Subacute sclerosing panencephalitis was probably first described by Schilder in 1924 (1) under the name “encephalitis periaxialis diffusa.” Other cases were studied by several investigators who, because of the natural variation of the disease and the use of various staining procedures, tended to stress the differences among cases rather than the similarities (2–6). Not until the late 1940s did it become clear that Dawson’s inclusion body encephalitis, van Bogaert’s subacute sclerosing leucoencephalitis, and the panencephalitis of Petté and Döring were indeed all one and the same disease, now known as subacute sclerosing panencephalitis (SSPE) (7).

CLINICAL SIGNS AND SYMPTOMS

The clinical course of the disease is now usually divided into four stages (8). Stage 1 is often very subtle in its manifestations and includes decreased intellectual skills, rapid swings in mood, inappropriate affect, poor attentiveness in school, and reduced scholastic ability. Drooling and speech changes are occasionally seen in stage 1. Since these changes are usually not indicators of serious organic disease within the age group who contract SSPE, it is not surprising to find that many children are first brought to school principals’ offices for discipline and to child psychologists for evaluation before coming to a physician. Stage 2 is heralded by dramatic neurologic signs which belay any question of objective neurologic disease. It is at stage 2 where the physician usually makes first contact with the patient. Myoclonic jerks and stumbling while walking are the hallmarks of the major motor signs. Ataxic, choreoform, and athetotic movements are also seen. Generalized convulsive fits will complicate a small percentage of cases. Ocular signs are seen in approximately 50% of the cases. The signs vary: cortical blindness, optic atrophy, chorioretinitis frequently involving the macula, and extrinsic ocular palsies all have been reported (9). Stage 2 is the level at which the disease shows greatest variability (10). “Spontaneous remission” (11) or perhaps more properly arrest can occur at this time. Although
up to 80% of patients in some series (12) perish in 9 months, survival for over 8 years has also been reported (13).

The disease usually passes quickly into stage 3, which is characterized by marked mental loss, loss of speech function, coma, opisthotonus, extensor plantar responses, decerebrate rigidity, and decorticate posturing. The coma may last several months. Derangements in autonomic nervous function such as pallor, flushing, and instability of temperature homeostasis are also seen. If the patient does not succumb to the complications of long term coma, usually respiratory or urinary infection, he passes into stage 4. The stage 4 patients may seem improved, but in fact a state of near total loss of cortical function exists. Startle responses to noise may be seen but other than this, very little integrated nervous system function remains. Wandering eye movements, episodic laughing or crying, hypotonia, and flexing of the arms and legs with turning of the head to one side complete the picture of stage 4 SSPE. The derangements of autonomic function and complications of care for such a neurologically crippled patient usually lead to the patient's demise, and death ensues due to vasomotor collapse and/or infectious complications.

EPIDEMOLOGY

Due to the relative infrequency of SSPE and the possible decline in incidence, current epidemiologic data are scant. Though exact numbers vary, there appears to be a male preponderance with attack rates of up to 3.3:1 (8). The geographic data suggest that there is a proclivity to occur in the southeastern United States. It occurs with an incidence of approximately one per million in the United States (14). More than 50% of the patients have a history of clinical measles at less than two years of age (14), suggesting that immaturity of the immune system may be a contributing factor (15) (see Figure 1). The clinical onset usually occurs between ages five and twelve with a mean of near ten (see Figure 2). The "incubation period" following clinical measles is usually six years (16). There is evidence (14, 17) in favor of an increased incidence in rural areas. The incidence in cities with populations greater than one million is 0.475 per million, but this is confounded by the fact that there are few cities with populations in excess of one million in areas where SSPE is most prevalent (17).

DIAGNOSIS

Prior to the demonstration of recoverable measles virus from brain tissue of patients with SSPE, much circumstantial evidence was accrued to implicate the measles virus as the etiologic agent (1). It was from this work that practical tests for diagnosis were developed (18). The most useful and specific clinical tests involve serologic and biochemical examination of cerebrospinal fluid (CSF) and serum. Routine examination of CSF from patients with SSPE rapidly disclosed a high frequency of patients with an elevated gamma globulin level and paretic colloidal gold curve (19, 20). The globulin level is often elevated well beyond the normal range of less than 10% of the total protein (21). Finding a normal level does not exclude
Figure 1 Age of reported measles infection registry through 1971. Figure courtesy of Dr. J. T. Jabour.

