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Multiple Sclerosis in the Tropics

Four Additional Cases

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ABSTRAK

Harsono — *Multiple sclerosis di daerah tropis: Empat kasus*

Multiple sclerosis merupakan penyakit yang bersifat kronis progresif, yang dalam perjalanan kliniknya dicirikan oleh sifat yang khas, yaitu remisi dan eksaserbasi. Sampai dengan saat ini *multiple sclerosis* masih dianggap sebagai suatu penyakit auto-imun atau suatu penyakit yang disebabkan oleh infeksi virus.

Prevalensi *multiple sclerosis* di Indonesia belum diketahui. Pada umumnya prevalensi *multiple sclerosis* di negara-negara Asia sangat rendah, kurang dari 5 per 100 000; bahkan ada anggapan bahwa *multiple sclerosis* tidak ditemukan di negara tropis.

Dilaporkan empat kasus *multiple sclerosis* yang ditemukan di Daerah Istimewa Yogyakarta dalam kurun waktu 9 tahun terakhir. Di Indonesia laporan kasus ini merupakan laporan yang kedua. Pada tahun 1987 untuk pertama kali telah dilaporkan 3 kasus *multiple sclerosis* yang dirawat di RSUP Dr. Soetomo, Surabaya.

Key Words: multiple sclerosis – autoimmune disease – echovirus type II – latitude and disease – Schumacher criteria

INTRODUCTION

Multiple sclerosis (MS) has been recognized in all countries, but there is marked variation in the incidence of MS that appears to be related to latitude. MS has a high prevalence rate in Europe between latitudes 65° and 45° with similar distribution in the northern United States and southern Canada. A similar prevalence rate is found in comparable latitudes in the southern hemisphere covering New Zealand and southern Australia (Gilroy & Meyer, 1979).

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Studies on incidence of MS were initiated in 1922 by Davenport (*cit.* Olvera-Rabiela *et al.*, 1971), and the conclusion was that the frequency of MS declined from north to south and was practically absent in tropical areas. Meanwhile, the prevalence rate of MS in Asian countries is less than 5 per 100 000 (Ebers, 1986); however, the exact incidence and prevalence rate of MS in Indonesia is not yet known.

Indonesia is a tropical country, and comprises approximately 13 000 islands. It is located between latitude 6° north and 11° south. The temperature ranges from 18°C to 35°C, with humidity of 60%–90%. According to the *World Population Data Sheet*, the population estimate mid-1989 is 184,6 million. The overall land area is 1 926 170 sq. km.

The Yogyakarta Special Region is in the south-central part of Jawa island, located between 7° 33' and 8° 12' south latitudes, with an area of 3 185 sq. km and a population of nearly 3 million (mid-1988). Most of the area is mountainous (2 944 sq. km).

To the best of my knowledge, the first report of MS in Indonesia was presented by Hardhi *et al.* (1987). They reported three cases of MS, two men and one woman. All were admitted to Dr. Soetomo Hospital in Surabaya. This city is approximately 300 km to the east of Yogyakarta.

This paper describes four additional cases of MS found in Yogyakarta during the last 9 years. The diagnosis was made on clinical grounds using the criteria of the Schumacher Committee.

REPORT OF THE CASES

There were four women of Indonesian native origin, who had a history of neurological deficits with a pattern of remissions and exacerbations. They lived in Yogyakarta Special Region, three in the rural area and one in the urban area. They have never been overseas. The patients were encountered for the first time, respectively, in July 1980, June 1986, September 1986, and May 1988. The year of onset reported by the patients was 1978, 1984, 1978, and 1988, respectively. Details of the natural history, clinical course and diagnostic evidence are shown in the tables. Some extra information on each case follows:

Case 1

A 32-year old woman was admitted to hospital in July 1980. She complained of acute weakness and paresthesia, with disturbance of micturition. Since 1978 she had been very ill and she had required a cane for ambulation. No history of injury, fever, backache, or pulmonary problem.

The pattern showed a relapsing and remitting course and involved more than one part of the central nervous system (LIST 1). During the bouts of neurologic disturbances, she never had any medical treatment; she was under a traditional healer's care.

There was no abnormality of the vital signs. Neurological examination showed spastic paraplegia with disturbance of sensation below the level of D-4, impairment of vibration, retention of urine, nystagmus, intention tremor of the arms, scanning speech, bilateral optic atrophy, and marked depression.

LIST 1.– Sequence of clinical symptoms and signs, laboratory and radiological findings of case 1.

