[2] High-dose albendazole (25–50 mg/kg/d) given early in the infection has the potential to prevent or halt the progression of CNS disease.[2,10,11] Treatment with albendazole would be most beneficial before larvae

TABLE 2. Laboratory Values in Patient 2 With *Baylisascaris* Encephalitis

Illness day	3	33	60	79	109
CBC					
Hemoglobin (g/dL) Normals: 11.5–13.5	12.3	14.8	13.9	12.6	13.7
WBC (per mm^3) Normals: 6,000–17,000	12 400	11 100	9 400	5 700	14 300
Platelets (per mm^3) Normals: 150 000–450 000	387 000	279 000	347 000	542 000	378 000
Absolute eosinophil count (per mm^3) Normals: 180–510	2 232	2 442	2 068	57	3 718
CSF					
White cells (per mm^3) Normals: 0–5	121	165	20	1	36
Red cells (per mm^3) Normals: 0–10	8 000	23	2	76	61
Eosinophils (%) Normal: 0	4	19	13	5	67
IL-5 (pg/mL) Control values: undetectable	-	55	9	<4	167
MBP (ng/mL) Control values: <8 ng/mL	-	88	<8	<8	229
EDN (ng/mL) Control values: ≤5 ng/mL	-	112	<5	<5	768

WBC indicates white blood cells; MBP, major basic protein; EDN, eosinophil-derived protein.

reach the CNS. Because they abrogate inflammatory reactions, steroids are of likely benefit in cases of *B procyonis* encephalitis, provided that CNS damage is not too extensive or advanced. One nonfatal case was treated with thiabendazole, prednisone, and ivermectin, but without obvious improvement.[5] Ivermectin does not cross the blood–brain barrier, except perhaps through hemorrhage, and was undetectable in the CSF of the patient. Another child was treated with high-dose albendazole (40mg/kg x 28 days) and steroids, again without obvious clinical improvement but with apparent stabilization.[7] In both of these cases, the duration and extent of CNS damage and inflammation were likely too great, so that anthelmintic and steroid treatment offered little or no clinical benefit. However, such a combination of potent anthelmintic and antiinflammatory agents would still be recommended in similar cases, with treatment beginning as early as possible. From a diagnostic standpoint, the combination of CSF eosinophilia, white matter changes on MRI, and positive serology (serum and CSF) for *B procyonis* should allow for earlier consideration of this infection so that appropriate therapy can be initiated promptly. Unfortunately, in severe or advanced cases, therapy cannot be expected to reverse, but may rather abate the course of the illness.

Our patients were treated for idiopathic hypereosinophilic syndrome[12–14] while laboratory tests were undertaken to determine the etiology of their hypereosinophilia. Without an early diagnosis of *B procyonis* encephalitis, the idiopathic hypereosinophilic syndrome was an alternate explanation for our findings. However, this syndrome is rare and occurs most often in 30- to 70-year-old males; it is extremely unusual in childhood.[15,16]

B procyonis is a common parasite of raccoons, especially in the Midwest, Northeast, and on the west coast of the United States, where infection rates range from 68% to 82%.[1,2] Given the very high raccoon populations in many major metropolitan areas, and the tendency of many people to lure these creatures to their outdoor living areas through feeding, contamination of the domestic environment is common.[1,2,7] Infected raccoons shed an average of 20 000 to 26 000 *B procyonis* eggs/g of feces; thus, they can shed millions of eggs each day.[1,2] Infective eggs are very resistant and, given adequate moisture, can last for years in the soil. Because of the concentration of *B procyonis* eggs at raccoon latrines, these sites are important long-term sources of infection for both animals and humans.[1,2] Raccoon latrines contain an abundance of undigested seeds and other items, which are attractive to various animals and probably also to inquisitive young children.[2] Other areas contaminated with raccoon feces (eg, barns, decks, patios) are also potential sources of infection.[1,2] Infants and toddlers who exhibit pica and geophagia are at the greatest risk of heavy infection, and most cases of *B procyonis* encephalitis can be expected in this age group. It is interesting to note that one of our patients (patient 2) had a variant of Klinefelter syndrome and another reported fatal case had Down syndrome.[4] Individuals with developmental impairment may be at special risk for infection because of a greater tendency to exhibit those behaviors that result in egg ingestion. It is clear that prevention of this devastating infection in young children and others is of considerable importance.

