JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Case Report

Oligoclonal bands: a laboratory diagnosis of subacute sclerosing panencephalitis (SSPE)

Weny Rinawati[1,2], July Kumalawati[3]

[1] Laboratory of Clinical Pathology and Blood Bank, Mahar Mardjono National Brain Center Hospital, East Jakarta, Indonesia
[2] Resident of Clinical Pathology Consultant Study Program, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia
[3] Department of Clinical Pathology, Faculty of Medicine University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Abstract

The oligoclonal band indicates presence of antibodies specific to the disease, possibly due to the activation of certain clones of B lymphocytes. This intrathecal immunoglobin synthesis can be persistent for months to years, for example, in respons to paramyxoviruses, herpes virus, coxsackievirus, and *Treponema pallidum*; or can be synthesized for life, for example in multiple sclerosis and subacute sclerosing panencephalitis (SSPE). We report a case of SSPE in a 15-year-old male patient. The patient had myoclonic jerks that occurred in the thoracal femoral region. Necessary laboratory tests identified reactive anti-measles IgG, which indicates a previous measles infection or exposure to vaccination. This report describes the usefulness of the oligoclonal bands in the diagnosis of the neurodegenerative disease SSPE that is progressive and fatal to the central nervous system due to persistent measles virus infection in the gray and white matter.

Key words: measles, oligoclonal bands, panencephalitis, SSPE.

J Infect Dev Ctries 2022; 16(6):1096-1100. doi:10.3855/jidc.15200

(Received 19 April 2021 – Accepted 26 January 2022)

Introduction

Presence of discrete lines or bands in the electrophoretic patterns of cerebrospinal fluid (CSF) suggest that the patient has multiple sclerosis and nervous system infection. These lines or bands were first reported by Lowenthal *et al*. in 1960 from patients with neurologic disorders and their occurrence was designated as the "oligoclonal aspect" [1].

Under normal conditions, antibodies in the central nervous compartment come from the blood that enters through the blood-brain barrier. Synthesis of intrathecal antibodies can persist for months to years, and is caused by: a) acute central nervous infection with a highly specific immune response to microorganisms; b) past infections with persistent immune response, for example in neurosyphilis, or herpes simplex encephalitis; and c) chronic inflammation or infection of the central nervous system with a polyspecific intrathecal immune response without a suitable antigen, for example in multiple sclerosis or systemic autoimmune disease involving the central nervous system [1].

One of the characteristics of intrathecal synthesized antibodies in subacute and chronic diseases of the central nervous system is the limited heterogeneity of mobility in the electric field or high-resolution migration during electrophoresis. This shows that B cell activity is clonally limited. In general, cerebrospinal fluid immunoglobulin G (IgG) expresses varying antibody specificity (polyspecific immune response), hence the term oligoclonal IgG [1]. The oligoclonal bands indicate that there are antibodies specific to the cause of the disease, possibly due to the activation of certain clones of B lymphocytes [1,2]. This is known as the oligoclonal band of IgG if > 2 clones of lymphocytes are found in CSF, or > 2 IgG bands are found in CSF but not found in the serum [1].

The standard method for examining the oligoclonal IgG band of CSF is the isoelectric focusing (IEF) followed by immunofixation. When performed simultaneously for serum specimens and CSF, the most sensitive examination detects oligoclonal IgG bands because many abnormalities cause oligoclonal IgG

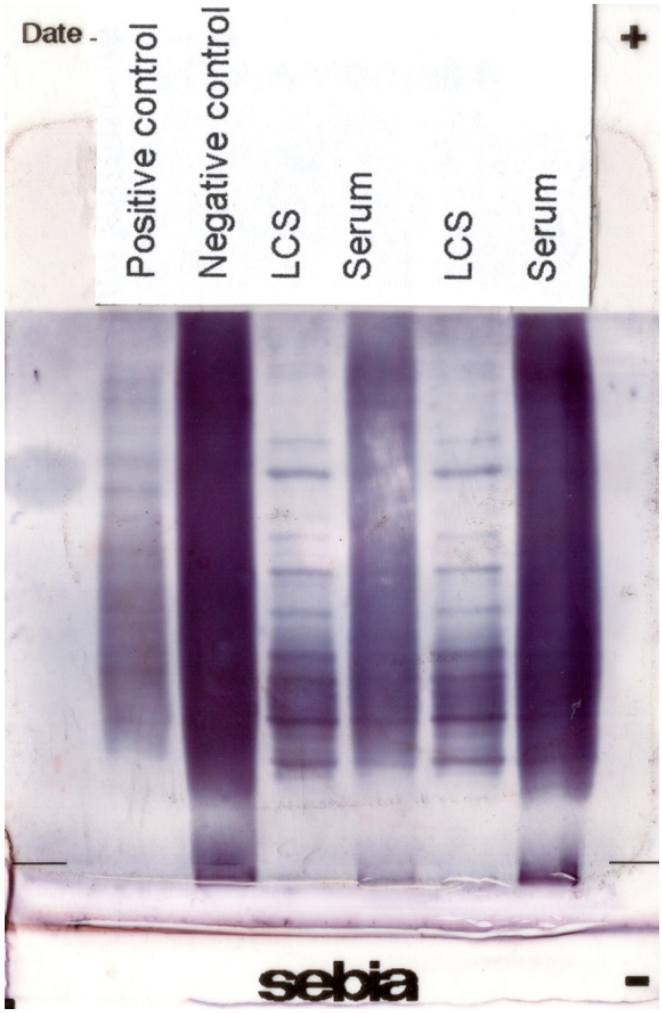
bands in serum that may be found in CSF due to impaired blood-brain barrier [2,3].