Year	Symptoms and Signs	Laboratory and Radiological Findings
1978–1979	Consisting successively of: a. acute weakness of lower extremities with retention of urine, no history of previous illness, lasted 6 weeks; b. slurred speech; lasted 5 weeks; incomplete recovery; c. acute weakness of lower extremities with bladder dysfunction and tingling sensation of the legs, lasted 7 weeks, incomplete recovery of motor function; d. subacute partial loss of vision; e. diplopia and slurred speech, lasted 3 weeks, complete recovery and f. scanning speech, lasted 4 weeks incomplete recovery.	No laboratory and radiological data, she was under a traditional healer's care.
1980 July	Acute weakness of lower extremities with retention of urine, paresthesia of the legs, nystagmus, blurring of vision, primary optic atrophy, intention tremor of the arms, scanning speech, impairment of vibration.	CSF: clear, no abnormality of protein and glucose content, normal cell count. Skull and spine X-rays: normal.
1980 Oct.	She died due to septicemia.	No necropsy

Tests for IgG and oligoclonal band, evoked potential, and CT scan were not yet available.

Under medical care the clinical course showed no significant improvement. The administration of prednisolone gave a little improvement of motor function. She became bedridden and suffered from urinary tract infection and pneumonia. Finally she died of septicemia. No necropsy could be done.

Case 2

A 34-year old woman was admitted to hospital in February 1986 with acute weakness and paresthesia of her legs, disturbance of micturition and loss of appetite. No history of fever, injury, pulmonary disease, backache or malignancy. Further history taking revealed an experience of acute total loss of vision bilaterally in April 1984, one week after delivery of her third baby.

The blindness lasted six weeks and recovered completely. According to the ophthalmologist who had conducted fundoscopy at the time, there was no abnormality of the fundi, and the diagnosis was retrobulbar neuritis.

On physical examination, there was no disorder of vital signs. Neurological findings were spastic paraplegia with impairment of sensation below the level of D-4, retention of urine, and depression. Both retina and optic discs were within normal limits. She had slurred speech.

Laboratory findings were normal, including IgG and electrophoresis. The examination for viruses, isolation and antibody, was negative.

A clinically incomplete recovery occurred within 6 weeks. She was still paraparetic and required a cane for ambulation. She felt a tightness of her back and abdominal muscles. The depression decreased markedly and the appetite improved, too. The bladder function improved adequately.

Subsequent bouts of relapsing and remitting started in June 1986. The features of clinical course and the results of laboratory and radiological examinations are mentioned in LIST 2.

The last clinical examination in September 1989 showed that she suffered from complete loss of vision due to optic atrophy bilaterally, and required a walker for ambulation. The most frequently relapsing and remitting condition in the last two months was bladder dysfunction together with tingling of the legs. Sometimes she became depressive and had loss of appetite.

LIST 2.– Sequence of clinical symptoms and signs, laboratory and radiological findings of case 2.

Year	Symptoms and Signs	Laboratory and Radiological Findings
1984	Acute total loss of vision bilaterally, one week after delivery, lasted 6 weeks	
1986 Feb.	Acute spastic paraplegia, retention of urine, no fever, depression, paresthesia, slurred speech; lasted six weeks; incomplete recovery of motor function.	CSF: clear, protein and glucose content within normal limits, normal cell count. Virus negative; spine-X-ray: normal; myelogram: normal
1986 June	Acute right hemiparesis, followed by abrupt loss of vision bilaterally, primary optic atrophy of right eye, lasted 4 weeks, incomplete recovery of motor function, required a cane for ambulation.	No abnormality of hemoglobin, hematocrit, cholesterol, triglyceride, uric acid, and white cell count. CSF: clear, no abnormality of protein and glucose content, and cell count. CT scan: normal
1987 Jan.	Retention of urine, subacute spastic para-paresis, paresthesia, no fever, followed by total loss, of right vision, tightness of abdominal muscles, depression; lasted 4 weeks, required a walker for ambulation, poor recovery of the vision.	CSF analysis: normal IgG: normal Electrophoresis: normal
1987 June	Total loss of left vision, the right one remains blind; lasted 4 weeks, poor recovery of the left sion, pallor of optic disc bilaterally.	—
1980 Apr.	Acute weakness of lower extremities, retention of urine, disturbance of sensation below the level of D-4, tightness of back and abdominal muscles, lasted 6 weeks, both eyes remain blind. No hospitalization.	—
1989 Aug.	Weakness of right leg, retention of urine, marked meteorism, depression, lasted one week; no improvement of her vision, no hospitalization.	—
1989 Sept.	Slurred speech, required a walker for ambulation.	

