Review of 38 Cases of Subacute Sclerosing Panencephalitis: Effect of Amantadine on the Natural Course of the Disease

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Thirty-eight cases of subacute sclerosing panencephalitis (SSPE) were reviewed. Deterioration in school performance, personality changes, and seizures were common early symptoms. Initial examination frequently showed myoclonus, spasticity, and extrapyramidal dysfunction, and in two-thirds of the patients these findings were asymmetrical or focal. Retinitis or papilledema was present on initial examination in 50% of the patients. At last follow-up 24 children had died, with a mean survival of 42 months. Most patients reached a state of severe neurological impairment within 13 months. Subsequent evidence of improvement was noted in 10 children and was sustained in 4. Fifteen patients received antiviral treatment. Ten treated patients died from 5 to 133 months (mean, 58) from onset of their illness, while 15 untreated patients survived a mean of 33 months.

Duration of survival appeared to be affected most by treatment with amantadine. Three patients treated with the drug were alive 97 to 139 months after onset of SSPE, and 5 died with a mean survival of 78 months. Five of 6 individuals treated with rifampin died after a mean survival of 27 months. Prolonged remissions occurred only in patients treated with amantadine. Although the number of treated individuals was small, our data suggest that amantadine may affect the natural course of SSPE.

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Since Dawson [1] first described what is now called subacute sclerosing panencephalitis (SSPE), the clinical features of the disorder have become well recognized. Symptoms begin during the first two decades of life and usually consist of dementia and personality changes [12]. Seizures and myoclonic jerks are common. The disease has a relentless course, with death frequently occurring in less than two years [4]. Prolonged spontaneous remissions and survival for more than four years are said to be rare [11]. There are, however, few studies from the United States of a large number of children with SSPE who have been followed by a single institution. We describe 38 patients with SSPE evaluated and followed at the University of Kentucky Medical Center (UKMC) since 1965.

Materials and Methods

We reviewed the clinical, roentgenographic, laboratory, and pathological data of patients seen at UKMC from 1965 through 1978 with a diagnosis of SSPE. All patients were seen on at least one occasion by one of the authors and were followed at intervals by members of the neurology department. Criteria for diagnosis included progressive mental and motor deterioration associated with periodic myoclonus. In addition, all patients met at least two of the following four criteria: (1) an electroencephalogram (EEG) with periodic complexes; (2) increased rubeola titers in the cerebrospinal fluid (CSF) and blood; (3) increased CSF gamma globulin (IgG) content; or (4) cerebral biopsy showing cortical and white matter changes, including neuronal degeneration, perivascular inflammation, microglial nodules, and inclusions in oligodendroglial cells.

A clinical staging system was modified from those of Foley and Williams [3] and Freeman [4] (Table 1), and patients were staged at different times during their illness. Remission was defined as clinical improvement lasting more than 1 month and sufficient to allow reclassification to a less severe stage.

Results

Thirty-eight patients were identified who had clinical, EEG, biopsy, CSF, or serological evidence of SSPE.

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Table 1. Clinical Progression of SSPE

Stage	Clinical Findings
I	Insidious intellectual deterioration, subtle personality change
II	Further intellectual deterioration, myoclonic jerks, seizures, mild motor impairment
III	Progressive neurological impairment, profound intellectual deterioration
IV	Marked rigidity and/or spasticity, bulbar symptoms, cortical blindness
V	Amentia, decerebrate rigidity, hypothalamic dysfunction
VI	Death

Age at onset varied from 3 to 18 years, with a mean of 10.3. Seven patients had their initial symptoms after age 16. The EEG showed a typical periodic pattern in 35 patients, and cerebral tissue was consistent with SSPE in 4 of 5 biopsies. CSF contained elevated IgG levels, elevated measles antibody titers, or both in all 34 children so studied. Serum rubeola antibody titers were measured in 30 patients and were consistently high.

The disorder usually began with deterioration in school performance. Personality changes, seizures, and clumsiness were common initial symptoms. Findings on first evaluation usually included myoclonus, spasticity, or signs of extrapyramidal dysfunction which were often focal or asymmetrical; some patients had combinations of these signs. Twelve patients were noted to have retinitis on initial examination, and another 7 had papilledema.