the diagnosis. Using albumin as a marker of the integrity of the blood-brain barrier, Tourtellotte (20) was able to calculate that 95% of the increased gamma globulin was due to local production within the central nervous system (CNS). Other investigators (22), using intravenous administration of radioisotopically labeled immunoglobulin G, demonstrated by kinetic analysis that the major portion of CSF immunoglobulin G in patients with SSPE was derived from a nonvascular source. This added credence to the concept of endogenous synthesis of immunoglobulin G within the CNS of SSPE patients. Electrophoretic separation of SSPE spinal fluid frequently shows a pattern of from one to five distinct bands migrating to the far cathodic region of the globulin smear (23). This pattern is called the oligoclonal aspect and is seen in few other diseases, e.g. CNS syphilis, multiple sclerosis, and CNS trypanosomiasis. There is increasing evidence that these bands represent homogeneous groups of measles-specific antibody (24, 25). It was ultrastructural examination suggesting myxo- or paramyxovirus viral inclusions coupled with elevated CSF gamma globulin levels that led to investigations of viral antibody titers in patients with SSPE. Connolly described three patients in 1967 with elevated titers
to measles in both serum and CSF (26, 27). Connolly’s observation was rapidly supported by other investigators (28–33). The high serum titer to measles in patients with SSPE was surprising, often being higher than the titers observed in recovery from acute natural measles (28, 33). The specificity of elevated measles titers was strengthened by the demonstration that the ratios of CSF to serum titers of measles were significantly reduced compared to polio titers (28), and by the demonstration that only the measles titer remained elevated at high titer on longitudinal examination of two patients with 13 different viral antigens over a seven-month period (32). The corollary to the experiments using complement fixation (CF) and hemagglutination inhibition (HI) titers was the demonstration of measles antigen within the inclusion bodies of neurons and oligodendrocytes by immunofluorescence (34). Though immunofluorescence is very sensitive, it does require brain biopsy. Determination of serum and CSF measles titers requires only a venipuncture and a lumbar puncture. Due to the relative ease and great specificity of these simpler tests, they have virtually replaced the need for brain biopsy in making the diagnosis (36). Of the four tests, HI and CF done on both serum and CSF, the CF test on CSF is clearly the best single test. However, reliance on a single test will miss a percentage of cases (35). Currently, only six states provide all four tests. Twenty two states provide CF testing CSF. A complete listing of the tests available in the various states has recently been reviewed (35).

The electroencephalogram (EEG) can be very helpful in making the diagnosis. Examination of the EEG also has helped to reveal that the measles virus may exhibit more neurotropism than was once appreciated. In one study of 680 patients with
clinical measles without any outward evidence of CNS involvement, 51% of patients demonstrated abnormalities in their EEGs during the acute or postacute phase of their illness (37). In the same study, 37 patients from the total population of 717 had clinical encephalitis. Multinucleated giant cells and typical inclusions were seen in pathologic specimens. In addition, the measles virus has been isolated from brain specimens of patients with measles encephalitis (38), suggesting that this illness may represent true measles infection of the brain and not simply an immunologically mediated response to measles virus.

In SSPE, the EEG pattern of suppression, burst is characteristic. The pattern consists of high amplitude slow delta waves occurring at regular 3-sec intervals (8) (see Figure 3). These findings are, however, variable and repeat tracings may be required to demonstrate the typical EEG pattern. Once seen, the suppression burst pattern is quite specific. The EEG may revert to normal after abnormal records have been obtained (11). In one series (39), 6 of 11 patients examined an average of six months after onset of disease and normal EEGs. One patient had a normal EEG at the time of well developed myoclonus. Though all patients eventually developed abnormal encephalograms, only 4 showed the classical suppression burst pattern.

PATHOLOGY

It was from close inspection of the cellular changes in pathologic brain specimens obtained both by biopsy and necropsy that the clues to viral pathogenesis of SSPE were manifest. Among the early investigations of SSPE brain, it was Dawson in 1933 and 1934 (2, 3) who called attention to eosinophilic Cowdry type-A inclusion bodies in the cytosol and nucleus of cortical neurons. Both oligodendroglia and neurons are involved in the process. With the exception of inclusion bodies the pathologic picture is not unlike that of any primary viral encephalitis.