Case 3

This patient was a young 26-year old woman. She was admitted to hospital in September 1986 with severe weakness of all extremities and incontinence of urine. The natural history of the disease revealed bouts of neurological disturbances with a pattern of relapsing and remitting since 1978 (LIST 3). The examinations of spine X-rays, myelography, CT scan, blood and CSF analysis, had been done.

The radiological examination showed no abnormality of the brain parenchym, spine and spinal cord. CSF analysis showed no abnormality of cell count, protein and glucose content. The diagnosis at the time had not been confirmed yet.

The neurological examination showed spastic quadriplegia, impairment of sensation below the level of C-4. There was no muscle atrophy of the hands, and no fasciculation. The optic discs were pale. She experienced incontinence of urine and stool.

Viral detection was carried out and the result was negative. The level of IgG was within normal limits. Skull X-rays and myelograms were normal.

Her vision became blurred in October 1986 and this condition lasted 5 weeks. At the end of October 1986 she was essentially bedridden. Motor and

LIST 3.– Sequence of clinical symptoms and signs, laboratory and radiological findings of case 3.

Year	Symptoms and Signs	Laboratory and Radiological Findings
1978	Subacute partial loss of vision bilaerally, painful sensation behind the eyeballs, lasted 5 weeks.	—
1980 Oct.	Nausea and vomiting, backache, followed by blurring of vision, weakness of lower extremities with retention of urine, lasted 12 weeks. Incomplete recovery of motor function, required a cane for ambulation.	CT scan: normal Myelogram: normal Spine X-rays: normal CSF analysis: no abnormality of cell count, protein and glucose content.
1981 Sept.	Stepwise weakness of lower extremities with retention of urine, lasted 16 weeks; incomplete recovery.	—
1982 Dec.	Sudden onset of quadriplegia without any involvement of cranial nerves; normal micturition; lasted 10 weeks. Incomplete recovery; the activities of daily living were worse than in previous remissions.	—
1986 Jan.	Stepwise quadriplegia, upper motor neurone type, incontinence of urine and stool, depression, paresthesia of all extremities.	Myelogram: normal CSF: Virus negative IgG level analysis: normal Electrophoresis: normal
1986 Oct.	Blurring of vision, pallor of optic disc bilaterally. She was essentially bedridden. Poor recovery of motor and sensory function until July 1989.	—
1989 July	She died due to severe respiratory weakness.	No necropsy

sensory function improved poorly and then she was discharged. Finally, in mid-July 1989 she died subsequent to severe respiratory weakness. No necropsy could be done.

Case 4

A woman aged 30 years was admitted to hospital with retention of urine in May 1988. Two days later she had high fever and chills, and she also experienced weakness of her right leg, followed by the left leg. The tendon reflexes of the legs increased and the plantar responses were extensor. On the sixth day she had severe headache, nausea and alteration of consciousness. No convulsion or neck stiffness was present.

The results of CSF analysis were as follows: xanthochromic, protein content 150 mg, cell count 175/cubic mm – lymphocytic, glucose content 60 mg%. Echovirus type-II was isolated from the CSF and the CT scan showed massive brain edema without density changes of the parenchym.

A stepwise remission occurred within 8 weeks. The consciousness recovered completely and the headache ceased completely. She required a walker for ambulation; meanwhile the bladder dysfunction was still prominent and hindered her activities of daily living. She was discharged and 4 weeks later the bladder dysfunction had recovered completely.

Based on clinical signs and symptoms, laboratory and radiological findings, the diagnosis was acute encephalomyelitis. The causative factor was Echovirus type-II.

The subsequent bouts of exacerbations and remissions started in September 1988 (LIST 4). The last examination was conducted in September 1989. She was quadriplegic and confined to bed. The bladder function was normal. The left optic disc was pale without evidence of previous papilledema. She had slurred speech and felt paresthesia throughout the extremities. She was hindered by tightness of back and abdominal muscles and spasticity of legs. Sometime she had retrobulbar pain for about 3 days which then ceased by itself.

DISCUSSION

Multiple Sclerosis usually runs a course of varied neurologic symptoms and signs so that the physician risks misdiagnosing a curable disorder. A firm diagnosis can rarely be made during the first attack, although it can be suspected. Clinical diagnosis remains the standard method of diagnosing MS, since no laboratory tests are yet specific for the disease. Thus, various neurologic disorders may be diagnosed incorrectly as MS (Rudick *et al.*, 1986).