Case report

A 15-year-old male patient, with a history of seizures in the past 5 years was examined. During the disease, there was a history of seizures while sleeping, however, electroencephalogram (EEG) reports were normal. The patient was on irregular anti-epileptic (Depakote) medication. The patient was born by cesarean section, following a full-term gestation. The history of subsequent growth and development was good, and he received complete immunization.

The patient was admitted to the hospital with a diagnosis of myoclonic jerks. The myoclonic jerks occurred in the thoracal femoral region in the two weeks prior to admission to the hospital, followed by weakness of the left leg in the two days prior to being admitted to the hospital.

Figure 1. The oligoclonal band was found in the CSF and serum.



Initial physical examination was normal, Glasgow Coma Scale (GCS) score was E4M6V5, nutritional status was good, heart rate was 100 beats per minute, blood pressure was 100/70 mmHg, respiratory rate was 18 breaths per minute, and there was no episode of fever (36.5 °C) or left lower limb weakness.

The laboratory parameters were within normal range, with haemoglobin 13.6 g/dL (range 13-16), leukocyte count 8.4×10^6/mm^3 (range 4.5-13$\times10^6$, differential counts showed 2% eosinophils, 1% stab neutrophils, 49% segmented neutrophils, 46% lymphocytes, and 2% monocytes), and thrombocyte count was 281×10^6/mm^3 (range 140-392$\times10^6$). Other laboratory parameters were within normal range, with the serum glucose level 91 mg/dL (normal < 100 mg/dL), sodium 142 mmol/L (range 136-146), potassium 4.2 mmol/L (range 3.5-5.0), chloride 102 mmol/L (range 98-106), calcium 9.2 mmol/L (range 8.4-10.2), and magnesium 1.9 mmol/L (range 1.5–2.3). The CSF protein was 26 mg/dL, glucose 62 mg/dL, chloride 125 mmol/L (range 98-106), white blood cell 3×10^3/mm^3 (range 0-5$\times10^3$, with 33% polymorphonuclear and 67% mononuclear cells). To determine the cause of the disease, the patient was tested for anti-toxoplasma, anti-rubella, anti-HSV, anti-CMV, and anti-measles IgG. The laboratory parameters were positive for anti-measles IgG, others were negative.

Examination of CSF showed that the oligoclonal band was found in CSF and serum, similar to the type 3 oligoclonal bands (Figure 1).

Thorax radiologic imaging showed no abnormalities in the heart and lungs. Computerized tomography (CT) scan without contrast showed no infarction, bleeding, or space-occupied lesion. EEG examination revealed cortical myoclonus. There was an increase in choline levels and decrease in levels of N-acetyl aspartate (NAA) in the white matter of the right and left frontal lobe, left and right lateral periventricular, pons, and right-left cerebellum leading to the demyelination process in Magnetic Resonance Spectroscopy (MRS).

The patient was treated with NaCl infusion, injected with Diazepam 5 mg, and prescribed Haloperidol tablet 10 mg, Clobazam tablet 500 mg, Depakote tablet 100 mg, Alpentin capsule, and Valproic acid syrup 250 mg. The patient was discharged after 14 days of stay at the hospital.

Discussion

In normal CSF, IgG migrates homogeneously. The oligoclonal bands move discretely and appear as bands.

