INTRODUCTION

Neuromyelitis Optica Spectrum Disorders (NMOSD) is an inflammatory disease of the optic nerve and spinal cord characterized by severe immune mediated axonal damage and demyelination. Incidence and prevalence of NMOSD depend on geographic area and ethnicity. Asian and African ethnicity are at higher risk. Female sex is known to be more at risk than male due to hormonal factors with an incidence ratio of approximately 3-10:1. Pediatric NMOSD was found in 3-5% of all pediatric cases with an incidence ratio of approximately 3-10:1. Pediatric NMOSD is known to be more active than other pediatric demyelinating diseases including pediatric multiple sclerosis. Aquaporin-4 (AQP4-IgG) was found to be seropositive in 65% of pediatric patients with NMOSD. Symptoms of postrema syndrome such as intractable nausea, vomiting, and hiccups are less commonly occur in pediatric NMOSD. The treatment of choice for NMOSD are immunosuppressant drugs and immunotherapies which are known to have variable outcomes. In this case report we discuss a rare initial presentation of pediatric NMOSD with limited choices and availability of current treatment.

CASE PRESENTATION

A 10-year-old male child presents with fever, nausea, and vomiting for approximately 3 weeks before admission. He also complained of hiccups and vertigo 2 days before admission. He had previous admission and showed no improvement. Patient had a Glasgow Coma Scale (GCS) 15. Neurological exam revealed positive nystagmus test, disturbed left upper extremity coordination, and unclear lateralisation on motoric examination. Fluid Attenuated Inversion Recovery (FLAIR) sequences on Magnetic Resonance Imaging (MRI) of the brain with contrast demonstrated a pathological intensity lesion without contrast enhancement on the right medulla oblongata posterior or wall of the 4th ventricle and on the periventricle of the 3rd ventricle extends to the bilateral optic tracts, right caudate nucleus, right internal capsule posterior, right thalamus, and right cerebral peduncle with a differential diagnosis of neuromyelitis optica and wernicke encephalopathy (Figure 1).

Whole spine MRI showed no abnormalities. Aquaporin-4 was found seropositive on lumbar puncture examination. A diagnosis of neuromyelitis optica spectrum disorder (NMOSD) was established. The patient was treated with methylprednisolone 125 mg every 8 hours IV for 5 days followed by IVIG 0.4 gr/kg/day for 5 days. 10 days after admission, the patient showed a significant improvement in symptoms. Patient then showed a significant improvement in symptoms. Relapse may occur, requiring further follow-up and maintenance therapy. We should raise awareness on the possibility of postrema syndrome in pediatric NMOSD cases that are intractable with medication.
DISCUSSION

Neuromyelitis Optica Spectrum Disorders (NMOSD) is an inflammatory disease of the optic nerve and spinal cord characterized by severe immune mediated axonal damage and demyelination.1

The key factor of NMOSD diagnosis is aquaporin 4, found in the astrocytes foot of CNS as a water channel protein. Half of patients with AQP4-IgG negative patients are categorized in myelin oligodendrocyte glycoprotein (MOG)-antibody positive oligodendrocytopathic NMOSD. NMOSD had several criteria that are standardized by the International Panel for NMO Diagnosis (IPND) 2015, core clinical syndromes include, acute myelitis, bilateral optic neuritis, acute brainstem syndrome, area postrema syndrome, diencephalic syndrome, and symptomatic cerebral syndrome. Area postrema syndrome presents with symptoms such as nausea, vomiting, and intractable hiccups. Diencephalic syndrome presents with narcolepsy, insomnia, and inappropriate diuresis. Brain stem syndrome characterized by ataxia, long tract symptoms, and cerebral nerve palsy. Along with the presence of seropositive AQP4-IgG, which confirms the diagnosis of pediatric NMOSD, the patient's core criteria such as fever, nausea, vomiting, and intractable hiccups demonstrated the classic symptoms of demyelinating lesion in the chemoreceptor trigger zone at brainstem which is area postrema syndrome.2 There are various differential diagnoses of NMOSD. Multiple sclerosis shares some phenotypic features and was debated for a long time. The distinct feature that confirms the difference is aquaporin-4 that is a specific autoantibody for NMOSD.