Meanwhile, Foster Kennedy said (*cit.* Kurtzke, 1988):

> The diagnosis of MS is not just a diagnosis. It is also a prognosis, a prognosis of utter disaster to any human to whom it is given. It would be an especial disaster to give it when the disease is absent. We must refuse to diagnose multiple sclerosis if multiplicity (in time and space) be absent; though as will be said later, multiplicity may occur and be due to factors other than those of multiple sclerosis.

LIST 4.– Sequence of clinical symptoms and signs, laboratory and radiological findings of case 4.

Year	Symptoms and Signs	Laboratory and Radiological Findings
1988 May	Retention of urine, fever, subacute spastic paraplegia, stepwise alteration of consciousness, severe headache, and nausea; remission within 8 weeks, required a walker for ambulation.	CSF: xanthochromic, protein content 150 mg%, cell count 175 lymphocytic. Positive Echovirus type-II (antibody & isolated). CT scan: massive — brain edema.
1988 Sept.	Acute paraplegia, tightness of abdominal muscles, incontinent of urine, blurring of left vision, paresthesia of legs, lasted 8 weeks. Incomplete recovery of blurred vision. No hospitalization and no medication.	—
1989 Jan–Apr.	Subacute paraplegia followed by weakness of the arms – upper motor neurone type – hypesthesia of all extremities, impairment of vibration. During 3 months hospitalization the remissions and exacerbations alternated between lower and upper limbs. Again, she experienced blurring of left vision for 3 weeks and then recovered incompletely: pallor of left optic disc. She became bedridden and subsequently she was discharged on May first 1989.	CSF: xanthochromic, protein content 102 mg%, normal cell count, normal IgG level. Myelogram: normal Spine X-rays: normal
1989 May–Sept.	Living at home, stepwise recovery from quadriplegia without any medication. The arms were better than the legs. She was hindered by a tightness of back and abdominal muscles, and spasticity of both legs.	—
1989 Sept.	Pain behind the eyeballs followed by transient blurring of vision bilaterally; marked pallor of left optic disc.	—

However, all we know – or think we know – about MS as to its manifestations, its management, its risk factors, its course, and its prognosis are based upon the clinical disease as evidenced by history and examination. Until we have a pathognomonic laboratory test, if we wish not to erase 120 years of clinical experience and start de novo to characterize this illness as a clinical entity, then we must adhere to the clinical phenomena. In this regard the best available, and safest, diagnostic criteria remain those of the Schumacher Panel, although without incorporating any absolute age restriction. This judgement is true "for research purpose" as well as for day-to-day clinical care (Kurtzke, 1988).

Of the four patients, I experienced diagnostic problems with case-1 and case-4.

Firstly, the history and clinical evidence of case-1 caused a confusing diagnosis, although the clinical features were strongly suggestive for MS. This situation was based on the argumentation of some colleagues, that MS was an unusual disease and practically absent in a tropical country.

Therefore, other diseases were first excluded as far as possible. Unfortunately, by the year 1980, CT scan was not available yet in Yogyakarta. However,

some supporting examinations such as lumbar puncture, spine and skull X-rays and meylography could be done. The results of the examinations were normal.

In accordance with the previous bouts of exacerbations and remissions, and regarding the last neurological condition, *i. e.* spastic paraplegia, proprioceptive sensory loss, cerebellar signs (intention tremor, nystagmus, scanning speech – the so-called Charcot triad), and pallor of the optic disc, and also the results of laboratory and radiological findings, I was encouraged to adhere to a diagnosis of MS. Finally, the diagnosis was confirmed by a senior neurologist from the Netherlands, who accidentally visited Yogyakarta. He agreed that the diagnosis was MS regardless of the tropical area. Nevertheless, the diagnosis was made only on clinical grounds since a necropsy could not be done.

Secondly, the clinical course of the last case was really surprising. The patient had experienced an acute encephalomyelitis. In accordance with this diagnosis, I expected complete recovery of the disease, although it can take a long time. But in fact, she just experienced exacerbations and remissions the signs and symptoms of which indicate lesions "scattered in time and space" in the central nervous system white matter, and then followed by transformation to a chronic progressive state. The clinical features and evidence fulfilled the Schumacher criteria. On the basis of the clinical phenomena, the diagnosis of MS seems not to be in doubt.

Nevertheless, I wonder if a change from acute encephalomyelities to MS is possible.

The etiology of MS appears to be best explained as an autoimmune disease or a virus infection. Curiously, if autoimmune is the answer, it is quite probable that a viral infection may trigger the reaction. On the other hand, if viral infection is the primary cause, a delayed hypersensitivity reaction to the invading virus undoubtedly would contribute significantly to the damage inflicted on the nervous system. In either event, it seems reasonable to assume that another mechanism is superimposed on the disease (Soll, 1972).