At the time of review, 24 patients had died after a mean survival of 42 months. For those in whom SSPE began after age 10 years the mean duration of survival was 25 months, compared with an average of 59 months when symptoms began before age 10. Follow-up was available for 12 of the 14 survivors, who were alive an average of 60 months into their illness. Patients often reached a level of severe neurological impairment (stage III or IV) within 13 months (range, 2 to 38 months) and usually went on to demonstrate additional signs of neurological deterioration. Ten children, however, showed sufficient improvement to be restaged to a level of less severe involvement. The duration of remissions varied from 1.5 to 84 months, with a mean of 19 months.

The 10 patients who improved did not appear to differ from the children without remission with respect to age at onset, calendar year in which measles was acquired, or age at which rubeola was diagnosed (Table 2). Patients with and without remission also had similar initial clinical courses, physical findings, and laboratory data. However, 8 of the 10 patients who experienced remissions had received antiviral treatment (amantadine, rifampin, or intermittent ether anesthesia), while only 7 of the remaining 28 patients had been given similar therapy.

The length of survival was compared between 15 treated patients and 21 untreated patients for whom adequate follow-up was available, and the difference was found to be significant ($p < 0.01$). Ten of the treated patients died an average of 58 months after their initial symptoms. Five of the treated patients were still alive at the time of this study, with a mean survival of 91 months. Among the untreated group, 6 patients were still alive some 43 months (mean) into their illness. Fifteen children in the untreated group had died after a mean survival of 33 months. Eight patients in the treated group received amantadine (3.5 to 10 mg/kg/day) for 60 days to more than four years. There were no serious side effects except for vomiting in 1 patient that led to discontinuation of treatment after approximately 2 months. Rifampin (11 to 15 mg/kg/day) was given to 6 patients for an average of 11 months and was also well tolerated. In addition, 1 child in stage III received intermittent ether anesthesia for five days. Four of the children treated with amantadine were at stage III of the disease when therapy was begun, 3 were at stage II, and 1 was at stage IV. Three of the children began re-

Table 2. Characteristics of Patients with Remission versus Patients without Remission

Patient Data	Patients without Remission	Patients with Remission
Age at onset (yr)	Mean, 11; range, 3–18	Mean, 8; range, 3–13
Years when measles was diagnosed	1960–1970	1960–1971
Age at diagnosis of measles (yr)	3.2 (N = 18)	2.8 (N = 10)
Severe case of measles	4/18	3/10
Interval between measles and SSPE (yr)	Mean, 8; range, 5–17	Mean, 8; range, 2–13
Interval to Stage III or IV (mo)	Mean, 13; range 3–38	Mean, 14; range, 2–36
Clinical findings	Initial examination and laboratory data similar	Initial examination and laboratory data similar
Therapy[a]	7/28	8/10

[a]Treated patients received either amantadine (8), rifampin (6), or intermittent ether anesthesia (1).

ceiving rifampin during stage II, 2 in stage III, and 1 in stage IV.

Three patients treated with amantadine were still alive from 97 to 139 months into their illness (Table 3). The other 5 children had died from 41 to 133 months after onset of SSPE (mean survival, 78 months). Five of the 6 patients treated with rifampin had a mean survival of 27 months (range, 5 to 50 months). The sixth patient was still living 55 months after his initial symptoms. The child who received intermittent ether anesthesia was surviving 108 months into his illness. The severity of SSPE among treated patients did not appear different from that in untreated patients. For example, 7 of the 8 patients treated with amantadine progressed to stage III or IV within 12 months after onset.

Improvement was recorded in 10 patients (Table 4). Four of these received amantadine, 4 were given rifampin, and 2 did not receive specific antiviral treatment. Sustained improvement was seen only in the 4 patients treated with amantadine (mean, 48¼ months). Two of the 4 children who received amantadine improved two stages and a third went from stage IV to stage I. This last patient was the only child to regain independent function. Only individuals treated with amantadine improved by more than one stage.

Table 3. Comparison of Effectiveness of Different Modes of Treatment in SSPE

Therapy	No. of Patients	Duration of Survival in Living Patients (mo)	Time from Onset to Death (mo)
Untreated	21[a]	16–93 (N = 6); mean, 43	2–108 (N = 15); mean, 33
Amantadine	8	97–139 (N = 3); mean, 123	41–133 (N = 5); mean, 78
Rifampin	6	55 (N = 1)	5–50 (N = 5); mean, 27
Ether	1	108	

[a] Adequate follow-up not available on 2 patients.

Table 4. Duration of Remission in 10 Patients with SSPE

Therapy	Duration of Remission (mo)	
	Range	Mean
Amantadine (4 patients)	13–84	48¼
Rifampin (4 patients)	2–12	7½
No antiviral therapy (2 patients)	1½, 2	...

