Treatment of Subacute Sclerosing Panencephalitis with Human Leukocyte Interferon

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Leukocyte Interferon*. Tohoku J. exp. Med., 1985, **146** (3), 277-284 — In five
patients with subacute sclerosing panencephalitis (SSPE), human leukocyte inter-
feron (IFN) therapy was tried. IFN was administered intramuscularly,
intravenously, and intrathecally. The total dose of administered IFN ranged from
 13×10^6 to 116.92×10^6 IU. There were no severe side effects except for temporary
high fever and vomiting. Observation of the clinical course were made for 26-60
months. At the beginning of the treatment, one of the patients was at the first
stage of Jabbour's classification and the other four at the second stage. No clinical
improvement was observed and the clinical course was progressive in all patients.
At present, one of the patients was at the second stage and the other four were at
the fourth stage. EEGs showed progressive deterioration, and cranial CT scan
demonstrated progressive cortical atrophy and ventricular enlargement. Measles
antibody titers in the serum and CSF also unchanged. On the other hand,
permeability of IFN at blood-brain barrier (BBB) was relatively good. ———
blood-brain barrier; interferon; subacute sclerosing panencephalitis (SSPE)

Subacute sclerosing panencephalitis (SSPE) is an uncommon, progressive
central nervous system disease in children and young adolescents. It is consid-
ered to be slow virus infection caused by measles-like paramyxovirus (Connolly et
al. 1967; Baublis and Payne 1968; Horta-Barbosa et al. 1969). However, the
pathogenesis of SSPE is still unclear (Burnet 1968; Saunders et al. 1969; Brody
and Detels 1970; Allen et al. 1973; Ahmed et al. 1974; Oldstone et al. 1975).
Up to the present, there have been some attempts to treat the patients with SSPE
with the progress of the research on its pathogenesis (Haslam et al. 1969; Kertesz
et al. 1970; Robertson et al. 1979). But the effectiveness of these agents is still
unsettled. Recently, there are some descriptions which report the effect of
transfer factor (TF) (Vandvik et al. 1973) and inosiplex therapy on the patient

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with SSPE (Streletz and Cracco 1977; Huttenlocher and Mattson 1979; DuRant et al. 1982; Dyken et al. 1982; Jones et al. 1982). However, their effects are also unclear (Silverberg et al. 1979; Haddad and Risk 1980).

Since 1978, we have been treating the patient with SSPE with interferon (IFN). The aim of this study is to report the results of IFN therapy in five patients with SSPE, and to investigate the permeability of IFN at blood-brain barrier (BBB) after intramuscular or intravenous IFN administration.

CASES AND METHODS

Five patients with SSPE were studied. Their clinical features and laboratory findings are summarized in Table 1. The diagnosis of SSPE was based on their characteristic clinical features, periodic myoclonus, periodic bursts in electroencephalogram (EEG), elevated measles antibody titers in the cerebrospinal fluid (CSF) and serum, and increased CSF IgG content.

All patients were male aged 6 to 12 years. One of the patient (case 1) was at the end of the first stage by Jabbour's classification at the beginning of the IFN treatment, and the other four were at the second stage. The clinical course was very slowly progressive in case 1, and relatively progressive in the other four.

The patients presented with generalized tonic and clonic convulsion, gait disturbance, changes of the character or mental deterioration. They caught measles at the age of 6 to 12 months. The age at the onset of SSPE ranged from 5 to 12 years, and the interval between measles and the onset of SSPE ranged from 4 to 12 years. The EEGs revealed typical periodic bursts in all cases. The cranial CT scan performed at the initial diagnosis revealed low density areas in the basal ganglia in case 3, but were normal in other four.

Human leukocyte IFN was obtained from Professor T. Kishida (Department of Microbiology, Kyoto Prefectural University of Medicine). Human leukocyte IFN was produced by in vitro induction in human buffy coat leukocytes by the method of Cantell and Hirvonen (1977). As a rule, IFN was administered intramuscularly at a dose of $1.0\text{--}1.5 \times 10^6$ unit per day, at a dose of $0.3\text{--}1.5 \times 10^6$ unit per day intravenously, and $10\text{--}120 \times 10^3$ unit per day intrathecally.

The assessment of the clinical effect was based on the changes of clinical symptoms, EEG findings, cranial CT scan findings, and measles antibody titers in the CSF and serum before and after IFN administration.