The presence of two or more bands in the globulin γ area is considered abnormal [1]. By using high-resolution electrophoresis on agarose gels, proteins are separated based on their isoelectric points. The band in the globulin γ zone is not always a true oligoclonal band and it can be IgG, IgA, or IgM. Therefore, it does not have the diagnostic significance of the oligoclonal band. Immunofixation is the technique of choice for detecting immunoglobulins from the oligoclonal band. Immunofixation with enzymes labeled antibodies to IgG, IgA, IgM, and/or κ or λ chain-bound immunoglobulins, is used to detect oligoclonal IgG bands in cerebrospinal fluid based on differences, or lack of distribution of immunoglobulins in serum and cerebrospinal fluid [3]. The international consensus for detection of oligoclonal IgG proposes five types of results for parallel examination of CSF and serum: a) Type 1, normal CSF; b) Type 2, oligoclonal IgG in CSF, indicating intrathecal synthesis; c) Type 3, oligoclonal IgG in CSF, accompanied by identical bands in CSF and serum (combination types 2 and 4), indicating intrathecal synthesis; d) Type 4, identical oligoclonal bands in CSF and serum (mirror pattern with oligoclonal pattern), indicating the absence of identical synthesis, generally in systemic disease; and e) Type 5, monoclonal IgG bands in CSF and serum (mirror pattern with monoclonal bands), can be found in monoclonal myeloma or gammopathy (but are not significant) [2-4].

One of the major problems that may occur in the interpretation of the IEF pattern is the monoclonal IgG. The classic monoclonal IgG bands seen in the electrophoresis of patients with monoclonal gammopathy produce a specific ladder pattern of 4-5 bands at equal distance from each other and decreased intensity towards the anode. This pattern is caused by modification after antibody synthesis and does not represent specific antibodies. The presence of a single IgG band in the IEF does not always mean monoclonal IgG, because the IgG band detected by the IEF can consist of several points, such as those produced by several plasmacyte clones [2]. The frequency of obtaining oligoclonal IgG depends on the patient's diagnosis [5,6]. The increased oligoclonal bands found in the brains of humans with infectious CNS diseases have been shown to be antibody directed against the causative agent. Oligoclonal bands in the CSF of patients with disorders such as cryptococcal meningitis, mumps meningitis, progressive rubella panencephalitis, Herpex Simplex Virus (HSV), encephalitis, Human T-Lymphotropic Virus Type 1 (HTLV-1) myelopathy, SSPE, and Lyme disease are directed against the respective fungus, virus, or bacteria [7]. The majority of the patients with multiple sclerosis and all patients with subacute sclerosing panencephalitis (SSPE) showed the presence of an oligoclonal band [5,6]. Thus, the absence of an oligoclonal IgG band in cerebrospinal fluid ruled out the possibility of multiple sclerosis and SSPE [1,2].

SSPE is a neurodegenerative disease, that is progressive and fatal in the central nervous system due to persistent measles virus infection in gray and white matter of the brain [8-11]. This disease is rare with less than 10 cases per year in the United States of America. Saha *et al*. [12] reported the annual incidence of SSPE in South India was 2.4/million population, or 4.3/million population below 20 years of age. The onset of this disease is insidious, with an incubation period of 6-8 years, and generally < 10 years, therefore the incidence of SSPE is often seen in childhood [9-11]. Most cases of SSPE have a history of primary measles infection at < 2 years of age. The onset of progressive neurological disorders occurs after a latent period of 6-8 years. Boys have a three times higher risk of getting SSPE than girls. If a child's measles infection occurs at < 1 year age, the risk of getting SSPE will increase 16 times compared to the risk if measles infection occurs at > 5 years age. Other risk factors associated with measles exposure include children living in overcrowded environments. Immunization can reduce the incidence of SSPE by > 90% in developed countries. If there is an incidence of SSPE in children with a history of immunization, generally the disease is due to subclinical measles infection that occurs before the age of 1 year [9].

Stage 1 SSPE is characterized by subtle behavioral changes, cognitive decline, emotional lability, lethargy, and nonspecific neurological symptoms. At this stage, it can last for weeks to months. Stage 2 is characterized by intellectual decline, myoclonus, focal seizures with secondary generalization, choreoathetosis, apraxia, and visual changes with optic atrophy, dysarthria, and tremors. A variety of visual disturbances may occur, including papilledema, chorioretinitis, optic nerve pallor, homonymous visual field deficits, and cortical blindness. This stage can last three months or less. In stage 3, continued neurological decline is characterized by a decreased level of consciousness, autonomic instability with variable heart rates, highly fluctuating blood temperature and pressure, dystonia and stiffness, decorticate or decerebrate posture, and slow speed. These symptoms can be stable for 1-2 years. Symptoms in stage 4 include active shock reflex, flexor limb position, quadriparesis, akinetic mutism, wandering eye movements, and coma. Myoclonus, convulsions, and

stiffness are less common than in the previous stages [10,11].

The diagnosis of SSPE includes clinical features, electroencephalography (EEG), examination of cerebrospinal fluid, identification of measles antibodies, and brain biopsy. The clinical symptoms of SSPE can be distinguished from other neurodegenerative symptoms since they are accompanied by cognitive decline and progressive neurological disorders, and stereotyped myoclonus. Stereotypic myoclonus is continuous, for example in truncal myoclonus, leg extension, protruding tongue, and brief loss of speech followed by loss of tone at the last second. Lateralization features, partial seizures, or papilledema may mimic the symptoms of a space-occupying lesion. The EEG showed a change in characteristics [9,10].