It has been noted that there is more white matter demyelination and sclerosis in late cases while intranuclear inclusions are more readily demonstrable in cases of short duration (40). The histology is one of varied neuronal loss with occasional neuronophagia, leptomeningeal infiltration with lymphocytes and plasma cells, perivascular cuffing in both central white matter and throughout the cortex, and scattered microglial nodules. If examined post mortem, the inflammatory reaction may be minimal or nonexistent with neurons showing Alzheimer's neurofibrillary changes (40). The earliest change is the appearance of small intranuclear inclusion bodies approximately 1–2 μm in diameter (41). They are frequently multiple and differentiable from the nucleolus by their eosinophilic staining characteristics. These bodies do not stain with the Feulgen reaction for DNA but rather show intense pyroninophilic staining, indicating a high content of RNA. The inclusions occasionally measure up to 3 μm and are no longer differentiable from Cowdry type-A inclusions. On ultrastructural analysis these inclusions termed the nucleoliform inclusions appear as collections of loosely packed granules measuring 300–500 Å. The Cowdry type-A particles enlarge, nearly filling the nucleus and leaving a pale halo surrounding the inclusion. These inclusions are a second type called the multitubular inclusions due to their appearance on electron microscopy.
Figure 3  Typical electroencephalogram in subacute sclerosing panencephalitis. Periodic bursts of high voltage activity are demonstrated. Reproduced from J. Am. Med. Assoc. 207:2248 (1969).

(40). The multitubular inclusions show much less staining with pyronin but have a high affinity for protein stains. Multitubular inclusions are collections of tubules with an outside diameter of 170–190 Å and an inside diameter of 40–60 Å. They measure up to 12 μm. The tubules are usually randomly dispersed but occasionally are closely packed as a pseudocrystalline array. The third type of inclusion, the cytoplasmic inclusions, vary in size but ultrastructurally are very similar to the multitubular inclusions seen in the nucleus. They consist of the 180-Å tubules with a superimposed course and dense granular component. The cytoplasmic inclusions show high affinity for both pyronin and bromosulfalein, indicating the presence of both RNA and protein (40, 42–44). By using immunochemistry several investigators have shown that immunoglobulin G, immunoglobulin M, and complement (45–47) are bound by the cellular inclusions in SSPE brain tissue. Neutralizing antibody against measles virus has been eluted in low concentration from SSPE tissue and was shown to be directed against the nucleoprotein core of the virus and not against any of the surface antigens (47).

ETIOLOGY

It was the clues from electron microscopy and serology (discussed under diagnosis) which led investigators to make attempts to isolate a myxovirus or paramyxovirus
particle from patients with SSPE. Many techniques were tried by investigators only to end in failure (30, 48–50). Eventually measles antigen, syncytia formation, and recovery of fully infectious virus was achieved using the technique of co-culture of SSPE brain tissue with HeLa cells (51–53).

Thus, it became clear that SSPE is a slow virus infection of the brain caused by measles virus (54). What is not as yet clear is what events allow the rare patient who is exposed to wild measles to develop a smoldering, progressive infection within the CNS. Central to this issue is whether the virus is different from the usual measles virus or whether the host’s response to a common agent is somehow varied from normal so as to allow a chronic infection to occur.

Genetic susceptibility is unlikely, as the disease has occurred in only one of a pair of identical twins (55). The age of measles infection (14, 15) and/or simultaneous infection with other viruses such as varicella (17) seem to be important factors in the pathogenesis of SSPE.

SSPE may be more of a systemic disease than is clinically apparent. With the use of indirect immunofluorescence, measles antigen has been found in lung, kidney, and spleen in addition to brain (47). Co-cultivation techniques have rescued live measles virus from lymph nodes of patients with SSPE in some cases (56). To date there are no viral isolations from the thymus glands of SSPE patients (57).