Furthermore, to investigate the permeability of IFN at BBB after intramuscular or intravenous administration, serial changes of IFN titers were studied in CSF and serum simultaneously. IFN assays in CSF and serum were performed according to the cytopathic effect inhibition method using FL cells and vesicular stomatitis virus (VSV) as a challenge virus (Havell and Vilcek 1972).

RESULTS

Therapeutic effect of IFN on patients with SSPE (Table 2)

From October 2, 1978 through June 29, 1982, a total of $13.0\text{--}116.92 \times 10^6$ unit of IFN was given to each patient. Period of IFN therapy ranged from 3–26 months. The observation of the clinical course was made for 26–60 months. High fever was observed 3 hr after intramuscular or intravenous IFN administration in case 2, but was temporary. There were no other severe side effects. Intrathecal administration of IFN was made in three cases.

TABLE 1. *Summary of clinical and laboratory findings of five patients with SSPE*

	1. Y.T.	2. Y.H.	3. O.M.	4. N.M.	5. N.A.
Age of onset (years)	13	5	9	7	5
Sex	Male	Male	Male	Male	Male
Past history of measles	11 mo moderate	10 mo moderate	12 mo moderate	12 mo moderate	6 mo moderate
Period between measles and SSPE (years)	12	4	8	6	4
Stage of Jabbour's classification	I	II	II	II	II
First chief complaint	Generalized convulsion	Changes of character	Gait disturbance	Mental deterioration	Delayed speech
	Mental deterioration	Gait disturbance	Mental deterioration	Myoclonus	Myoclonus
Initial diagnosis	Epilepsy	Brain tumor	Degenerative disease	Epilepsy	SSPE
Initial EEG findings	Periodic burst & suppression	Periodic burst & suppression	Periodic burst & suppression	Periodic burst & suppression	Periodic burst & suppression
Initial cranial CT scan findings	Normal	Normal	Low density in basal ganglia	Normal	Normal
			Ventricular enlargement		
Measles titer (HI)					
Serum	×512	×512	×512	×128	×128
CSF	×32	×32	×16	×16	×16
CSF findings					
IgG (mg/100ml)	23	8	21	25	ND
Protein (mg/100ml)	80	40	75	ND	109
Cell count	5/3	1/3	2/3	3/3	0/3

mo, month; ND, not done

TABLE 2. Summary of IFN treatment

	Case				
	1. Y.T.	2. Y.H.	3. O.M.	4. N.M.	5. N.A.
The start of the treatment	1979.1.22.	1978.10.2.	1980.8.19.	1981.4.30.	1982.3.30.
Stage at the start of the treatment (Jabbour's classification)	I-II	II	II	II	II
Doses of IFN ($\times 10^6$ IU)					
I.M. ($\times 10^6$ IU)	58.7	116.92	23.82	23.05	13.0
I.V. ($\times 10^6$ IU)	58.7	103.0	8.0	12.5	13.0
I.T. ($\times 10^6$ IU)		13.5	15.5	10.5	
Period of IFN treatment	2 yr 2 mo	0.42	0.32	0.05	
Period of observation (1984.8.31.)	2 yr 2 mo	1 yr 8 mo	3 mo	3 mo	3 mo
Clinical course (during & after IFN therapy)	Very slowly progressive	Progressive	Progressive	Progressive	Progressive
Measles titer (HI)					
Serum	$\frac{\times 512}{\times 512}$	$\frac{\times 512}{\times 512}$	$\frac{\times 512}{\times 512}$	$\frac{\times 128}{\times 128}$	$\frac{\times 128}{\times 128}$
CSF	$\frac{\times 32}{\times 32}$	$\frac{\times 32}{\times 64}$	$\frac{\times 16}{\times 32}$	$\frac{\times 16}{\times 16}$	$\frac{\times 16}{\times 16}$
EEG finding	Progressive	Progressive	Progressive	Progressive	Progressive
Cranial CT scan finding	Normal $\rightarrow$ Brain atrophy Ventricular enlargement	Normal $\rightarrow$ Brain atrophy Ventricular enlargement	Low density of Basal ganglia Ventricular enlargement	Normal $\rightarrow$ Brain atrophy Ventricular enlargement	Normal $\rightarrow$ Brain atrophy Ventricular enlargement

I.M., intramuscular administration ; I.V., intravenous administration ; I.T., intrathecal administration.

