"MYELIN OLIGODENDROCYTE GLYCOPROTEIN SERO-POSITIVTY IN CHILDREN WITH NON INFECTIOUS ACUTE ENCEPHALITIS SYNDROME"

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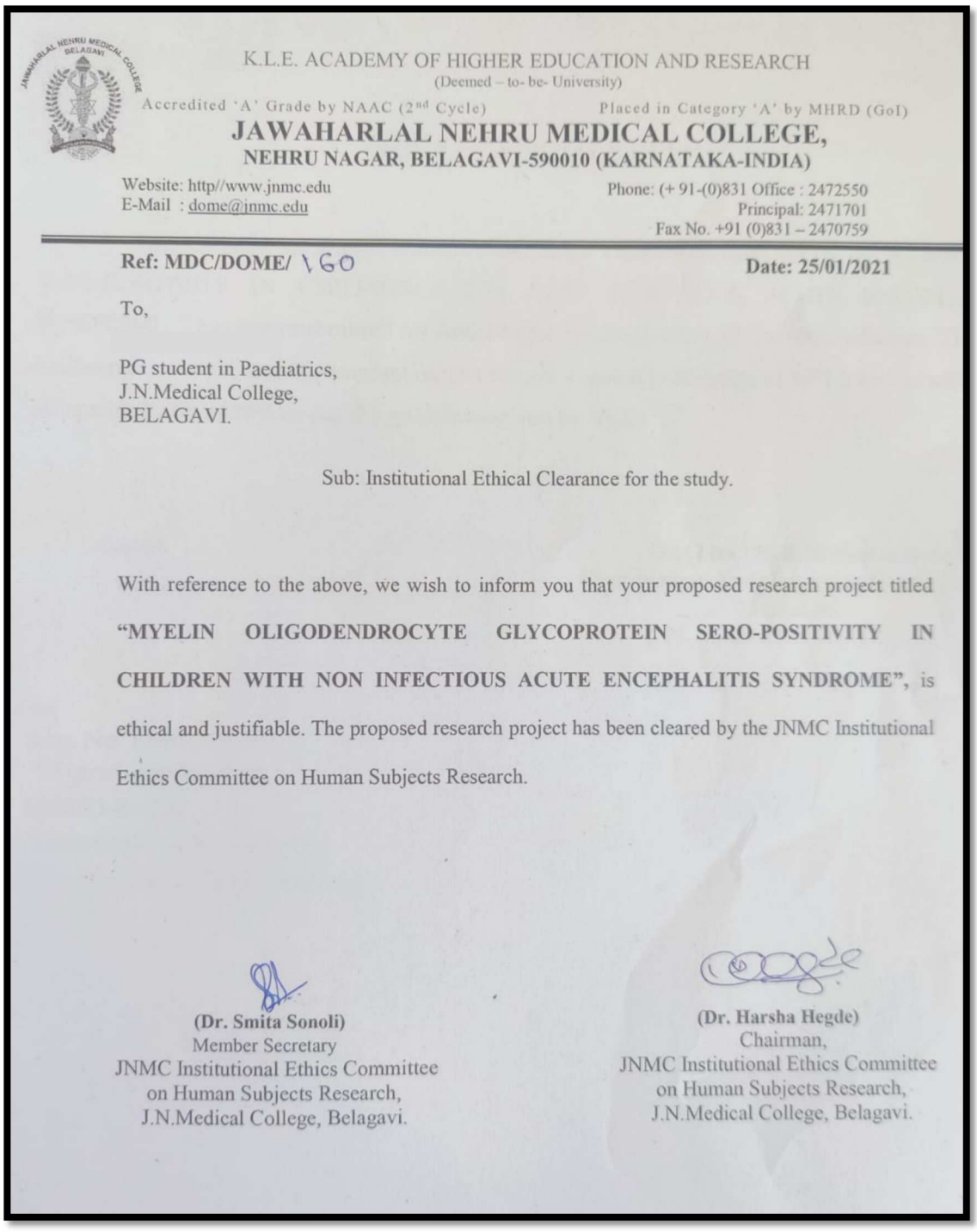

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"MYELIN OLIGODENDROCYTE GLYCOPROTEIN SERO-POSITIVITY IN CHILDREN WITH NON INFECTIOUS ACUTE ENCEPHALITIS SYNDROME"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

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ABSTRACT

Background and aims: Majority of the acute encephalitis syndrome cases have unidentified etiology, with many recent studies suggesting underlying autoimmune pathology. The primary objective is to study the myelin oligodendrocyte glycoprotein (MOG) sero-positivity in children with non infectious acute encephalitis syndrome. The secondary objectives are to study the MOG sero-positivity in acute demyelineating encephalomyelitis (ADEM) & in non demyelineating encephalitis syndrome, & to study outcome of MOG sero-positive cases with MOG sero-negative cases.

Material and Methods: A cross sectional observational study was done at single centre – Dr. Prabhakar Kore's hospital & MRC, Belagavi for a duration of one year. A total of 61 cases of diagnosed or suspected non infectious acute encephalitis syndrome were enrolled & investigated for the myelin oligodendrocyte glycoprotein sero-positivity. The inclusion criteria encompassed all cases above 1 month of age & less than 18 years of age getting admitted in pediatric ICU, presenting with acute onset of fever & change in mental status (confusion, disorientation, inability to talk or coma) and / or new onset of seizures. Follow ups of all cases was done at 1,3 & 6 months to assess outcomes between MOG positive & negative cases using few scores.

Results: 9 out of 61 cases turned out to be MOG POSITIVE. 5 cases out of those 9 MOG positive cases were ADEM & 4 cases were non ADEM (2 autoimmune encephalitis, 1 varicella encephalitis, 1 transverse myelitis).

Conclusion: The myelin oligodendrocyte glycoprotein antibody was more prevalent than other autoimmune antibodies in the region of study. The demyelineating

encephalitis had marginally more prevalence of MOG than non demyelineating encephalitis.

Keywords: Myelin oligodendrocyte glycoprotein, Acute encephalitis syndrome, Acute disseminated encephalomyelitis, Autoimmune encephalitis

LIST OF ABBREVIATIONS

ASM	-	Anti Seizure Medication
CNS	-	Central nervous system
MOG	-	Myelin oligodendrocyte glycoprotein
MOGAD	-	Myelin oligodendrocyte glycoprotein associated disorder
MS	-	Multiple sclerosis
WHO	-	World health organization
AES	-	Acute encephalitis syndrome
ADEM	-	Acute disseminated encephalomyelitis
ON	-	Optic neuritis
TM	-	Transverse myelitis
NMOSD	-	Neuromyelitis optica spectrum disorder
CBA	-	Cell based assay
PCR	-	Polymerase chain reaction
JE	-	Japanese encephalitis
JEV	-	Japanese encephalitis virus
mRS	-	Modified Rankin scale
NMDAR	-	N methyl D aspartate receptor
AIE	-	Autoimmune encephalitis
MRI	-	Magnetic resonance imaging

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INTRODUCTION

In India, acute encephalitis syndrome (AES) is a significant public health issue. Acute onset of fever and clinical neurological symptoms such as mental confusion, disorientation, delirium, or coma are characteristics of acute encephalitis syndrome (AES)(1) . The condition can cause significant morbidity and mortality and typically affects children and young people(1).