The virus recovered from patients with SSPE is a measles-like virus which shows an antigenic composition which differs from both the wild-type measles and the Edmonston vaccine strain (58). As more strains of SSPE virus are being isolated from patients it is becoming apparent that there is significant biologic and antigenic heterogeneity of the viral SSPE isolates (58, 59), as is the case with both wild and vaccine strains of measles. For example, Hamilton & Barbosa reported on a comparison of two strains of SSPE and Edmonston strain (60). They showed that one of the SSPE strains (Dean) was similar to Edmonston when examined by growth characteristics, morphology, infectivity, and antigenicity. The other SSPE (Halle) strain was markedly different from both the Edmonston strain and the DEAN strain. There is little doubt that significant biologic changes in SSPE virus occur as a consequence of sequential in vivo passage while infecting human brain, not to mention the possible effects of cellular fusion during co-culture required to rescue live virus. When antibody assays from patients with SSPE were measured by complement fixation of hemagglutination inhibition, similar titers were obtained whether SSPE or Edmonston strain antigens were used in the assay (58, 59). However, the neutralization titers revealed a 4- to 8-fold decrease in titer of SSPE sera assayed against SSPE virus as opposed to wild-type measles virus (59). This is consistent with the findings of greater CF titers than HI titers in patients with SSPE, and has been interpreted to represent antibody response elicited against the nucleoprotein core as opposed to the site of neutralizing antibody, namely the outer envelope (35).

One very interesting strain has been isolated in Japan by Doi et al (61). This particular variant of SSPE virus appears to be absolutely cell associated. It causes isolated plaques in tissue culture as virus seemingly spreads from cell to cell without cycles of liberation of free virus into the supernatant fluid with subsequent infection.
of nearby cells. Ultrastructurally the virus causes several differences compared with a productive SSPE measles infection in the same cell line (62). However, the virus does induce surface membrane changes. The membrane changes with the Japanese strain appear continuous along the cell surface, and not as discontinuous areas with alignment of tubules followed by formation of mature budding particles as seen in productive infection. Though no free virus is formed, anti-measles serum will block infection of tissue culture if applied prior to cellular fusion. Hence, it seems that the measles virus is expressed in an incomplete form at the level of the plasmalemma.

One other question which has arisen with respect to SSPE virus is whether it is a paramyxovirus closely related to measles, but which resides primarily in an animal reservoir. This search was promulgated by the relative rural distribution of SSPE cases. Indeed antibody to canine distemper virus is present in patients with SSPE (63). Though such antibody is seen in patients convalescing from wild measles infection, the titer is significantly increased in patients with SSPE (63). The relevance of this is unclear as distemper virus causes a homotypic antibody response whereas measles infection frequently leads to positive, albeit low, titers to distemper (32). In addition, superinfection with canine distemper is a possibility (63). There is evidence for such a suggestion since the Japanese strain of Doi did not block superinfection with other viruses in chronic in vitro SSPE viral infection (61). Transfer of vaccine measles, SSPE virus, and canine distemper virus to lambs and calves is relevant to this problem. Attempts to do this resulted (64) in neurologic symptoms in a few of those animals given SSPE virus. The animals given vaccine measles and canine distemper developed homotypic antibody but no neurologic symptoms. On the other hand, the animals given SSPE virus did not show any HI antibody response, but measles antigen could be demonstrated in brain material by fluorescent antibody techniques. Whether infection from an animal reservoir carrying a variant of measles is relevant to human SSPE is an unresolved point at present and further study will be needed to answer the question.

The nature of the host immune response in SSPE continues to be a source of confusion. Earlier it was felt that cellular immunologic abnormalities were present in patients with SSPE. Gerson & Haslam (65) reported depressed cellular immune function to six common skin test antigens, dinitrochlorobenzene responsiveness, and delayed allogenic skin rejection in four patients with SSPE. They also showed decreased germinal center activity in lymph nodes following diphtheria-tetanus toxoid boosters. The question arose as to the specificity of these immunologic anomalies and indeed whether they were primary or secondary events in pathogenesis. Good et al (66) reported on several children with congenital agammaglobulinemia who were unable to produce antibodies and had only insignificant levels of immunoglobulins in the circulation. On contracting measles, these children showed a normal progression of signs and symptoms and were subsequently immune to reinfection, suggesting an important role for cellular immunity in measles infections. Enders (67) reported on leukemic children who were immunosuppressed with cortisone as part of their treatment, and in whom measles may take the form of a virulent giant-cell pneumonia. Furthermore, Hanissian et al (68) reported a case of subacute encephalitis clinically resembling SSPE in a patient with X-linked hypogamma-
globulinemia. The boy's illness was consistent with SSPE by clinical and EEG findings. However, he lacked any measles antibody in both serum and CSF by both CF and HI techniques. Although no virus was recovered from the brain, electron microscopy showed occasional cells with nucleoliform inclusions and fluorescent microscopy showed measles antigen in approximately 5% of primary brain culture cells. This report supports the tenet that cellular immune mechanisms play a significant role in the development of SSPE.