It is well-known that *B procyonis* migration in the CNS stimulates marked CNS inflammation, and that the primary manifestation is eosinophilic inflamma-

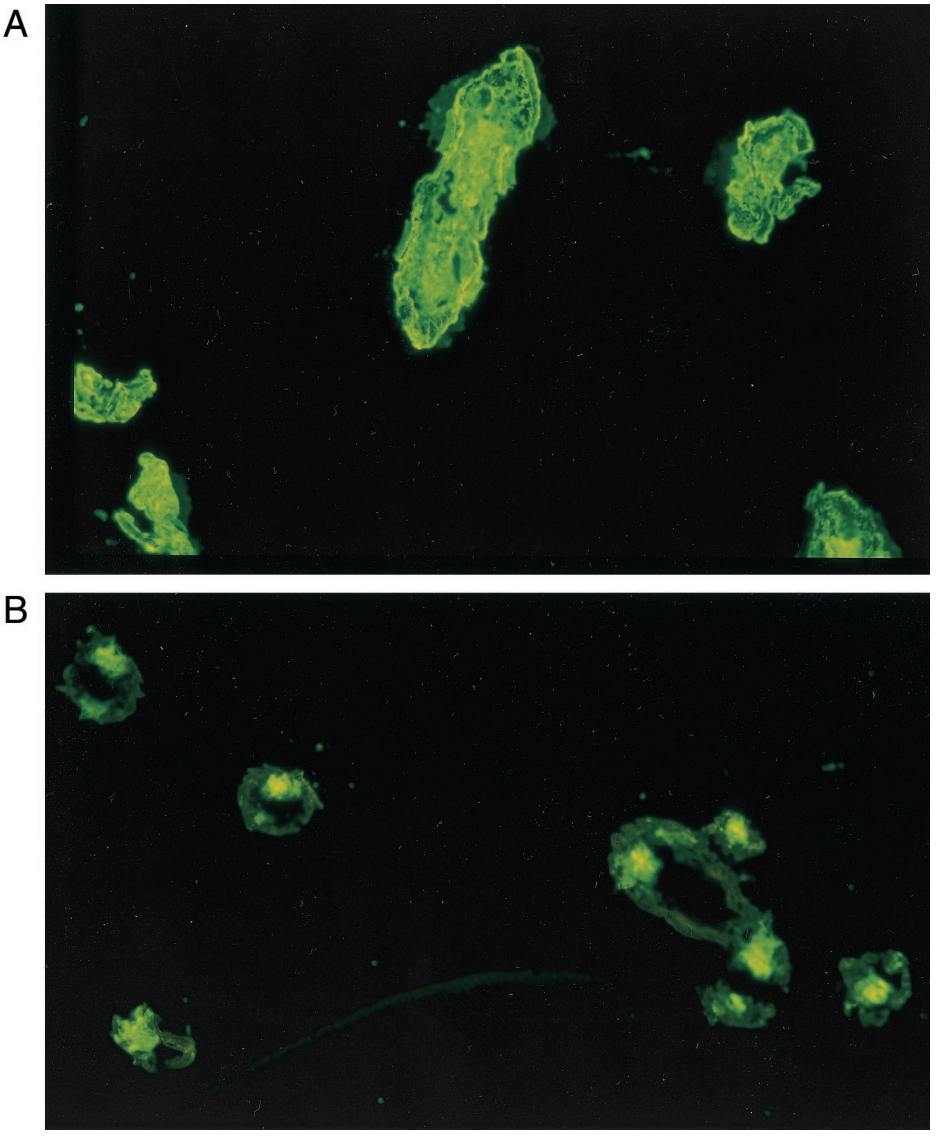

Fig 3. Positive indirect immunofluorescence assay of CSF from patient 2 showing: A, bright staining of *B procyonis* larval cuticle and internal organs (undiluted CSF) x 50. B, differential staining of larval intestine (central, brighter area in worm) (1:16 CSF dilution) x 50.