Although other causes like bacteria, fungus, parasites, spirochetes, chemicals, poisons, and non-infectious agents have also been described over the past few decades, viruses have been the primary causal agents in AES cases. The AES-causing agent changes depending on the season and geographic region, and it primarily affects people under the age of 15. Clinicians must contend with a constrained window of opportunity between diagnosis and treatment due to the diversity of causative agents and the quick rate of neurological deterioration caused by pathogenesis(2).

In India, JEV (which can cause AES in 5%–35% of cases) is the main culprit. Other causes of AES in India include Herpes simplex virus, Influenza A virus, West Nile virus, Chandipura virus, mumps, measles, dengue, Parvovirus B4, enteroviruses, Epstein-Barr virus, scrub typhus, and S. pneumoniae. Zika and the Nipah viruses have also been identified as potential AES causative agents. In a significant portion of cases of AES, the cause is still unknown(3).

The World Health Organization first used the term AES back in 2008 to simplify AES surveillance and research in India. The state of AES in India has substantially improved over time in terms of research and medical facilities. Despite

the creation of a vaccine against JEV and the clinical testing of minocycline, AES cases in India have not been limited to the JE aetiology(4).

An ethical and scientific requirement is the clinical classification of AES into acute encephalitis, encephalopathy, meningitis, ADEM, or as consequences of any condition that may induce brain dysfunction; proper care will depend on the accurate diagnosis. Numerous illnesses included in the "basket of AES" can be effectively treated with particular medicines(4)`.

Even after thorough research, it is not always easy to pinpoint the origin of AES. Over a 7-year span, the California Encephalitis Project enrolled 1570 patients with probable encephalitis (1998–2005). For 16 agents, a basic battery of tests was run. Only 16% of patients had an etiologic agent proven or suspected; 69% of these agents were viral, 20% were bacterial, 7% were prion, 3% were parasitic, and 1% were fungal. 13% of the remaining cases had potential aetiologies found. There were several agents in this group that had not before been linked to encephalitis as a cause. 8% of cases had an autoimmune origin, making it more frequent than any one infectious disease. The cause of the remaining 63% was not determined(5), most of which are assumed to have underlying autoimmune pathology.

The term "autoimmune encephalitis" refers to a group of similar disorders in which the brain becomes inflamed as a result of the body's immune system attacking it. Antibodies are molecules made by the immune system that mistakenly assault brain cells(35). The illness can be relapsing-remitting or progressive, similar to multiple sclerosis (becoming worse over time) (with alternating flare-ups and periods of recovery). There are numerous subtypes of autoimmune encephalitis, depending on the antibodies present - intracellular type like GAD65, ANNA or cell surface antigen

type like AMPAR, GABA A, GABA B, NMDAR (N-methyl D-aspartate receptor) & MOG (Myelin oligodendrocyte glycoprotein)(6).

Non-infectious encephalitis with serum MOG antibodies represents a distinct form of auto antibody mediated encephalitis in children. In many acquired demyelinating syndrome subgroups throughout the past ten years, antibodies against myelin oligodendrocyte glycoprotein have been identified. Children with solitary or recurrent optic neuritis, isolated or mixed with myelitis, or acute disseminated encephalomyelitis are the main populations in which MOG spectrum illnesses occur. There aren't many reports of kids with clinical and radiological MOG presentations. The whole range of MOG antibody-associated syndromes may not yet be represented by these syndromes and clinical course variants. The discovery of novel MOG antibody-related illnesses is crucial since it may have effects on prognosis and treatment. Therefore, after ruling out viral causes of encephalitis, testing for such antibodies should be undertaken in all cases of encephalitis, not just demyelinating diseases(26).

OBJECTIVES

- Primary objective – To study the MOG sero-positivity in children with non infectious acute encephalitis syndrome
- Secondary objectives –
    1) To study the MOG sero-positivity in acute disseminated encephalomyelitis & in non demyelinating encephalomyelitis.
    2) To study the outcomes of MOG sero-positive encephalitis cases & compare with MOG sero-negative encephalitis cases.

REVIEW OF LITERATURE

In India, unquestionably acute encephalitis is a serious public health emergency. In our country, encephalitis epidemics with unclear aetiologies have often occurred. Acute encephalitis can be defined as acute beginning of fever and the change in mental status—as well as new-onset seizures (as opposed to simple febrile seizures). In India, there were more than 44,000 cases and approximately 6,000 fatalities from encephalitis between 2008 and 2014(8).

The disease, which is known for its high case-fatality rate (CFR), causes seasonal outbreaks each year and claims a significant number of lives, particularly in young children under the age of 15. The patients frequently have an abrupt start of fever and altered mental status, and their clinical condition rapidly deteriorates, leaving them dead within hours. Many survivors can have ongoing disabilities that affect their quality of life in the long run(14). Acute encephalitis can have a variety of origins, including viruses that are prevalent in the area. The most frequently identified cause of acute encephalitis is the Japanese encephalitis virus (JEV). However, this is not always the case, and these cases are generally referred to as acute encephalitis syndrome (AES)(8).

In particular, etiology of sizable fraction of AES instances, is yet to be fully understood. The cause of other occurrences of encephalitis is still largely unknown, despite the fact JEV currently accounting for around 10-14% of encephalitis cases. Effective prevention and management of AES are severely hampered by the majority of cases' inability to isolate an infectious aetiological agent. Without a thorough understanding of the aetiology and method of transmission, preventative and treatment strategies cannot be properly developed or put into practise(12).

It is challenging to distinguish between cases of encephalitis, encephalopathy, another neurological illness, or any combination of those conditions due to the clinical uncertainty. It is essential to carefully gather information about the clinical presentation in order to create a case definition that is applicable in this circumstance. In India, this has not yet happened. Additionally, obtaining medical attention at the first sign of disease is crucial to ensuring better health outcomes due to the rapid deterioration and fatal outcomes. It takes more than just clinical expertise to manage critically ill children at the primary care, secondary, and tertiary care levels, and to enhance the ability of the health system's trained staff to address this issue(43).

Many cases of acute encephalitis are linked to JEV, a disease that can be prevented by vaccination and is spread by the bite of infected mosquitoes, even though the origin of acute encephalitis is still largely unclear in the majority of cases. A study on acute febrile encephalopathy with special reference to viral etiology done by Karmarkar S. A. & co in 2008 revealed 85.4% of their study group (151 patients) had some kind of infection as the cause(21).

The World Health Organization (WHO) developed the word "AES" in 2008 to describe surveillance reporting of suspected encephalitis cases accurately in India. According to the World Health Organization, an AES case is "a person of any age, at any time of year, with an acute onset of fever & change in the mental status, including symptoms like confusion, disorientation, coma, or inability to talk, &/or new onset of seizures, excluding simple febrile seizures" (4). Because the causative agent of AES varies depending on the season and geographical location, regional data on epidemiology and aetiology of AES outbreaks were necessary for the development and successful implementation of outbreak management approaches.