There are differences in the initial presentation of pediatric NMOSD, a first clinical episode typically revealed either transverse myelitis in 30-50% of patients, optic neuritis in 50-75% of patients, or a mix of both.4 Area postrema syndrome (APS) was infrequently described as an initial presentation of pediatric NMOSD.4 The incidence of area postrema syndrome symptoms at onset is 7.1% to 10.3%.7 Pediatric NMOSD with APS accounts for 3% to 5%.4 Pediatric case series study of NMOSD showed that area postrema syndromes were frequently developed as a relapse, not as the first clinical attack. Out of seven cases, there were 3 cases that presented with optic neuritis, 2 cases with transverse myelitis, and 2 cases combination of both with 1 of the cases showing area postrema syndrome.8

The two components of NMOSD therapy are acute phase management and preventative care. Treatment for all suspected case of NMOSD must begin in the acute phase due to relapses might result in permanent sequelae.4 Intravenous methylprednisolone (IVMP) 20 mg/kg/day for five consecutive days, up to a maximum dose of 1000 mg is the common approach continued with oral glucocorticoids that are gradually tapered off.4 In case of response to steroids in inadequate, plasma exchange (PLEX) or intravenous immunoglobulins (IVIG) should be considered. IVIG 2 g/kg is recommended.4 Preventative care usually starts after the initial attack to reduce relapses and permanent disability.4 Clinicians generally recommend maintenance therapy for at least 5 years. First line therapies in pediatric patients include IVIG, AZA, MMF, and RTX.8 Patient was given Cellcept (Mycophenolate Mofetil [MMF]) 2x250 mg that is widely used and well tolerated in a variety of autoimmune diseases to reduce relapses, stabilized or improved disability.

Rituximab (RTX) is a monoclonal antibody to the CD20 epitope found on all B cells. It suppresses antibody-mediated immunity and lowers AQP4 antibody levels in NMO by reducing CD20+ B cells, which are precursors of short-lived antibody-producing plasma cells. MMF acts as an inhibitor of inosine-5’-monophosphate dehydrogenase. Mycophenolic acid (MPA) selectively depletes guanosine nucleotides in T and B lymphocytes which lowers cell proliferation and inhibits the formation of antibody and cell-mediated immune responses. As an antagonist of purine metabolism, AZA inhibits the synthesis of protein, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA). Azathioprine is a purine analog that is converted by the enzymes thiopurine methyltransferase (TPMT) and hypoxanthine-guanine phosphoribosyltransferase (HPRT) into its active metabolites, mercaptopurine (6-MP) and thioguanine (6-TGN).8

RTX pediatric dose of 375 mg/m2 weekly for four consecutive weeks or 500 mg/m2/dose for two infusions spaced 2 weeks apart with CD19 cell counts.
monitored are well tolerated, known to stabilize or improve neurologic disability and lower the annualized relapse rate. Study by Magdalena et al showed that RTX to be more superior than AZT and MMF in reducing disability, relapses, and fewer adverse events. Study by Lin et al showed that RTX is mostly harmless than other immunosuppressive medications for long-term use due to less adverse events. The cost of medications may influence the choice of treatment regardless the safety and effectiveness of RTX and MMF.

NOMOSD is known to be relapsing which highlights the significance of a precise evaluation and effective treatment to prevent relapses. Relapse in NOMOSD occurs in approximately 47.7% patients. 3% of all relapses and 9% of initial relapses were caused by area postrema syndrome. Attacks of optic neuritis were more common in younger patients with later episodes of transverse myelitis occurring more frequently. Patients with AQP4-IgG seropositive tend to have >50% greater chance of recurrence within a year after diagnosis.

Ongoing follow-up and examination for children with NOMOSD is recommended for at least 3 to 6 months after diagnosis with routine laboratory follow-up specific to AQP4-IgG and immunosuppressive therapy used, MRI brain, orbits, and spine at 3, 6, 12 months continued annually after diagnosis, and comprehensive visual evaluation including OCT.

CONCLUSION

Pediatric NOMOSD with core criteria of area postrema syndrome is less common and usually appears as a relapse, not as the first clinical attacks. Clinicians should raise awareness on the possibility of postrema syndrome in case of gastrointestinal symptoms such as nausea, vomiting, and hiccups that are intractable with medication. To the best of the authors’ knowledge, this was the first reported case of a postrema syndrome in pediatric NOMOSD as the first clinical attack in Indonesia. Educating the family on possible relapse in the future and further follow-up to evaluate symptoms while initiating long-term immunosuppressive therapy is needed. Maintenance therapy with immunosuppressive therapy using currently available options such as IVIG, azathioprine, mycophenolate mofetil, and rituximab is recommended to prevent relapses and permanent disability in pediatric NOMOSD. RTX is the treatment of choice due to its benefits in reducing disability, relapses, and fewer adverse effects than MMF.

CONFLICT OF INTEREST

There is no conflict of interest.

ETHICAL STATEMENT

Written informed consent was obtained from the patient or the parent, given their consent in the form of the images and other clinical information to be published in the journal. They understand that the names and initials will not be published, and that while every attempt will be utilized to conceal their identities, anonymity cannot be guaranteed.

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AUTHORS’ CONTRIBUTION

All authors contributed in planning and preparation of the report’s concept, study design, execution and analysis; took part in drafting, revising and critically reviewing the article in all areas; have agreed on the final version of the report’s content; and have taken part in the decision to submit the report to the journal to be published.

REFERENCES