There are three types of enteroviruses: the Coxsackie viruses, echoviruses, and polioviruses. All have been associated with chronic progressive systemic disease in hypogammaglobulinemic children and CNS involvement is often prominent. Infection may be acquired naturally or through immunization with live virus vaccine. Most cases of chronic enterovirus encephalitis have been caused by echoviruses of numerous serotypes. Clinical symptoms may include intellectual deterioration, fever, headache, motor and sensory deficits. Virus can usually be isolated from the SCF, which is often characterized by mononuclear pleocytosis, an elevated protein, and mildly depressed glucose (Griffin, 1986).

During the past decades speculation has grown that virus may be the cause of MS. The concept of a viral cause of MS is not new. In recent years epidemiological and virological evidence and some clinical evidence have supported the viral hypothesis. The greatest impetus to considering a viral cause has been the epidemiological data accumulated over the past 30 years, which indicate that MS is related to an environmental factor or factors encountered in childhood. First, the disease has a unimodal age-specific onset curve. MS rarely begin before the age of 15 or after the age of 50, and the age-specific onset curve shows a sharp peak at age 30 for both men and women (Johnson, 1982).

The remissions and exacerbations of clinical signs and the multifocal areas of demyelination typical of MS are also consistent with a viral infection. Remissions and exacerbations not only are typical of herpes infections but also can occur in visna, a virus-induced CNS demyelinating disease. Virus-induced demyelination is also seen in man in parainfectious encephalomyelitis and in progressive multifocal leukoencephalopathy (Johnson, 1982).

Distinguishing acute encephalomyelitis from MS may be difficult, especially since acute encephalomyelitis may be a forme fruste of MS or part a continuum of demyelinating disease which includes MS. When acute encephalomyelitis recurs, it generally does so at the same level of neuraxis. In MS, second attacks tend to incolve other areas of the neuraxis, although this is not invariable (Rosenberg, 1980).

On the other hand, the nervous system changes in acute encephalomyelitis are more acute and much more severe than those usually seen with MS, and the disease is nonrecurrent and without exacerbations. The course is rapid and often fatal; severe residual defects are present in survivors (Chusid, 1976).

Occasionally, MS runs an acute or subacute course leading to death in weeks or months. Alternatively, an acute course may develop rapidly, then remit partially or completely, to be followed by characteristic relapses. In some of these, the onset is marked by headache, vomiting, delirium, and a succession of symptoms indicating severe involvement of the brainstem or the brain, optic nerves, and spinal cord. In the so-called "cerebral" cases, there may be mental changes, convulsions, aphasia, hemianopia, and variable long-tract signs; the spinal type shows the picture of tranverse myelitis. These forms of the diseases are uncommon and are difficult to distinguish from disseminated encephalomyelitis, with which we tend to group them (Poskanzer & Adams, 1977).

In accordance with the clinical and laboratory phenomena of the fourth cases, and the reasoning above, the case seems to be an acute encephalomyelitis which would be a forme fruste of MS, or was it the infection which triggered MS?

Meanwhile, the remaining two patients namely the second and the third cases, there is no difficulty in establishing the diagnosis since the clinical features are typical for MS and fulfill the Schumacher criteria. Nevertheless, the etiological factor of the first three patients is unknown. All efforts associated with the detection of causative factor, did not reveal any positive result.

There are two survivors up to present, namely the second and the fourth cases. The third case died in mid-July 1989 due to severe respiratory weakness.

Severe respiratory weakness can be expected in patients with MS who are severely paraparetic, and the weakness increases as the upper extremities become increasingly involved. Respiratory compromise is likely to be particularly severe and dangerous in patients with preexisting pulmonary problems, particularly those with increased expiratory resistance such as chronic obstructive pulmonary disease. It is suggested that smoking and attendent emphysema represent significant hazards for patients with MS (Smeltzer *et al.*, 1988).

SUMMARY

The presence of four cases of MS in the Yogyakarta Special Region supports the first report that the awareness of the presence of MS in Indonesia must be kept alive. This report proves that MS is a disease which also occurs in tropical areas.

It is possible that MS would prove more prevalent in the tropics if doctors were more aware of it, although the prevalence rate is less than in the temperate countries. In fact, the diagnosis depends on certain conditions such as clinical skills and experience, availability of laboratory and radiological equipment, and last but not least, the awareness of MS itself.

It has become of interest now to conduct a good clinical and epidemiological study to document the real prevalence and compare with factors associated viruses in tropical and temerate areas.

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