After the laboratory diagnostic component, acute encephalitis syndrome surveillance was the area that received the second-most attention. Following the classification of the case in accordance with laboratory results, the monitoring process comprises the identification of an AES using WHO case definition. Four categories of suspected AES cases exist: laboratory confirmed cases, probable cases, AES caused by causes other than JE, and AES with uncertain aetiology(5,7,8).

A study done by Modi A. & co on the etiological diagnosis & outcome in patients of acute febrile encephalopathy : a prospective observational study at tertiary care center in Lucknow in 2012 revealed 87.5% of their study group (120 patients) had any of identifiable infections as it's cause while the remaining cases didn't have any identifiable etiology(61).

Growing evidence points to autoimmune encephalitis (AIE) as a substantial and frequent cause of encephalopathy in children. Despite a large number of antibodies being found against the central nervous system, a sizable portion of paediatric auto-immune encephalitis do not produce detectable recognised antibodies, providing a diagnostic challenge. These children may possess immune systems or antibodies that have not yet been recognised. AIE includes established syndromes based on autoantibody correlations and clinical phenomenology. Of these, there is evidence to support the pathogenicity of syndromes involving cell surface antigens and antibodies. Antibodies to intracellular antigens may on occasion serve as biomarkers, however this has not been established(44,57).

A study on the etiology, clinical presentations and outcome of febrile encephalopathy in children by ANGA G. & co revealed that 121 put of their 149

children they studied had a definite pathogen identified to be it's cause while 28 cases of meningitis where of unspecified etiology(31).

Anti-NMDA receptor (NMDAR) antibodies are the most often reported antibodies linked to AIE in children. Children are less likely than adults to develop cancer after contracting AIE. Better neurocognitive outcomes result from early diagnosis and therapy. Pediatricians and intensivists must be aware of this condition in order to provide prompt and effective diagnosis and care. The most frequent cause of seropositive AIE in children and accounting for 4% of all the encephalitis cases is anti-NMDAR encephalitis. Nearly 40% of all reported cases involve people under the age of 18(25).

There are other autoimmune disorders that can present with encephalitis in addition to the antibody-mediated and paraneoplastic forms of encephalitis. Encephalitis is a typical presentation for ADEM. The distinctive brain lesions, and occasionally spinal cord or optic nerve involvement, are crucial diagnostic indicators. As a result of its more concentrated symptoms and distinctive brain imaging findings, multiple sclerosis (MS) is typically easier to distinguish from autoimmune encephalitis.

Multiple sclerosis (MS), which affects more people than any other chronic inflammatory demyelinating disease of the nervous system, is currently being thoroughly studied in terms of its pathogenesis, clinical course, outcome, treatment, and epidemiology. The classification of MS and other related demyelinating illnesses is one example of how later discoveries have had significant clinical ramifications. While the historical Schumacher and Poser's criteria have not changed in many years, the present McDonald criteria have already undergone multiple changes and do not

appear to be final(42). Additionally, for a long time, patients with acute transverse myelitis and optic neuritis were treated as though they had a kind of MS-Devic's disease which is now known as neuromyelitis optica (NMO). The discovery of IgG directed against the water channel aquaporin-4 (AQP-4 IgG) expressed by astrocytes, describing their function in NMO pathogenesis, and describing their distinctive clinical course, neuroimaging, and neuropathological findings allowed for the identification of NMO as a distinct disease entity. However, it soon became clear that AQP-4 antibodies were not found in 9–24% of NMO patients. In 21% of AQP-4 IgG seronegative patients, antibodies to the myelin oligodendrocyte glycoprotein (MOG) were discovered(52).

MOG structure & function -

The immunoglobulin (Ig) superfamily's myelin protein, known as myelin oligodendrocyte glycoprotein (MOG), is only expressed on the outermost surface of oligodendrocyte membranes and myelin sheaths. In inflammatory demyelinating disorders, MOG becomes a potential target of cellular and humoral immune responses. MOG is a crucial marker for oligodendrocyte maturation because of its late postnatal developmental expression(19).

For experimental autoimmune models of multiple sclerosis, MOG is one of the most well researched autoantigens which was first identified about 30 years ago. However, investigations on humans have produced conflicting findings regarding function of MOG, particularly MOG antibodies, as biomarker in multiple sclerosis(13,16).

In fact, clinical research has indicated that MOG may be a key CNS antigen that initiates autoimmune-mediated demyelination in a manner similar to MS. It was mostly found in children with acute disseminated encephalomyelitis(23). The findings of numerous studies on this subject point to the occurrence of a clinical state distinct from MS and NMO in some patients who have anti-MOG antibodies. Anti-MOG antibodies' potential contribution to MS pathogenesis hasn't been completely ruled out, either. Remember that even in the absence of antibodies recognising MOG in its original state, denatured MOG protein can still activate T cell immunity. Recent years have seen the postulation of criteria for the novel MOG encephalomyelitis (MOG EN) entity(73).

One transmembrane domain, 1 cytoplasmic loop, 1 extracellular immunoglobulin variable domain, a cytoplasmic tail & a membrane-associated region make up the Ig superfamily member MOG. It has been demonstrated that these isoforms can be detected secreted, on the cell surface, in the endoplasmic reticulum, or in the endocytic system(41,43). There may be substantial repercussions that result in autoimmunity if the secreted form is released into the cerebrospinal fluid (CSF) and then drains into the peripheral tissue. The different splice variants' intracellular location is determined by the cytoplasmic tail of MOG, which may also be involved in intracellular signalling. The cross-linking of antibodies (Abs) reactive with the extracellular domain of MOG resulted in the activation of intracellular signalling cascades that produced survival signals, alterations to cytoskeletal integrity, and cellular stress responses. Due to molecular mimicry, MOG, which is extremely similar to butyrophilins produced in mammary glands, may result in autoimmunity(36).

MOG's architecture at the surface of myelin and oligodendrocytes, as well as its distinct characteristics, suggest that MOG will be a prominent target of autoantibodies and cell-mediated immune responses in inflammatory demyelinating illnesses even though its biological function is yet fully understood. After immunising guinea pigs with CNS tissue, MOG was initially identified as a dominant target of autoantibodies (they dubbed it M2 antigen). The significance of MOG as an autoantigen for T and B cell responses in experimental models and inflammatory demyelinating disorders has since been proven by numerous investigations(12).

The distribution of MOG at the external lamellae of myelin sheaths & on surface of oligodendrocytes membrane is a sign that it may contribute to pathogenesis of demyelinating diseases & interaction with immune system.. The MOG gene is situated in the major histocompatibility complex (MHC) locus in both humans and rats. Additionally, the gene and the proteins encoded by the B7-CD28 superfamily have certain structural similarities(16).

