DEVIC'S DISEASE IN AN UNUSUALLY YOUNG BOY :
THE INCIDENCE, CONSIDERATION ON ETIOLOGY
AND THERAPEUTIC TRIAL WITH CORTICOSTEROID

TOSHIHIRO HIDAKA, MAKOTO YOSHINO, MASASHI YAMAMOTO,
YOHZO YOSHINAGA, FUMIO YAMASHITA¹⁾, TAMOTSU FUJIMOTO²⁾
AND TAKAAKI ARAMAKI³⁾

*Department of Pediatrics and Child Health¹⁾, Section of Virology,
Department of Microbiology²⁾, and Department of Ophthalmology³⁾,
Kurume University School of Medicine, Kurume, 830, Japan*

(Received for publication January 26, 1977)

The present paper reported a patient with Devic's disease, who had an attack at 5 9/12 years of age and was treated with corticosteroid, resulting in a complete cure. Immunological examinations revealed no evidence that this case was related to measles or rubella. Three years has already passed without recurrence since the settlement of his illness.

INTRODUCTION

In children or adults, disorders involving myelin occasionally lead to a tragic fate.

Devic's disease, which belongs to the "demyelinating disease", is characterized by a sudden onset of visual and gait disturbances due to retrobulbar neuritis and transverse myelitis, respectively. This disease has been believed to be rare in children under 10 years of age.

The present report deals with a patient with Devic's disease typical in symptoms occurring at 5 9/12 years of age.

CASE RECORD

Case : H. T. (# 1973-165)

A 5 9/12 year old boy was admitted, Jan. 24th, 1973, to the Kurume University Hospital because of visual loss and

slight disturbance of gait.

He was the product of uneventful delivery and developed normally, and had been healthy until 4 days before admission. There was a history of measles at 3 years of age.

Three days before admission, he bumped with a friend at the kindergarden and had a chest pain thereafter. Contusion of the head was denied by himself, slight pains of the throat and the calves were present.

Two days prior to admission, because of frequent yawns and sore throat, he visited a medical office, being said to have "the common cold" and was treated symptomatically. In the evening, however, severe pain of the calves and visual blurring of both eyes occurred on waking from sound sleep of about 6 hours' duration. He was taken to the medical office of Y. Y. (one of authors) and was referred to the Pediatric Cli-

Fig. 1 Course during admission.

nic of Kurume University for medical work-up in suspicion of brain tumor.

On the day of admission, chest pain, sore throat, pain of the calves were noted. Visual loss was present, completely in the left eye; finger-countable in the other. The patient walked with a drunk gait. Neurological examination disclosed the following. Consciousness was clear. His expression was relatively poor. The patient was well-oriented and cooperative to the examination. The ocular movements were slightly limited in all direction. There was no nystagmus. His visual acuity was impaired bilaterally, the left more serious than the right. The pupils were severely mydriatic, but reacted promptly to light directly and indirectly. It was impossible to evaluate the visual field because of poor vision. Examination of the eyegrounds showed blurring of temporal boundary of the optic discs. Slight speech disturbance was recognized, namely, inability to pronounce accurately "pa pi pu pe po" and "ba bi bu be bo". There was slight atrophy of the left side of the tongue. Swallowing was not disturbed. Examination of the other cranial nerves revealed no significant change. Superficial reflexes of the abdomen were equivocally absent. The knee and ankle jerks were exaggerated. On both sides, the Babinski's reflex was positive, and Chaddock's sign and ankle clonus were also recognized.

Course during admission was shown in Fig. 1. Chest pain and sore throat lasted for 3 to 4 days. Visual loss was worst for the first one week of hospital days and later on became better bit by bit, however, color blindness was revealed with recovery of vision. They remained to some extent on discharge. Blurring of the optic discs severely extended, getting suggestive of papillitis

Fig. 2 Left ocular fundus. Details in the text.