Discussion

Our findings that deterioration in school performance, personality changes, and seizures were common early symptoms of SSPE are similar to previous observations [3, 4, 12]. The presence of myoclonus, spasticity, and signs of extrapyramidal tract dysfunction on initial examination was also expected. There were, however, 24 children in whom signs of disturbed motor function were asymmetrical or distinctly focal, which occasionally led to suspicion of an intracranial mass. Nineteen children were also found to have either retinitis (12 patients) or papilledema (7 patients) at the time of their initial evaluation. Although retinitis has previously been reported in SSPE [6], we are unaware of prior descriptions of its early occurrence in a large number of cases. The early appearance of papilledema is also considered uncommon.

A study of a large number of cases of SSPE from a single institution in the United States is not available, so previous reports have emphasized the variability in the natural course of the disease. However, studies from the Middle East have suggested that only 10 to 20% of patients can be expected to live for more than four years [7, 13]. A smaller series from Great Britain showed 7 of 26 patients (27%) surviving more than four years [2]. Therefore, the finding that 16 of 38 patients (42%) survived or were surviving for longer than 48 months in our study was surprising.

Our review suggests that treatment with antiviral agents may have been partially responsible for prolonged survival. The mean duration of survival among the 10 patients who received treatment but who were dead at the time of our review was 58 months (range, 5 to 133). The average survival for the 15 nonsurviving patients who had not received antiviral therapy was 33 months (range, 2 to 108). The age at onset and clinical characteristics of the disease did not differ between the treated and untreated patients. Review of hospital records did not suggest that patients who received treatment had a less virulent form of SSPE. Nevertheless, enrollment into a therapeutic program might have preselected patients with a less severe type of SSPE. It is also possible that treated patients received more enthusiastic care by family members and by medical personnel. However, mean survival among the patients treated with rifampin was only 27 months (range, 5 to 50), which was similar to mean survival in the untreated patients (33 months). In contrast, the 5 nonsurvivors who received amantadine lived for 41 to 133 months (mean, 78). It seems unlikely that those factors influencing

enrollment in the rifampin treatment program versus the amantadine program would have differed appreciably. It is also unlikely that the level of care, at least initially, would have been different for rifampin- versus amantadine-treated patients. Although survival was longer in patients whose illness began before age 10, 5 of the 8 patients receiving amantadine had their initial symptoms in the second decade.

Our data suggest not only that treatment with amantadine prolonged survival, but also that it was associated with periods of sustained improvement. Ten children demonstrated sufficient improvement to be restaged to a level of less severe involvement. Only 4, however, maintained such improvement for more than 12 months, and all 4 had received amantadine. Three of these children improved by at least two stages but only 1 returned to stage I. Some improvement in function occurred months after therapy was begun, and in some cases after amantadine had been discontinued.

Long-term remissions in SSPE are rare. Haddad and co-workers [7] found prolonged spontaneous improvement in 4% of their cases, compared with half of our patients treated with amantadine. Haslam et al [9] previously reported from this institution that amantadine had little effect on SSPE. They did suggest, however, that amantadine appeared to stabilize the disease in some patients. They also noted that none of their patients had been followed for longer than 6 months.

Amantadine hydrochloride has been used as an anti-RNA viral agent [10, 16]. It works presumably by blocking penetration of sensitive strains of virus into host cells. Amantadine is readily absorbed from the gastrointestinal tract and is known to cross the blood-brain barrier, so that any potential antiviral effect would be available in the central nervous system. Two recent reports have suggested that it may be of value in treating Creutzfeldt-Jakob disease [14, 15].

Although the number of patients treated with amantadine was small, our data suggest that the drug affected the natural course of SSPE. The results of our study do not indicate that amantadine has a permanent beneficial effect, but only that it may produce periods of mild improvement and retard the relentless progression of the disease. Further treatment of greater numbers of SSPE patients, especially in the earliest detectable phases of the disease, is needed to better define the effectiveness of the drug. Because a recent study suggests that isoprinosine may be useful in treatment of SSPE [11], it may be more appropriate to consider a controlled study using a combination of isoprinosine and amantadine. Although the precise mechanism of action is not known, isoprinosine may enhance cellular immune responses [5, 8]. Presumably, the two agents would be exerting antiviral actions by different mechanisms, and amantadine and isoprinosine in combination might be more effective than either agent alone.

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