The complement cascade's traditional mechanism can be immediately activated by MOG. Experimental studies have shown that MOG can activate the complement system by attaching to the C1q and C3d subunits(31,32). The presumed role MOG plays in the complement cascade may shed light on its role in demyelinating processes.

The low levels of MOG in myelin and the experimental evidence demonstrating MOG-associated demyelinating activity served as the basis for the theory regarding the strong immunogenic potential of this protein. The majority of patients with MOG antibody-positive lesions had features of MS pattern II lesions, including T cell infiltrations & IgG deposition. This was particularly notable given

that the neuropathological findings in these patients were somewhat consistent. It thus supports the theory that MOG antibody illness is caused by humoral immunological pathology(63).

Accurate detection of antibodies against native, properly folded, glycosylated MOG with intact tertiary structure is ensured by the development of more specialised procedures. One of them is an optimised cell-based assay, the method retains the conformational shape of a full-length human MOG and determines the humoral immune response to this protein. A different approach is radioimmunoassay, which detects antibodies using soluble tetramers of the four human MOG extracellular domains(68).

The results of a study that examined the repeatability of various antibody assays, including ELISA, live flow cytometry CBA [FACS], and fixed and live immunofluorescence CBA [IFT], have only just been published. Excellent agreement was seen between positive and negative samples using live MOG-IgG CBAs. The gold standard test is (IFT/FACS), which combines full-length human MOG as antigen with the secondary antibody designed to prevent Fc- or IgG1 reactivity(61).

CLINICAL PICTURE :

ADEM Presentation - Acute disseminated encephalomyelitis (ADEM) is an autoimmune, demyelinating condition that usually affects children and inflames the brain and spinal cord. The CNS nerves' myelin sheath is damaged due to immunological activity, and it often manifests clinically as new-onset multifocal neurologic impairments. Neuroimaging can identify demyelination as T2 hyperintense white matter lesions, either with or without the addition of contrast. In the differential diagnosis of CNS demyelinating disease, the condition frequently manifests similarly

to multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). The disease affects children more than adults. The mean age of onset of ADEM is between 3.4 to 8 years of age. Males are more frequently affected than females. In the days before vaccination, ADEM and measles were commonly linked. Today, viral infections of the gastrointestinal or respiratory tracts are more frequently linked to ADEM. In 67% of cases, ADEM has been shown to be triggered by an inciting antigenic stimulation, which frequently happens in the post-infectious or post-vaccination environment(23,44,56,68,74).

Although the pathophysiology of ADEM is not fully understood, genetically susceptible people may become ill after being exposed to an antigen through mechanisms like molecular mimicry and/or T-cell-driven inflammation.. When a host tissue (such the myelin sheath) and an external antigen have a high degree of molecular identity, this is known as molecular mimicry. The body develops antibodies against epitopes that resemble substances found in the CNS as a result of antigenic exposures from infections or vaccinations. It has been proposed that autoantibodies cause an autoimmune reaction that results in ADEM(18,46).

On early presentation, ADEM may resemble other demyelinating illnesses as MS and NMO. The start, duration, aggravating circumstances, and history of past neurologic episodes should all be elicited from the patient. The patient's age should also be noted by the healthcare professional because, in contrast to MS, where the median age is 29, ADEM more frequently affects young children between the ages of 5 and 8. Recent infections or vaccinations may raise clinical suspicion for ADEM even though this historical finding does not necessarily support the diagnosis of ADEM. Because there is no biomarker that distinguishes ADEM from MS, NMO, or

other demyelinating disorders, physicians should have broad differential diagnoses in place while suspecting any demyelinating condition after reviewing the patient's history(9,11,14).

To ascertain the nature of any neurologic deficit in individuals with suspected ADEM, a thorough neurological examination should be carried out. Additionally, if the patient exhibits symptoms that point to optic neuritis or another visual pathology, ocular assessment is advised. Testing should be done for extraocular movements, relative Afferent Pupillary Defect (rAPD), extraocular movements, pupil responsiveness, pupil size, visual acuity, stereopsis, colour vision, and confrontation visual field. To rule out any problems with vision impairment, the patient should be checked under a slit lamp. It is necessary to see the fundus to check for optic disc edema(14,18).

A major clinical trait that distinguishes ADEM from MS is encephalopathy. A prodromal disease may include symptoms like fatigue, fever, headaches, nausea, and vomiting may signify a bacterial or viral antecedent infection. This prodrome typically lasts 3–4 days before neurologic symptoms begin to manifest. The neurologic deficits peak 2 to 5 days after they first appear. Children with ADEM need to be admitted to the hospital for intensive care in 15 to 25 percent of cases. The most commonly reported neurological symptoms include – fever, headache, vomiting, meningeal signs, ataxia, weakness of limbs, palsies of cranial nerves & vision loss(16,21,23,27).

While patients with ADEM initially come in, they may have dyschromatopsia, subacute vision loss, unilateral or bilateral optic neuritis, as well as pain when moving their eyes. Edema of the optic disc may also exist. In ADEM as opposed to MS,

bilateral optic neuritis manifests more commonly. Optic neuritis relapses can also occur in ADEM or multiphasic DEM (MDEM) patients. When recurrent optic neuritis develops following an ADEM or MDEM diagnosis, the illness is referred to as ADEM-ON(73,76).

The cranial nerves III–XII and the white matter tracts that pass through the brainstem may not work effectively in people with brainstem involvementDiplopia caused by inflammation of the gaze control centres or cranial nerve palsies, which restrict extraocular movements, fits under this group. Patients with brainstem involvement often have a worse prognosis than those without brainstem lesions and typically undergo a fulminant illness course(74).

Patients with clinical symptoms suggestive of ADEM should have their doctors rule out treatable CNS infections and other causes of CNS demyelination first. The studies ought to cover:

1) A full blood count 2)The rate of erythrocyte sedimentation 3) C-reactive protein 4)Nuclear antibody (ANA) 5) Anti-aquaporin 4 antibody & MOG titers, which are highly related with neuromyelitis optica 6) EBV, enterovirus, and HSV & COVID19, 7)Mycoplasma (60)

Notably, according to the most recent diagnostic guidelines, all people who meet the requirements for ADEM and are MOG-Ab positive would also meet the requirements for MOG-Ab-associated illness. A non-MS relapsing disease history is significantly related with MOG-Ab titers, which are seen in 31-64% of juvenile patients. Anti-aquaporin 4 antibody (AQP4-Ab) titers are negative in nearly all ADEM patients, while 40% of NMOSD patients whose AQP4-Ab titers were negative also tested positive for MOG antibodies. A diagnostic workup should be guided by

the existence of atypical symptoms in order to support or rule out less plausible aetiologies(29,34).

The diagnosis of ADEM is aided by neuroimaging. When presented, MRI results for MS and ADEM might be comparable. When T2-weighted and fluid attenuated inversion recovery (FLAIR) brain MRI is performed on ADEM patients, it frequently reveals large, bilateral, hyperintense, diffuse, and ill-defined lesions (>1-2 cm). ADEM lesions can affect both white and grey matter. T1 hypointense black hole white matter lesions, more typically observed in MS, can sporadically also occur in ADEM lesions. Only 30% of ADEM lesions have gadolinium enhancement. Patients with optic neuritis may have one or both optic nerves with gadolinium-enhanced T2 hyperintense lesions. The nerve will appear thicker and swollen, and the improvement is typically homogeneous(36,43).