Fig. 3 Loss of sensation occurred from inside of the left ankle and extended to the left half of the body.

and/or papilledema (Fig. 2) and lasted for 10 days. On the first hospital day, loss of sensation occurred from the median aspect of the left ankle and extended to the left half of the body (Fig. 3), then disappeared in a month. The atrophy of the tongue was followed by its deviation to the left, which lasted for 3 weeks. In addition, the bladder control was slightly impaired and dysuria lasted for about 6 weeks without urinary tract infection. Respiratory movement seemed to be impaired to some extent, as was detected through the decreased maximum volume of forced expiration. Disturbance of gait became much more severe and he could not walk at all for the last 5 days of January. Fortunately aside from the misfortune, it improved little by little. His gait was spastic in the left leg but paralytic in the right leg, which also disappeared by the beginning of March. The left arm was weaker than the right. Grasping power of the left was 3 times weaker than that of the right at the beginning of February but they completely improved by the end of March. At the worst stage, superficial reflexes of the abdomen were not elicited. The elbow jerk of the left and the knee and ankle jerks of both sides were exaggerated. Superficial reflexes returned to normal soon after, but the

tendon reflexes remained a little hyperactive on discharge.

Three years after the discharge, physical examination was carried out. Movement of the 5th toe of the left foot was disturbed. Color blindness remained slightly, though he could distinguish all colors from experience. Vision was within the normal level. Babinski's sign was left abnormally on both sides, but without progressing.

Many tests for urine, blood and cerebrospinal fluid were carried out through the course. Some data for incipient stage or initial few days after admission were described in Table 1. Immunological and serological tests for rubella, mumps and measles performed 3 years later from the discharge showed no significant elevation in titers as printed in Table 2. But tuberculin test had already gotten positive.

Summary of symptoms and signs

Sudden visual loss of both eyes, followed by symptoms and signs compatible with transverse spinal cord involvement, without significant abnormalities of blood, urine and cerebrospinal fluid. Healing without relapse.

Differential diagnosis

During the first few days of admis-

TABLE 2
Immunological examinations performed 3 years after recovery

CF to mumps	less than	4 ×
CF to measles	less than	4 ×
HI to rubella	less than	8 ×
MIT for measles		110.4 %

Abbreviation: CF : complement fixation titer

HI : hemagglutination inhibition titer

MIT : macrophage migration inhibition index

Values of less than 85.0% indicates past history of measles.

TABLE 1

Blood Analysis		Blood Chemistry		Serum Protein	
RBC(/cmm)	502×10 ⁴	GOT (U)	17	Total (g/dl)	7.5
Hb(g/dl)	13	GPT (U)	6	A/G ratio	2.07
Ht(%)	25	LDH (U)	320	Albumin (%)	67.5
CI	0.81	T.Chol.(mg/dl)	170	Alpha ₁ -G1 (%)	2.5
VI	0.77	Alk.P.(U)	19	Alpha ₂ -G1 (%)	10.0
MCV(μ ³)	70	T.T.T.(U)	2	Beta-G1 (%)	7.5
MCH(γγ)	26	Z.T.T.(U)	6	Gamma-G1 (%)	12.5
MCHC(%)	37	B.U.N.(mg/dl)	14	Ig-A (mg/dl)	157
WBC(/cmm)	11300	Blood Sugar (mg/dl)	68	Ig-M (mg/dl)	243
Baso(%)	0	ESR(mm)	14	Ig-G (mg/dl)	895
Eosin	3	Electrolyte		Serologic Test	
Band	2			CRP(-)	(-)
Seg	59			ASLO(U)	250
Lymph	36			RA Test	(-)
Mono	0			Wassermann R.	(-)
Blood type	O			HI Antibody for measles	8 ×
				Others	
				Tuberculin(mm)	4×4
			Skin T. for		
			Measles(mm)	2×2	
Cerebrospinal Fluid		Urinalysis			
Pressure	110 mmH ₂ O	pH	8		
Appearance	Clear	Pretein	(-)		
Protein	20 mg/dl	Glucose	(-)		
pre-alb.(%)	6.7 (1.8~ 6.0)	Urobilinogen	Normal		
alb.(%)	58.8 (55.9~65.3)	Bilirubin	(-)		
alpha ₁ -glob.(%)	10.1 (3.5~ 8.3)	Occult Blood	(-)		
alpha ₂ -glob.(%)	6.7 (4.3~ 6.3)	Sediment	Normal		
beta-glob.(%)	13.4 (12.1~15.1)	Stool Examination			
gamma-glob.(%)	4.2 (7.6~ 9.8)	Nothing special			
Sugar	60 mg/dl				
Cell Count	10/3				
Queckenstedt's Test	Normal				
Immunoglobulin					
Ig-A(mg/dl)	0.1				
Ig-M(mg/dl)	Not detectable				
IG-G(mg/dl)	0.16				
Other Examinations					
a) Skull radiogram	Normal				
b) Cerebral angiogram	Normal				
c) Electroencephalogram					
1) Resting record					
	θ-δ wave dominant in occipital area				
	No change either on opening eyes or with photic stimulation				
	Slight build-up on hyperventilation				
	No paroxysmal discharge				
2) Sleep record	Normal				
d) Echoencephalogram	Normal				