Clinical course: No clinical improvement was observed in all cases. Case 1 showed very slowly progressive course; simple speech and writing, and supported gait were possible. The other four cases deteriorated moderately. By the time of this writing, four cases except for case 1 had progressed to the fourth stage by Jabbour's classification. They were all in vegetative state without spontaneous speech and response to stimulation. The interval between myoclonic jerks was prolonged and myoclonus was diminished in two cases.

Laboratory findings: In all cases, there was no improvement in EEG findings. The EEG performed at the diagnosis showed periodic bursts, typical for SSPE in all cases. 26-60 month observation of EEG findings during and after IFN treatment revealed a progressive disorganization and slowing of the basic rhythm. Furthermore, sleep stage differentiation became unclear in all cases.

Cranial CT scans performed before IFN therapy were almost normal except for case 3, which showed slight enlargement of the lateral ventricles and slightly low density areas of the basal ganglia. In spite of IFN therapy, cranial CT scan performed 24-48 months after the start of IFN therapy revealed marked dilatation of the lateral and the third ventricles, severe enlargement of Sylvian fissures, and severe cortical atrophy.

Measles antibody titers in CSF and serum did not show any changes after IFN therapy. There was neither granulocytopenia nor thrombocytopenia. Liver function tests and immunological examination were also within normal limits.

IFN titers and permeability of IFN at BBB (Fig. 1)

Intramuscular and intravenous administration of IFN resulted in a gradual elevation of its serum levels with the peak level one and a half hour after the

Fig. 1. Interferon titers of serum and CSF after intramuscular (I.M.) or intravenous (I.V.) administration of human leukocyte interferon.

Fig. 2. Interferon titers of CSF after intrathecal administration of human leukocyte interferon.

administration respectively. IFN titers in CSF was not detected before IFN administration, but raised to a quarter to an eighth of that of serum 24 hr later, but was diminished rapidly. This indicates that the permeability of intramuscularly or intravenously administered IFN at BBB is relatively good. On the other hand, serum IFN titers diminished gradually.

Intrathecal IFN administration was performed in three cases. It was associated with temporary high fever and vomiting in all cases. Because of these side effects, a large amount of IFN could not be given at a time.

DISCUSSION

Subacute sclerosing panencephalitis (SSPE) is a rare progressive disorder of the central nervous system associated with persistent slow measles-like virus infection (Connolly et al. 1967; Baublis and Payne 1968; Horta-Barbosa et al. 1969). There are some hypotheses about the route of the infection, but the details of the pathogenesis are still unclear (Burnet 1968; Saunders et al. 1969; Brody and Detels 1970; Allen et al. 1973; Ahmed et al. 1974; Oldstone et al. 1975).

Recently, there are some reports that isoprinosine (inosiplex) (Streletz and Cracco 1977; Huttenlocher and Mattson 1979; Dyken et al. 1982; Jones et al. 1982; DuRant et al. 1982) or TF (Vandvik et al. 1973) is effective. On the other hand, there are a few reports to the contrary (Silverberg et al. 1979; Haddad and Risk 1980).

The persistence of virus-infected cells and the presence of high levels of serum and CSF antibody to measles antigen have led to a speculation that immunological mechanism may involved. Therefore, we expected the effect of IFN, which not only has antiviral properties but also modifies the immune response and activates natural killer cells. Up to the present, there have been only a few papers concerning the effects of IFN on SSPE (Behan 1981; Bartram et al. 1982). But the decision on the effects of IFN treatment must be made carefully, in view

of reported occurrences of spontaneous long-term improvement or remission (Risk and Haddad 1979).

In this study, although there seemed to be some improvement of general condition and cessation of the progress of disease stage, no definite improvement was observed in clinical symptoms or laboratory examinations. If IFN therapy had been started in the earlier stage, some effects might have been observed. But once clinical symptoms appear in the central nervous system disorders, the brain damage is usually relatively advanced and irreversible.

In the present study, there demonstrated relatively good permeability of IFN at BBB. De Clercq et al. (1975) reported that intrathecal administration of leukocyte IFN was ineffective for neonatal herpes encephalitis, and the permeability of IFN at BBB was bad. Billiau (1981) demonstrated that very little, if any, IFN penetrates into the brain when given intrathecally. On the other hand, this study showed that disappearance of IFN activity from CSF was rapid. This phenomenon may be attributable to a rapid turn-over of CSF in children.

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