2) Optic neuritis presentation - The most prevalent clinical characteristic in older adults is optic neuritis (ON). In the two large clinical trials conducted in Europe, between 46% and 60% of participants experienced anti-MOG disease onset with ON. According to some research, 88% of patients experienced acute ON at least once. Young cases of ON often developed unilaterally, but patients with the disease's late onset had both optic nerves inflamed. The majority of patients with MOG-IgG optic neuritis first experience severe vision loss and eye pain, but typically make a full recovery in terms of their vision(53). Chronic relapsing inflammatory optic neuropathy is the medical term for recurrent optic neuritis (CRION).

3) Transverse myelitis presentation - About 20% of individuals with MOGAD initially presented with isolated transverse myelitis (TM), whereas an additional 8 to 15% of patients experienced both TM and ON. Injury to the spinal cord typically affects three or more nearby vertebral segments in this syndrome. In contrast to NMO, acute flaccid myelitis (ATM) condition is caused by inflammation in the low regions of the spinal cord, particularly the medullary cone. Nearly 70% of individuals with TM also experienced at least one episode of urine retention/incontinence, bowel dysfunction, and/or erectile dysfunction(41,43,46,53).

4) Other Manifestations (Cortical & Brainstem Encephalitis) - Symptoms of brainstem encephalitis that manifest during MOGAD include dysarthria, dysphagia, internuclear ophthalmoplegia, third nerve palsy with diplopia, nystagmus, trigeminal hypesthesia, and facial nerve paresis. In one case, they impacted 30% of participants. Additionally, the area-specific postrema syndrome symptoms of uncontrollable nausea, vomiting, hiccups, and coughing can be brought on by lesions in the dorsal medulla oblongata. This symptom, which was previously thought to be highly specific for NMO, was present in roughly 17% of the anti-MOG positive patients in a trial; the majority of them (91%) manifested at the start of episodes(31,35,78).

Most often manifested as epileptic seizures, cortical inflammation linked to the MOGAD can also cause behavioural and awareness issues. Various studies comparing frequency of acute epileptic events in people with MOGAD and NMOSD, on the other hand, revealed that seizures are more than 20 times more common in the former illness(79).

The prognosis is often very good with effective steroid treatment for cortical encephalomyelitis. Sadly, there have also been recent reports of fatal cases of fulminant demyelinating encephalitis.

On the basis of expert consensus, the MOGAD diagnosis criteria proposal was issued in 2018. Three essential factors are required for disease confirmation:

- Clinical presentation,
- MRI findings or neurophysiological examination findings indicating demyelinating injury within central nervous system,
- Biochemical antibody confirmation

5) Anti - NMDAR encephalitis – The most coomon cause of seropositive AIE in children and accounting for 5% of all the cases of encephalitis is anti-NMDAR encephalitis. Nearly 40% of all reported cases involve people under the age of 18(14).

The prodrome, which lasts for weeks to months in 50% of cases and includes symptoms like malaise, headache, fever, gastrointestinal or respiratory complaints, is followed by neurological, psychiatric & autonomic dysfunction. Compared to adults who report with psychological problems, younger individuals frequently have seizures and mobility disorders. Anti-NMDAR encephalitis is generally accompanied with seizures and only 1% of patients have monosymptomatic cases, therefore it is doubtful that the condition is the source of isolated psychosis in youngsters. Up to 80% of patients experience seizures, which can be focal or widespread and include status epilepticus. They can also happen at any stage of the disease (35,73,84,94).

Extreme irritability, sleeplessness, and mutism were all observed in a Chandigarh study of individuals with anti-NMDAR encephalitis who were younger than 12 years old. The three clinical phenotypes that have been found are classic form, psychiatric form (with good findings) & catatonia-predominant form.

6) Overlapping encephalitis - According to a recent study, several patients with anti-NMDAR encephalitis shared clinical characteristics or MRI findings with neuromyelitis optica (NMO). Anti-NMDAR with anti-MOG & many such dual-positive antibody syndromes, have all begun to be characterised. Anti-GABA-B antibodies with overlap seem to make up a higher proportion of the population. Opsoclonus syndrome and anti-NDMAR encephalitis may coexist(74,75).
7) Autoimmune encephalitis - Nearly 40% of AIE patients test positive for antibodies. Rapid symptom progression, ruling out well-defined AIE syndromes like typical limbic encephalitis, lack of serum and CSF antibodies, and two of the following signs or symptoms—abnormalities on MRI suggestive of autoimmune encephalitis, CSF pleocytosis, CSF-specific oligoclonal bands, elevated CSF IgG index, or inflammation infiltrates on brain biopsy—along with ruling out other causes—are included in the definition(53,58,66).

All kids who experience a polysymptomatic syndrome including encephalopathy, seizures, movement problems, mental characteristics, gait difficulties, and autonomic disturbances should have the diagnosis of AIE considered. The premise for the diagnosis of AIE is the existence of a suitable clinical condition that is supported by a variety of auxiliary studies. Confirmatory antibody testing

should be performed together with the elimination of all additional potential causes. The most frequent differential diagnoses are primary psychiatric disorders, inborn metabolic abnormalities, toxic exposures, CNS infections, CNS vasculitis, and neoplasms. Characteristics that point to an autoimmune origin include CSF pleocytosis, a rise in IgG index or oligoclonal bands, elevated CSF neopterin, abnormalities in MRI scans, and a response to immunosuppressive medication. Classic neuroimaging abnormalities in AIE include unilateral or bilateral T2/FLAIR signal hyperintensities affecting the mesial temporal lobe (70,82,84). In 63% of patients with anti-NMDAR encephalitis, there are no abnormalities on the neuroimaging scans. Signal hyperintensities, which are anomalies, may be present throughout the entire brain.

The foundation for the diagnosis of autoimmune encephalitis is the confirmation of the pathogenic antibodies. Testing positive results are considered "definite" cases, whereas negative results are considered "suspected". These antibodies bind to proteins on the cell surface that have conformational extracellular epitopes, such as receptors, synaptic proteins, or ion channels. The antibody binding is determined by their conformation and shape(92). Therefore, it is advised to employ eukaryotic cells that are either fixed or alive for cell-based studies. Serum testing for these antibodies is non-inferior to CSF testing, with the exception of anti-NMDAR encephalitis, where CSF testing is more sensitive, with a sensitivity of 100% (vs. 84.7% in serum)(73).

When patients with MOGAD and NMO are compared, there are a number of distinctions. MOGAD was more common in Caucasians, but AQP4-seropositive NMO was more common in non-Caucasian ethnicities. While MOGAD displayed a

lower ratio range, NMOSD had a ratio of roughly 8:1 with a substantially stronger female preference. Compared to NMO, MOGAD seemed to have a younger age of onset. Finally, while having a frequently relapsing disease course, patients with MOGAD usually had a milder clinical history than NMO patients(48).