sion, a space taking lesion due to intracranial hemorrhage or brain tumor was suspected from the relatively sudden onset of visual or other neurological disturbances and papillary edema of the optic discs, although there was noticed no other symptoms suggesting pressure elevation of the cerebrospinal fluid, such as vomiting and headache. Lumbar puncture and encephaloechography, however, revealed no findings sufficiently indicative of these disorders.

On our way to exclusion of intracranial space occupying lesion, there appeared the possibility of so-called demyelinating encephalomyelitis such as subacute myelo-optico-neuropathy (SMON), diffuse sclerosis, acute disseminating encephalomyelitis (ADEM), multiple sclerosis (MS) and neuromyelitis optica (Devic's disease). SMON was easily excluded from differential diagnosis because of no abdominal signs including diarrhea and no history of ingesting "Chinoform". Diffuse sclerosis was also ruled out since cerebral signs were little noticed regardless of visual impairment and transient slight deviation of the tongue; in addition, spinal signs were rather dominant and not progressive. Clinically it is difficult to distinguish ADEM from acute MS including Devic's disease by a short follow-up study. Although peripheral blood examinations showed slight inflammatory reactions, CSF findings were not indicative of typical ADEM. The sudden onset of blindness was followed by spinal symptoms and signs within a few days, and no clinical course of remissions and exacerbations had been seen as yet in this case, which were much more suggestive of Devic's disease as compared with typical MS. However, a long-term follow-up study may be necessary to exclude the possibility of polyphasic demyelinating diseases such as polyphasic MS and acute relapsing

disseminated encephalomyelitis.

Clinical diagnosis

Devic's disease

Treatments

Prednisolon, antibiotics (ampicillin), vitamin B complex and adenosine triphosphate Na were administered orally.

DISCUSSION

Schumacher (1960) restricted the term demyelination to loss of myelin without proportionate loss of axis cylinders. Robbins' text book of pathology (3rd edition) defined demyelinating disease as one which has as its most important attribute a tendency to produce such an effect. Important diseases closely corresponding to this strict definition include postinfectious encephalomyelitis

Fig. 4 Distribution of age at onset and age in 1973 in the Japan Nationwide Series of patients with multiple sclerosis group. Solid line : age at onset ; broken line : age in 1973. (Kuroiwa, Y. et al, 1975)

TABLE 3

Diagnostic criteria of multiple sclerosis

-
1. Multiple sclerosis
    - a. Age of onset, 15-50 years (common in young adults).
    - b. Symptoms and signs due to multifocal lesions in the central nervous system (more than two lesions in the central nervous system, e. g., cerebrum, spinal cord, optic nerve, etc.).
    - c. Remissions and exacerbations (multiplicity in time).
    - d. Other diseases such as tumor, syphilis, cerebrovascular accident, cervical spondylosis, angioma, subacute myelo-optico-neuropathy, Neuro-Behçet, cerebellar degeneration, etc., can be excluded.
  2. Neuromyelitis optica (Devic's disease).
Acute bilateral visual impairment (optic neuritis) and transverse myelitis occur successively within an interval of less than several weeks. This is a variety of multiple sclerosis.
  3. Multiple sclerosis possible
Cases in which not all of the four criteria for No. 1 are fulfilled.