It was reported initially that SSPE patients' leukocytes did not show migration inhibition or blastic response when exposed to cell-free measles antigen, suggesting lymphocyte unresponsiveness to measles virus (69). However, there have since been reports (70–72) which offer strong evidence in favor of the immune competence of lymphocytes with respect to measles in patients with SSPE. The requirement for demonstrating a measles-specific immune lymphocyte response was the use of measles infected cells and not simply free measles virus (70). Ahmed et al (71) have recently reported on a high molecular weight heat-sensitive sialo-protein or protein complex which was able to block the expression of measles-sensitive lymphocytes from SSPE patients. The inhibitory substance was present in the cerebrospinal fluid at ten times serum concentration although the absolute amount of protein is nearly two orders of magnitude lower within the CSF. They were also able to demonstrate that the inhibitory substance was measles-specific and did not block elaboration of migration inhibitory factors when tested against several other antigens.

ANIMAL MODELS

Although SSPE appears to be a uniquely human disease, animal models of SSPE are available. In one model (73, 74), suckling hamsters from measles-immunized mothers were given Schwartz strain measles virus intracerebrally. These baby hamsters had high levels of maternal antibody acquired transplacentally. Of these animals, 83% did not develop acute encephalitis as did 100% of baby hamsters from nonimmune mothers. A small number of the passively immunized animals exhibited neurologic symptoms, and these animals had pathologic and tissue culture evidence of measles infection. In addition, when normally appearing, symptom-free hamsters which had survived 51 days postinoculation were given cyclophosphamide, a potent immunosuppressive agent, one third of them developed an acute measles encephalitis. Measles virus could be recovered from the brains of these animals as long as 90 days postinoculation. Another investigation (15) involved intracerebral inoculation of an SSPE strain into hamsters of varied ages. Adult animals developed an acute, nonfatal, self-limited inclusion-cell encephalitis. Newborn animals developed a uniformly fatal giant-cell encephalitis. However, weanling hamsters of 21 to 22 days of age showed a varied response. Some developed a subacute illness while others developed a chronic illness with survival throughout the entire 120-day course of the study. Cell-free virus was demonstrated in animals sacrificed up to 8 days postinoculation. However, cell-free virus could not be shown in those animals who developed chronic illness with neurologic signs, and co-cultivation techniques were required to rescue cell-associated virus from these animals (15, 64). Although the
animal models do not provide perfect corollaries to human SSPE, these models may provide great insight into the mechanisms of persistent measles infection.

TREATMENT

Several efforts in treating SSPE with amantadine, antimetabolites, and steroids (9, 75–77) have been made but none has shown any real promise. Two approaches currently under active investigation may change this. One involves the use of Lawrence's transfer factor, which is able to correct cellular immune deficits in some models (78). However, the best to be expected from this would be arrest of the disease at the stage of institution of therapy. Furthermore, if indeed the lymphocytes of patients suffering from SSPE are competent and their expression is being blocked by a circulating inhibitory factor as suggested by Ahmed et al (70), no response to transfer factor would be expected. Secondly, there is a single case report of improvement following institution of treatment with the agent isoprinosine (79). Whether the patient has truly demonstrated a response to treatment or is in remission as has been the case with other long term improvements (80) will require further time and investigation. At the time of this publication the patient has remained stable and is continuing to go to school (R. H. Mattson, personal communication).

FUTURE

Looking ahead into what may come of investigation of SSPE in the next few years, several interesting questions should be solved. First of all, can the disease be eliminated? It seems clear, at present, that no dramatic increase of SSPE has occurred as a consequence of mass immunization with the live vaccine. In fact, the incidence of SSPE may indeed be declining in the United States. Thus, continued mass vaccination may eliminate the disease. Seven years have now passed since the introduction of mass immunization against measles. Since the incubation period for SSPE is six years, any effects of mass immunization on the incidence of SSPE should soon become evident. Second, the role and mechanism of latency of paramyxoviruses may be elucidated more precisely as a result of further examination of the curious Japanese strain as well as by continued research into existing animal models for SSPE. Perhaps the most exciting advances may come from the elucidation of the nature and mechanism of the recently described measles-specific inhibitory substance which appears able to block expression of cellular immunity in SSPE.
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