In a study done in Spain on associations of pediatric demyelinating and encephalitis syndromes with myelin oligodndrocyte glycoprotein antibodies : a multicentre observational study, out of 535 children (239 with demyelinating syndromes and 296 with encephalitis other than Adem), 116 (21.68%) had MOG antibodies. Presenting syndromes in these 116 patients included ADEM (46), encephalitis other than ADEM (22), optic neuritis (20), myelitis (13), neuromyelitis optica spectrum disorders (6) and other disorders (9). Among the patients with non infectious encephalitis, MOG antibodies were common than all neuronal antibodies combined(67).

One-half to five percent of all demyelinating disorders in adulthood are caused by the MOGAD. In children (18 years old) who had anti-MOG antibody seropositivity after a first episode, studies from Europe have demonstrated that these antibodies are present in around 43% of all acute demyelinating syndrome presentations. 26 (24%) of the 110 kids with relapsing demyelinating syndrome also exhibited anti-MOG antibodies, and 26 (54%) of them had relapsing demyelination unrelated to multiple sclerosis. Only 34-44% of children presenting with optic neuritis and three (6%) of fifty patients with paediatric myelitis have MOG antibodies, but nearly all children who relapse after acute disseminated encephalomyelitis (multiphasic acute disseminated encephalomyelitis or acute disseminated

encephalomyelitis, optic neuritis) and up to 63% of children with acute demyelinating encephalomyelitis.(56,58)

The bulk of studies describing the incidence of anti-MOG antibodies and the clinical traits associated with them were carried out in tertiary referral centres for neuroinflammatory disorders due to potential selection bias. This is crucial when evaluating patients who may only be sent to these centres because of a severe or atypical presentation and who have clinical traits like optic neuritis or myelitis. Furthermore, the initial cohorts evaluated for anti-MOG antibodies using a cell-based assay excluded individuals with monophasic or recurrent optic neuritis or myelitis, which did not adequately reflect the prevalence of anti-MOG antibodies in all acute and chronic inflammatory demyelinating CNS illnesses(96).

Other CNS inflammatory disorders including MS and NMOSD are the most frequently occurring conditions to take into account that mirror MOGAD. Non-MOGAD ADEM is another diagnosis to take into account. The brain, spine, and occasionally the optic nerve are all affected by the classic non-MOGAD ADEM, a post-infection monophasic immune-mediated demyelinating CNS illness. On FLAIR or T2-weighted MRI, brain lesions that affect the brainstem, cerebral, and cerebellar white matter as well as symmetric involvement of the thalami and basal ganglia are typically bilateral, significant signal hyperintensities, and fluffy in appearance(79,86). The enhancement of gadolinium varies.

Based on evidence from (a) immunological studies suggesting a direct pathogenic impact of MOG-IgG, (b) neuropathological studies demonstrating discrete histopathological features, (c) serological studies reporting a lack of aquaporin-4 (AQP4)-IgG in almost all MOG-IgG-positive patients, and (d) cohort studies

suggesting differences in clinical and paraclinical presentation, treatment response and prognosis, MOG-IgG is now considered to denote a disease entity in its own right, distinct from classic MS and from AQP4-IgG-positive neuromyelitis optica spectrum disorders (NMOSD), which is now often referred to as MOG-IgG-associated encephalomyelitis (MOG-EM)(94).

MOG-EM is associated with a high risk of flare-ups after cessation of steroid treatment for acute attacks and may thus require close monitoring and careful steroid tapering. Patients positive for MOG-IgG might be particularly responsive to antibody-depleting treatments for acute attacks such as plasma exchange or immunoadsorption, to B cell-targeted long-term therapies such as rituximab, to treatment with intravenous immunoglobulins (IVIG), and to immunosuppressive treatments(82,83).

There is an unmet need for diagnostic criteria for MOG-EM. However, no specific clinical or radiological findings (except for the general requirement of a demyelinating CNS lesion) have yet been identified that are present in all MOG-IgG-positive patients. MOG-EM should be diagnosed in all patients who meet all of the following criteria(76):

a. Monophasic or relapsing acute ON, myelitis, brainstem encephalitis, or encephalitis, or any combination of these syndromes
b. MRI or electrophysiological (visual evoked potentials in patients with isolated ON) findings compatible with CNS demyelination
c. Seropositivity for MOG-IgG as detected by means of a cell-based assay employing full-length human MOG as target antigen

While the criteria proposed here can certainly help in identifying pediatric patients at high risk of being positive for MOG-IgG, they are primarily intended for use in adults and adolescents. Indications for MOG-IgG testing in children do not need to be as rigorous as in adults, since MOG-IgG is thought to be much more common in children with acquired demyelinating disease (up to 70% depending on age) than in their adult counterparts ($\leq 1\%$ in Western countries; probably $\leq 5\%$ in Japan and other Asian countries because of lower MS prevalence). In consequence, the risk of an unfavorable ratio of FP to TP results outlined above is lower in children. While ADEM is the predominant clinical association in young children, in older children with MOG antibodies there is a shift towards presentation with ON, myelitis, and/or brainstem symptoms(96).

NEURO-IMAGING:

Imaging of the optic nerves is essential for the diagnosis because ON is the most common presenting symptom of MOGAD. Injuries to the retrobulbar nerve segment and an anterior optic pathway lesion with considerable optic nerve head edema were found on MRI in these patients. Usually, the optic chiasm and the optic tract were unaffected. In addition, the posterior optic pathway, intracranial optic nerve, and chiasm were affected in the majority of NMO patients with ON (39,40). In a different study, bilateral and longitudinally extensive ON was found to be a symptom of the MOGAD and NMO, as opposed to MS, where ON was primarily unilateral and associated with shorter segments of optic nerve injury(17,47,84).

MRI of the spinal cord in TM patients revealed two likely lesion patterns. The first is the significant spinal cord involvement in LETM, which has been previously mentioned. LETM is characterised by abnormally intense T2 signals in at least three

adjacent vertebral body segments and edema that covers more than 50% of the axial section of the spinal cord. The symptoms of this MRI image, which may also appear in NMO, include sagittal line hyperintensity surrounded by a T2-hyperintense signal, concurrent with an H-shaped hyperintensity seen in axial sequences, and connected to grey matter involvement. The second type of injury is a T2-hyperintense alteration involving fewer than two spinal segments. The position in a medullary cone is regarded to be highly exact for the diagnosis of MOGAD, despite the fact that lesions can be observed anywhere along the spinal cord(32,39).

Imaging of brain was abnormal in about half of patients. In ADEM patients, brain MRI T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences commonly revealed an unspecific image with bilateral, poorly defined, fuzzy & widespread lesions affecting juxtacortical white matter, deep grey matter & occasionally cortical grey matter. Recent MRI scans of people who had MOGAD cortical presentations (seizures) showed unilateral cortical T2-FLAIR hyperintense changes without involvement of surrounding juxta-cortical white matter. These lesions were referred to as FLAMES, or FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures. They occasionally had FLAIR-variable unilateral enhancement of the leptomeninges (FUEL)(45,46).