Addendum

1. Multiple sclerosis is to be considered in the following situations:
    - a. Optic neuritis combined with other neurologic symptoms such as abnormal deep reflexes, paralysis, numbness, ataxia, etc.
    - b. Myelopathy associated with ophthalmoplegia or nystagmus.
    - c. Cerebellar symptoms, spinal cord symptoms, and cerebral symptoms occur successively.
    - d. Recurrent myelitis.
    - e. Recurrent optic neuritis.
  2. Acute disseminated encephalomyelitis and acute myelitis could develop into multiple sclerosis.
  3. Symmetry: Symptoms of multiple sclerosis are in most cases asymmetrical, while they are mostly symmetrical in subacute myelo-optico-neuropathy.
-

(Multiple Sclerosis Research Committee of Japan,
Ministry of Health and Welfare, 1972)

and multiple sclerosis. Devic's disease has been generally classified into multiple sclerosis group (Kuroiwa et al, 1975).

Kuroiwa et al. (1975) drafted the diagnostic criteria of multiple sclerosis as shown in Table 3 by modifying the criteria of Shumacher and associates, and reported Devic's disease in Japan to account for 7.6 per cent of 1086 patients with multiple sclerosis collected

on the basis of the criteria from all over the country. Concerning age at onset, 84 per cent of multiple sclerosis were between 15 and 49 years of age, the maximum around 33 years of age, as shown Fig. 4 (Kuroiwa et al, 1975). The accurate incidence of Devic's disease in Japanese children is unknown. Kuroiwa et al. (1962) reported that multiple sclerosis including Devic's disease also involves the teen agers, more predomi-

nantly the late teen agers, and that the incidence of Devic's disease is highest in the late teens and very infrequent below the age of 10 years. The patient reported here is a rare case who had an onset at 5 9/12 years of age. This indicates that typical Devic's disease can occur during preschool age among Japanese children.

The etiology and the pathogenesis of Devic's disease have been still obscure. Generally, multiple sclerosis has been believed to be due to infection of a certain viral agent followed by some unusual immunological processes (Hori-kawa et al, 1975). This is supported by the elevation of gammaglobulin in the cerebrospinal fluid and the elevation of the serum antibody titers to several viruses, especially, measles and rubella. In due course, similar etiology has been also suspected in Devic's disease. Our patient showed no elevation of gammaglobulin in the cerebrospinal fluid obtained at a cure stage. Simultaneously specific immunological reactions to measles were negative in serum hemagglutination inhibition titer and skin test in spite of the presence of past clinical manifestation of measles. Additional immunological examinations performed 3 years after withdrawal of the drug in order to check up the possibility of immunosuppression by intensive corticosteroid therapy were not positively indicative of past infection of measles virus, as well. There had been no prevalence of rubella in Japan during the period from his birth to the onset of the disease. This time, we could not obtain evidence supporting that Devic's disease is due to measles or rubella. But it is strange that the *in vitro* macrophage migration inhibition index to measles in this case was similar to noninfectious state in spite of the presence of past clinical manifestation of measles.

As seen in our case, the combination of visual impairment and gait disturbance without severe intracranial pressure elevation reminds us of multiple sclerosis, Devic's disease, ADEM and diffuse sclerosis. Clear distinction between them is frequently difficult because of the presence of intermediate or transitional forms, although it is true that there are classical forms of these diseases (Tsukagoshi et al, 1971; Kuroiwa et al, 1966; Ferraro, 1944). But Devic's disease differs from diffuse sclerosis in that the former gives rise to a main lesion in the spinal cord, while the latter in the brain. This is a very important feature in differentiation between them (Tsukagoshi et al, 1971). Our patient had a slight deviation of the tongue, which may be suggestive of a brain stem lesion. But we can not rule out the possibility of Devic's disease in the presence of cerebral or cerebellar lesion, because the clinical entity is not based upon etiological and pathogenic essentials, actually, many cases of Devic's disease with small cerebral lesions have been reported (Kuroiwa et al, 1975; Satoyoshi and Saku, 1975; Ikuta and Murone, 1970).