The SSPE diagnosis was made based on the fulfillment of 3 of the 5 Dyken criteria. In our case, the patient met 3 of the 5 diagnostic criteria for SSPE: a) Clinical features that support the diagnosis of SSPE, which is a progressive neurological disorder over 2 weeks, and a myoclonic seizure. To rule out the possibility of the sole as the cause of left lower limb weakness, an imaging examination was performed. On the CT scan, there was no infarction, bleeding, or intracerebral space-occupying lesion, while the MRS showed demyelination process; b) EEG examination indicated cortical myoclonus, pathognomonic for SSPE; c) Examination of CSF indicated no pleiocytosis, and other results were within normal range. IEF examination found oligoclonal bands in CSF and serum, possibly due to intrathecal IgG synthesis. In contrast to multiple sclerosis, examination of the CSF can indicate a mild increase in leukocytes. The measles antibody titer is not known because the patient has been tested for measles antibody only once, and there was no brain biopsy performed because it is invasive.

A serological examination was performed to determine the cause of SSPE in our patient and positive results were found in the case of anti-measles IgG. The presence of measles antibodies (IgG) indicates a previous measles infection or exposure to vaccination. SSPE may be due to measles infection in our patient, which is also supported by obtaining a demyelinating process on the MRS examination. The patient had a history of good growth and development, with complete immunization. This suggests the possibility of the SSPE due to subclinical measles infection occurring before one year of age.

Currently, there is no adequate treatment for SSPE [9-11]. Certain antiviral and immunomodulatory therapies can prolong life if long-term therapy is given. Successful treatment is often difficult because of the varied nature of the disease. Some of the therapies that can be given are: a) Isoprinosine, an antiviral that activates the general system by increasing CD4+ lymphocytes, killer cell function, increasing interferon function, increasing interleukin-1 and interleukin-2. Isoprinosine improves survival and results in clinical improvement. When combined with trihexyphenidyl it can control myoclonus if sodium valproate has no effect, and can be given at a dose of 100 mg/kg/day. The therapy can be continued even after remission. Uric acid examination is necessary because Isoprinosine can cause hyperuricemia and kidney stones; b) Interferon α, suppresses viral replication and boosts the immune system. Interferon α is given 100,000 units/m^2 and can be increased to 1 million/m^2 per day for 5 days/week, or can be increased up to 6 times, at intervals of 2-6 months; c) Ribavirin, an antiviral, can be combined with interferon α to inhibit disease progression. Patients with hypertonicity, bladder incontinence, and dysphagia can improve after 3 months of therapy; d) Amantadine, an anti-RNA that prevents virus maturation so that it does not replicate. This drug is well absorbed in the gastrointestinal tract, bypassing the blood-brain barrier; e) Symptomatic treatment can be given in the form of anticonvulsants such as Sodium Valproate and Clonazepam to control myoclonus, and Baclofen to control spasticity [9]. Our patient was given symptomatic treatment such as Haloperidol tablet 10 mg, Clobazam tablet 500 mg, Depakote tablet 100 mg, and Valproic acid syrup 250 mg.

Generally, death from SSPE can occur within 1-3 years [8]. Average patient survival is 18 months, 50% of patients survived < 3 months, and 20% of patients survived > 4 years. Death occurs in stage IV, often due to concomitant diseases such as pneumonia [9]. In the chronic progressive fulminant type, death may occur within a few weeks, and there may be remissions and relapses. About 5% of the patients experience spontaneous long-term improvement. Spontaneous remissions can occur during any stage of the disease and last for varying periods of time before relapse. Santoshkumar and Radhakrishnan [13] reported that a woman with SSPE who had progressive neurological deterioration, was bedridden and incapable of self-care. In the following seven years, there was spontaneous improvement, when she became an outpatient and independent for daily activities. Grunewald *et al*. [14], recently reported a 35-year-old patient who was in remission for nearly 25 years.

Conclusions

SSPE is a rare complication of measles infection. During the evaluation of any child with progressive myoclonic epilepsy and behavioral and intellectual changes, it is necessary to look for a history of previous measles infection as it can lead to latent infection. The oligoclonal band according to Dyken criteria can be used for diagnosis of SSPE. The absence of oligoclonal IgG bands in cerebrospinal fluid excludes SSPE.

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Corresponding author

Weny Rinawati, MD, Clinical Pathologist
Laboratory of Clinical Pathology and Blood Bank, Mahar Mardjono National Brain Center Hospital, Jl. MT Haryono, Kav. 11, Cawang, East Jakarta, Indonesia
Phone: (+6221) 2937 3377
Fax: (+6221) 2937 3445, 2937 3385
Email: weny.rinawati@rspon.co.id

Conflict of interests: No conflict of interests is declared.