The brainstem, cerebellar peduncles, or the area postrema were other poorly defined ("fluffy" or "fuzzy") areas located infratentorialy that were characteristic of MOGAD, though they were still not very specific because they can also occur in NMO. These areas were sometimes close to the fourth, third, and aqueduct. There were typically no more than three adjustments.

There is currently no substantially distinct radiological appearance that can distinguish MOGAD cases from non-MOG antibody instances(56,59).

MOGAD Diagnosis - The NMO and MOGAD differentiation issue is not resolved by the fact that NMO and MOGAD share a number of clinical symptoms but are different nosological entities, with NMO being an autoimmune astrocytopathy and CNS demyelination occurring after the astrocytic destruction(64).

Since neither the clinical nor the neuroimaging findings are very specific for MOGAD, the anti-MOG antibody testing results are crucial for accurate diagnosis. As a result, the global guidelines for trustworthy analysis are discussed. The gold standard method is the cell-based assay that uses full-length human MOG as the target antigen. They also suggest utilising Fc or IgG1-specific secondary antibodies to avoid cross-reactivity with IgM and IgA antibodies. Additional laboratory methods, such as immunohistochemistry, peptide-based ELISA, or Western blotting, are not suggested for the detection of anti-MOG IgG antibodies due to their low specificity. Because of the low antibody levels in cerebral fluid, serum is the ideal source for MOG IgG testing. If delivery can't happen within 1-2 days, samples should be kept at 4°C or shipped on dry ice. Another essential factor is sample time(67). The severity of the illness affects MOG-IgG serum levels, which are higher during acute attacks and lower after remission or in the chronic phase, or even nonexistent after a monophasic occurrence. The treatment strategy also has an impact on the test results. Therefore, when MOGAD is strongly suspected but anti-MOG- IgG testing is negative, patients should be retested. This should be carried out as soon as possible after receiving intravenous immunoglobulins, steroids, or plasma exchange, or during acute attacks, treatment-free intervals, or 1-3 months afterward (18). A combination of clinical,

imaging, and laboratory data should be used to determine whether MOG antibody testing is necessary in those who have a high risk of MOGAD and/or in the occurrence of symptoms that are unusual for MS and NMSOD. Patients who have negative AQP4-IgG levels and the NMOSD phenotype should be given extra consideration in the analysis(74).

TREATMENT:

Because of its recent onset, low prevalence, age-related differences in presentation, and wide range of clinical symptoms, conducting controlled multicenter, large therapeutic studies for MOGAD may be difficult. Actually, no such study has been conducted to this point. For the acute and continuous immunotherapy for MOGAD, there are no evidence-based guidelines. Given that this condition has been separated from MS and the NMO spectrum, it is not surprising that similar treatment techniques have been tested. High-dose intravenous methylprednisolone is the preferred medication for treating acute exacerbations (usually 0.5 - 2.0 grams for 5 to10 days). Plasma exchange and intravenous immunoglobulin were administered as soon as possible to patients who were experiencing more severe (or steroid-resistant) attacks (IVIG)(51). Studies on general populations with MOGAD have shown that these treatments are quite effective. More than 50% of ON patients who received IVMP showed practically complete recovery. Additionally, there are sporadic accounts of patients with brainstem and cortical encephalitis making a full recovery(22).

Unfortunately, after stopping or reducing the dosage of steroids, the likelihood of things getting worse increased(53,54,55). There were a significant number of second relapses recorded. In the UK experiment, over a two-year period, the

following incident happened in around 50% of cases (51). Relapses were discovered during a follow-up in as many as 80% of patients in another often referenced study. In contrast to MS, MOGAD disability progression is relapse-dependent, hence maintenance medication should be started in a proportion of patients, particularly in those who have positive anti-MOG antibodies. Higher antibody levels and persistent seropositivity over time were discovered to be associated with a recurring illness history and growing disability. The majority of immunosuppressive and immunomodulatory medications, including oral corticosteroids, rituximab, azathioprine, methotrexate, mycophenolate mofetil, and many cycles of IVIG, have been utilised in therapy regimens to prevent MOGAD attacks(89).

The typical and practical method for preventing relapses is a lengthy progressive taper off Oral corticosteroids with their anti-inflammatory activity (decrease of total antibody production). In a UK study, patients who received oral prednisolone 10 mg daily for more than three months saw a relapse risk of roughly 26%, compared to 48% for patients who received immunosuppression for less time or for no immunosuppression at all. Other groups verified the effectiveness of low dose oral prednisolone 10 mg daily. However, because long-term steroid therapy has potentially fatal side effects, switching to a steroid-sparing medication can be considered. Patients fared better with immunosuppressive drugs such AZT (adjunctively with oral steroids), MMF, and MTX in terms of relapses and disability. RTX has varying degrees of efficiency. Similar to individuals with AQP4-positive NMO, fresh relapses were observed in roughly 30% of MOGAD patients within a few weeks of the first infusion despite the medication's good biological action(98).

IVIG infusions showed promise in terms of effectiveness. Initial research and case reports revealed that MOGAD patients responded well to treatment. The IVIG-treated group showed the lowest yearly relapse rate. 21% of patients receiving IVIG, 58% receiving AZA, 62% receiving RTX, and 72% receiving MMF saw patient deterioration(54).

mRS SCORE :

The modified Rankin Measure (mRS) is a regularly used scale for assessing how dependent or disabled people who have experienced a stroke or other neurological disability are in their everyday activities. For clinical trials involving stroke, it has emerged as the most often utilised clinical outcome metric(78).

The scale runs from 0–6, running from perfect health without symptoms to death :

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 - Dead.

METHODOLOGY

PLACE: This study was conducted from January 2021 to October 2022 in the paediatric intensive care units of KLE'S Dr Prabhakar Kore Hospital and Medical Research centre (MRC), Belagavi, a 2400 bedded hospital including super-specialties, a teaching hospital affiliated with Jawaharlal Nehru Medical College.

STUDY DESIGN: A single teritiary hospital based cross-sectional observational study

STUDY PERIOD: One year and 10 months duration from January 2021 to October 2022. Study was extended by 10 months in view of less recruitment of patients due to covid pandemic.

SUBJECTS: A cross sectional study will be conducted at KLE's Prabhakar Kore hospital, Belagavi on children aged above 1 month & under the age of 18 years presenting as suspected case of non infectious encephalitis in emergency & intensive care units over a period of one year ten months.

SAMPLE SELECTION CRITERIA –

INCLUSION CRITERIA: All cases above 1 month and less than 18 years of age presenting with acute onset of fever & change in mental status (confusion, disorientation, inability to talk or coma) and / or new onset of seizures

EXCLUSION CRITERIA: 1) Cases where lumbar puncture cannot be done

2) Cases where MRI cannot be done

SAMPLE SIZE: Sample size was calculated assuming the prevalence as 19% as per the study by Thais et al. in Barcelona, Spain.