The age of 5 9/12 years at the episode reminds us of the optimum onset age of ADEM. However, Kuroiwa et al. (1962) suggested that typical multiple sclerosis and Devic's disease can also occur in childhood in the Japanese. Peripheral blood and CSF examinations in our case showed equivocal signs of inflammation on admission, which is unusual in ADEM. Multiple sclerosis and Devic's disease may be occasionally associated with inflammatory reactions. It has been said that ADEM is a clinical syndrome and it may rarely happen preceeding or following multiple sclerosis (Kuroiwa, 1966; Mc Alpine, 1958). Although ADEM and acute multiple sclerosis should be taken into consid-

ration in this case, we chose the diagnosis of Devic's disease since this case met its diagnostic essentials best, compared with those of the other.

Concerning therapy, corticosteroid has been used in the acute stage of multiple sclerosis, being reported to be clinically advantageous in half of the cases (Kuroiwa, 1975). ADEM is also curable by corticosteroid, which has been occasionally regarded as one of its properties when differentiating from the other myelinoclastic diseases (Kuroiwa, 1966; McAlpine, 1931). Our case reported here was treated with the same drug, resulting in a very good response. Until the present time, no recurrence has been seen.

ACKNOWLEDGEMENT

The authors are very grateful to Dr. Y. Kuroiwa for his kind comments.

REFERENCES

- FERRARO, A. (1944). Pathology of demyelinating diseases as an allergic reaction of the brain. *Arch. Neurol. Psychiat.*, **52**, 443.
- HORIKAWA, Y., AMAYA, N. and IWATA, I. (1975). The clinical immunology of multiple sclerosis*. *Advances in Neurological Sciences*, **19**, 44-59.
- IKUTA, F. and MURONE, I. (1970). Pathological investigation on the relationship between multiple sclerosis and so-called Devic's disease in Japan*. *Clinical neurology*, **10**, 18-24.
- KUROIWA, Y., INOUE, K., ARAKI, S. and INOUE, K. (1962). Multiple sclerosis occurred in childhood. *Kyushu J. Med. Sci.* **13**, 193-198.
- KUROIWA, Y., SANTA, T., FUKIYAMA, K. and KATSUKI, S. (1966). An autopsy case of demyelinating diseases in childhood*. *Clinical neurology*, **6**, 81-87.
- KUROIWA, Y. (1966). Clinical features of acute disseminated encephalomyelitis*. *Clinical neurology*, **6**, 683-689.
- KUROIWA, Y. and SHIBASAKI, H. (1975). Multiple sclerosis — General view* —. *Advances in Neurological Sciences*, **19**, 5-13.
- KUROIWA, Y., IGATA, A., ITAHARA, K., KOSHIJIMA, S., TSUBAKI, T., TOYOKURA, Y. and SHIBASAKI, H. (1975). Nationwide survey of multiple sclerosis in Japan. *Neurology*, **25**, 845-851.
- MCALPINE, D. (1958). Clinical aspects of the demyelinating diseases with special reference to multiple sclerosis. *Brain and Nerve*, **10**, 301-310.
- ROBBINS, S. L. (1967). Demyelinative diseases. In *Pathology*. 3rd Edition, pp. 1420-1423, Philadelphia, London. Igaku Shoin Ltd., Tokyo.
- SATOYOSHI, E. and SAKU, A. (1975). Clinical studies of multiple sclerosis in Japan*. *Advances in Neurological Sciences*, **19**, 32-43.
- TSUKAGOSHI, H., TOYOKURA, Y., YAMAZAKI, A., KOJIMA, O. and SHIMANO, K. (1971). An autopsy case with diffuse demyelinating optico-encephalo-myelitis. *Clinical neurology*, **11**, 593-600.

* In Japanese with English abstract.