tion. Our findings of markedly elevated CSF IL-5 (up to 167–281 pg/mL), eosinophil-derived neurotoxin, and major basic protein are novel. IL-5 is the predominant eosinophilopoietin produced by cloned T cells of hypereosinophilic patients.[17,18] IL-5 also functions as a chemoattractant for eosinophils[19] but is not known to possess neurotoxic or encephalopathic activity. Increased susceptibility to intracranial dissemination of *Angiostrongylus cantonensis* in IL-5α-deficient mice has been reported, reinforcing the importance of IL-5 in the induction of eosinophil-associated killing of invasive helminths.[20]

In addition to direct damage produced by the migrating larvae and their products, it is likely that eosinophil-derived neurotoxin contributes to the neurologic manifestations of *B procyonis* encephalitis. The link between eosinophils and neurotoxicity was first described by M. H. Gordon in 1933. Extracts of tissues from suspected cases of lymphadenoma (Hodgkin's disease) were injected into the brain and marginal ear veins of rabbits, which developed "muscular rigidity combined with incoordination and ataxia," often fatal within 10 days.[21] This phenomenon, originally thought to be caused by a thermostable virus, has since been known as the "Gordon phenomenon." More recent investigations have shown that the occurrence of the Gordon phenomenon depends on the presence of eosinophils in the tissue from which suspensions are derived.[22] A specific causative agent, eosinophil-derived neurotoxin, was eventually isolated and purified in 1981.[23] Experimental animals suffering manifestations of the Gordon phenomenon, such as paralysis or ataxia, are usually killed; animals with mild or moderate reactions may recover essentially all of their normal abilities. The Gordon phenomenon can be provoked by a single intrathecal dose of eosinophil-derived neurotoxin as low as 0.15 μg in New Zealand white rabbits.[24] Based on an estimated rabbit CSF volume of 10 mL,[25] this yields an approximate concentration of 15 ng/mL. The highest concentrations of eosinophil-derived neurotoxin measured in the CSF of our patients ranged from 159 to 768 ng/mL. In contrast, the mean value in CSF specimens from 12 nonaffected

patients was <5 ng/mL. The CSF levels of eosinophil major basic protein were also markedly elevated, with values from 50 to 229 ng/mL versus a mean of <8.0 ng/mL for controls. Although increased levels of eosinophil-derived neurotoxin and major basic protein in human sera have been recorded in tryptophan-associated eosinophilia-myalgia syndrome,[26] this report is the first to simultaneously record eosinophil-derived neurotoxin and major basic protein in the CSF of normal and parasite (*B procyonis*)-infected humans.

The development of the Gordon phenomenon after intrathecal injection of eosinophil-derived neurotoxin in animals closely parallels the clinical observations of *B procyonis*-infected animals and humans. Durack et al[22] described a syndrome of stiffness and ataxia, progressing to severe paralysis in rabbits after intrathecal injection of eosinophil-derived neurotoxin. Histopathologic examination of the central nervous system from these animals revealed diffuse spongiform demyelination, most prominent in the cerebellum, brainstem, and spinal cord.[23] In our patients, and other previously described cases of human *B procyonis* infection, ataxia and related CNS signs were early manifestations.[3–7] Severe white matter changes were also observed by MRI in our patients (Fig 1).

CONCLUSION

Two cases of severe *B procyonis* encephalitis with evidence of marked eosinophil-associated inflammation constitute the first report of a direct association of CSF eosinophil-derived neurotoxin and human disease, and may explain the severe neuropathologic manifestations of *B procyonis* infection. In addition to traumatic damage and necrosis caused by migrating larvae, eosinophil-derived neurotoxin from associated eosinophilic inflammation may be an important contributory factor in the pathogenesis of *B procyonis* encephalitis. Indeed, the inflammatory reaction to a parasitic infection is a double-edged sword, providing the ability to resist infection but at the expense of damage to normal host tissues.

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Eosinophil-Associated Inflammation and Elaboration of Eosinophil-Derived Proteins in 2 Children With Raccoon Roundworm (*Baylisascaris procyonis)* Encephalitis

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