

Cat-Scratch Encephalopathy

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The first case of encephalopathy associated with cat-scratch disease was published more than 50 years ago.¹ At that time, cat-scratch disease itself had been described only recently in the English-language literature, by Greer and Keefer,² but without allusion to neurologic involvement. As they reported, an acute febrile illness affecting patients with a history of close contact with cats or kittens had been noted since 1932 by Lee Foshay, MD, of Cincinnati, Ohio, who coined the term *cat-scratch disease* and prepared an antigen that he used for skin testing in similar patients. However, these cases were not reported, and the condition was not widely known.

As Greer and Keefer² reported,

“cat-scratch fever” . . . is a term first used by Dr Lee Foshay, of Cincinnati, to describe lymphadenitis of unknown etiology following cat scratches. The disease is suggestive of, but much milder than, tularemia. A cat contact is invariable. Although it is a systemic disease associated with malaise, fever and other general symptoms of an infection, the brunt of the infection is borne by lymph nodes. Symptoms referable to other systems are usually minor and transitory. . . . The infective agent has never been identified. . . . Debré and his co-workers have recently described this disease syndrome in the French literature under the name “La maladie des griffes de chat”. These authors stated that they had studied 10 such cases but reported in detail only 1 case. They also noted a positive reaction to the Foshay cat antigen.^{2(p545)}

Debré and colleagues³ in France had described the characteristic lymph node enlargement, suppuration, and prolonged drainage, and emphasized the benign course of the disease, but also did not mention neurologic involvement.

We usually speak of the condition using the imperfect designation, cat-scratch disease. . . . The essential lesion involves a self-

resolving subacute suppurative adenopathy that can be single or multiple in the given area of involvement. The fistula that develops dries up after several weeks or months. . . . Without inappropriate surgical or medical interventions, a spontaneous course towards cure is slow, but definite.^{3(pp76-78)}

These reports were rapidly followed by other articles, and it soon became obvious that this condition was not rare. Daniels and MacMurray⁴ reported their experience based on 160 cases, and the skin lesions and lymphadenopathy were analyzed in detail.

During the past four years hundreds of cases of cat-scratch disease have been reported from Europe and America. This newly recognized clinical entity . . . which has an excellent prognosis, may often mimic the more serious granulomatous and neoplastic diseases of lymph nodes. . . . Approximately half of the patients had an initial skin lesion that persisted for many weeks. It usually consisted of a scratch or a papule. If a scratch, it was either diffusely or locally inflamed, scabbed, or healed to a raised, indolent-appearing papule or dark red scar. If papular, it was sometimes surmounted by a vesicle or pustule, sometimes resembled an insect bite, and occasionally was ulcerated with scabbing or crusting. . . . The regional lymph nodes were usually markedly enlarged, often to the size of a golf ball or larger. Some were elastic and painless, but usually there was tenderness with redness, heat, and swelling of the

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overlying skin. . . . Suppuration, with sterile pus, occurred in 47 of the cases.^{4(pp1247-1248)}

NEUROLOGIC INVOLVEMENT

Encephalopathy was not described as one of the complications of the disease until 1952, when Stevens¹ made a retrospective diagnosis in a patient who presented in 1949 with features typical, albeit unrecognized, of cat-scratch disease.

L.H., a 13-year-old white boy . . . had been well until March 17, 1949, when he suffered headache, and a temperature of 100.4 F. was noted. At the same time a small, crusted papule was present on the right forearm, and the right epitrochlear and particularly the axillary lymph nodes were enlarged and tender on the right side. . . . The skin showed pale erythematous flat coalescent lesions on the trunk, and a small raised papule was noted on the right forearm, suggesting a bite to the examiner. . . . The eruption described above faded in the next two days, but the axillary lymph node on the right increased to the size of a large olive. . . . The right axillary lymph node enlarged, reaching the size of a small egg, and suppurated. On May 9 about 12 cc of greenish pus was aspirated from the axillary abscess and examined. There was an abundance of pus cells, a few red blood cells, some epithelial cells, and a large amount of fibrin; no organisms were found.^{1(pp219-220)}

This febrile illness was complicated by seizures, an altered mental state, and then an almost miraculous full recovery.

One week after the onset the patient had a generalized convulsion, lapsed into deep coma. . . . The neurological examination on that day revealed a restless, comatose, well-developed boy, who was incontinent of urine and feces. . . . Generalized convulsions, at times proximating status epilepticus, continued in spite of large intramuscular doses of phenobarbital sodium, and several paroxysms of opisthotonos, typical of mesencephalic seizures, were observed . . . fever and clinical symptoms showed a rapid defervescence . . . the temperature was normal and the patient was lucid. . . . The patient is a robust, energetic and well-adjusted boy at present.^{1(pp219-222)}

The excellent long-term neurologic outcome typically encountered in this disease was confirmed by later authors. In a series of 61 pa-

tients with cat-scratch encephalopathy, Carithers and Margileth⁵ stated:

There were no deaths in this series. . . . Approximately two thirds of the patients recovered fully in 4 weeks and none showed any evidence of encephalopathy after one year. . . . Over 50% of patients were followed up for more than 2 years. To date, no lasting neurologic impairment due to CSDE [cat scratch disease encephalopathy] developed in these 61 patients. This form of encephalopathy is probably the least hazardous of any caused by direct central nervous system infection or serious response of the central nervous system to infection or toxins.^{5(pp100-101)}

INVESTIGATIONS AND DIAGNOSIS

In the case reported by Stevens,¹ results of all investigations were negative at the time of initial examination, and the case remained a diagnostic conundrum. It was only much later, when descriptions of cat-scratch disease appeared in the English-language literature, that a retrospective diagnosis was made and the diagnosis was confirmed with a skin test:

. . . two lumbar punctures were obtained . . . the results were negative in every respect. Cerebrospinal fluid was examined for virus . . . the results were negative. . . . The heterophile antibody reaction was negative. Repeated tuberculin skin tests elicited negative reactions. Roentgenograms of the chest and skull were normal. . . . The reaction to acid-fast stain was negative, and a concentration test revealed no tubercle bacilli. No growth was obtained upon repeated culture. The pus was inoculated intraperitoneally and subcutaneously in guinea pigs, and the animals were killed and autopsies done about six weeks later. There was no evidence of tuberculosis or tularemia. . . . As a consequence of the recent publication of descriptions of cat-scratch fever, a retrospective diagnosis was made over two and one-half years after the illness occurred. . . . One-tenth cubic centimeter of antigen, kindly supplied by Dr Worth Daniels, was injected subcutaneously into the patient. The test was read in 48 hours, at which time a reaction measuring 3 in. by 3 in. was observed, which persisted for 10 days and then faded.^{1(pp219-220,222)}

This "antigen" was prepared from the lymph nodes of patients previously diagnosed as having the

disease, as described by Daniels and MacMurray,⁴ who, on the basis of their work, were able to supply this to other physicians. As would be expected, these extracts varied in potency. Nevertheless, this intradermal test was the only method for confirming the diagnosis of cat-scratch disease then.⁴

Antigen for the intradermal test was prepared from pus obtained from suppurative nodes by aspiration or at operation. It was diluted . . . when sterility had been proved, 0.1 ml was injected intracutaneously. At 48 hours a positive reactive was indicated by a central papule . . . or an area of erythema. . . . Twenty-four different antigens were used. The intensity of skin reaction to these varied considerably. Some produced a firm central papule . . . others only a small area of erythema. . . . It is obvious that each antigen must be tested on known positive reactors prior to relying on its value as a diagnostic material.^{4(pp1248-1250)}

ETIOLOGY

Daniels and MacMurray⁴ were emphatic on the association of this disease with feline contact: "It should be emphasized that in almost all cases there was known contact with cats. The majority of patients remembered a definite preceding instance in which a cat scratch was received." Indeed, this proved to be the case in Stevens' patient with encephalopathy¹: "Upon further questioning, the patient recalled being scratched many times by his pet cat before and after his illness, but he cannot recall the details."

The infective agent eluded identification for decades, partly because initial smears and cultures were negative, and a viruslike agent was presumed. It was only in 1983 that interest in a bacterial agent was rekindled when, using the Warthin-Starry silver stain, Wear and coworkers⁶ reported finding the presence of small pleomorphic gram-negative argyrophilic bacilli in lymph nodes. A novel organism, *Afipia felis*, was isolated by these workers and proposed as the cause of cat-scratch disease. However, doubt about the pathogenic role of *A felis* arose in 1992, when Regnery and coworkers⁷ reported the serendipitous finding of high serum titers to antigens from another organism, *Rochalimaea henselae*,

in patients with cat-scratch disease. In contrast, serum titers to antigens from *A felis* were low. The issue was settled in 1993, when Dolan and co-workers⁸ isolated *R henselae* instead of *A felis* from the lymph nodes of 2 patients who satisfied the clinical criteria for cat-scratch disease.⁸

Biopsy material was placed on saline-soaked gauze and carried directly to the microbiology laboratory . . . plated onto chocolate and CDC [Centers for Disease Control] anaerobic blood agar. . . . Analysis of whole-cell fatty acids was done. . . . The identification of the bacteria was confirmed by using a combination of the polymerase reaction (PCR) amplification. . . . *Afipia felis* (strain B.V.) was subcultured onto blood agar under identical conditions to show that *Afipia* could be grown using the method described here to isolate *R henselae*. . . . Both patients discussed had tender adenopathy in an extremity; cat exposure; and histopathologic findings compatible with cat scratch disease. Routine cultures of the nodes would ordinarily have shown no growth and would have been discarded at 72 hours . . . the isolation of *R henselae* requires that the culture plates be held much longer than is customary in clinical labo-

ratories and be incubated in an increased CO₂ environment.^{8(pp332-334)}

In retrospect, the early investigators' inability to isolate any organism despite the plentiful clinical material available can probably be attributed to fastidious culture requirements and the prolonged incubation times required. This organism has since been renamed *Bartonella henselae*, and serologic testing for antibodies to *B henselae* is now the usual method used to confirm a diagnosis of cat-scratch disease. This interesting condition, which carries a good long-term prognosis, needs to be remembered in patients presenting with an otherwise unexplained change in sensorium, with or without seizures, especially if there is a history of contact with cats.

Accepted for publication December 27, 2002.

This study was supported in part by a departmental grant (Department of Ophthalmology) from Research to Prevent Blindness Inc, New York, NY, and by core grant P30-EY06360 (Department of Ophthalmology) from the

National Institutes of Health, Bethesda, Md. Dr Newman is the recipient of a Research to Prevent Blindness Lew R. Wasserman Merit Award.

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