The other parameters considered for sample size calculation were 5% absolute precision and 95% confidence level. The following formula was used

Based on previous hospital records, approximate number of potential candidates eligible attending the study setting during the data collection period were considered as 80.

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1) + Z^2P(1-P)}$$

Where n= sample size, N=Population size, P= Expected Prevalence, Z=statistic for a level of confidence, d=precision.

N = 80, Z = 1.96, P = 0.19, d = 0.05

Using the formula the sample size comes out to be 61.

ETHICAL CLEARANCE: The institutional ethical committee of Jawaharlal Nehru Medical College, Belagavi, approved the study prior to its start.

INFORMED CONSENT: The study's nature was explained to the parents of children with diagnosed or suspected acute non infectious encephalitis syndrome, who met the eligibility criteria. A written informed consent was also collected prior to enrolment in a language that they were familiar with. (Annexure I).

All cases above 1 month and less than 18 years of age getting admitted in emergency & PICU with history of acute onset of fever with altered sensorium with or without seizures will be considered. Informed consent will be taken from the patient & parent after explaining to them about objective of the study, risks & benefits involved, privacy & confidentiality of patient, cost involved for the study. After taking verbal or written consent, patient will be enrolled for the study. Thorough history to be taken, complete neurological examination done along with all routine blood investigations, CSF analysis and MRI. Possible infectious causes would be ruled out by CSF cell count, culture, gram staining and HSV PCR, and MRI features. Based on MRI findings, cases would be divided into demyelinating and non demyelinating cases. Serum for MOG antibody taken & tested through cell bases array. All the MOG positive cases will be given methyl prednisolone pulse therapy. Follow up of all cases will be done at 1, 3 & 6 months to assess the outcome & response between MOG positive & MOG negative encephalitis cases will be assessed through modified Rankin scale.

STATISTICAL METHODS:

Descriptive analysis: For quantitative variables, the mean and standard deviation were used in the descriptive analysis, while frequency and proportion were used for categorical variables. The median and interquartile rangewere used to summarise non-normally distributed quantitative values (IQR). Data was also displayed using the relevant diagrams, such as box plots, pie charts, and bar charts.

Data was collected & stored in microsoft excel. Data was analysed using statistical software R & excel. Continuous variables was given by mean +/- sd/median (range). Categorical variables will be given by frequency. To check dependency between

attributes, chi square test was used. To compare mean/distribution over groups, t test was used. To analysed paired nominal dara, McNemar test was used. To check normality of variables, quantile – quantile plot was used. P value less than or equal to 0.05 shows statistical significance.

RESULTS

RESULTS FOR MOG SERO-POSITIVITY IN CHILDREN WITH ACUTE NON-INFECTIOUS ENCEPHALITIS SYNDROME –

A total of 61 cases were enrolled, who were above 1 month and less than 18 years of age who got admitted in pediatric emergency with history of acute onset of fever with altered sensorium with or without seizures. After thorough history, complete neurological examination, routine blood investigations, CSF analysis, CT/MRI scans were done. Possible infectious causes would be ruled out by CSF cell count, culture, gram staining and HSV PCR, and MRI features. Based on MRI findings, cases would be divided into demyelinating and non demyelinating cases. Serum for MOG antibody taken & tested through cell bases array. Almost all cases were given methyl prednisolone pulse therapy. Follow up of all cases were done at 1,3 & 6 months to assess the outcome & response between MOG positive & MOG negative encephalitis cases was assessed through modified Rankin scale.

DEMOGRAPHIC DATA :

1. **AGE DISTRIBUTION OF PATIENTS –**

Children who were above 1 month of age & less than 18 years of age were enrolled in our study. The age group distribution of the study is depicted in below table.

Table 1: Age distribution of cases

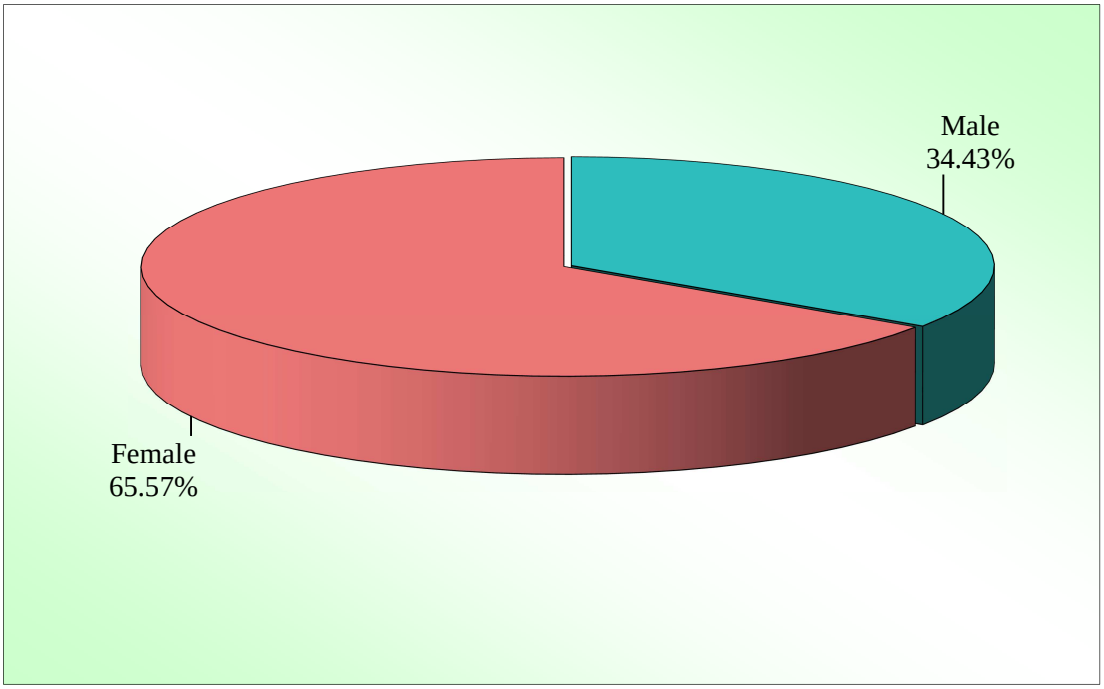
Age groups	No of patients	% of patients
1-5yrs	19	31.15
6-10yrs	17	27.87
>=11 yrs	25	40.98
Total	61	100.00
Mean age	8.72	
SD age	4.87	

In our study, total of 61 children were enrolled with the age distribution was from 1 month of age till 18 years of age, out of which the majority 25 (40.98%) were in the age group of 11-18 years. Mean age was 8.72 years & SD age being 4.87. This shows that olden children were more affected by acute encephalitis than younger children in our region.

2. GENDER DISTRIBUTION :

Out of 61 children who were enrolled in the study, 40 (65.57%) were females & 21 (34.43) were males. The females to males ratio in the study was 2:1. The gender distribution of subjects has been shown in the following pie chart.

Graph 1: Gender wise distribution of patients



3. CLINICAL PRESENTATION –

Out of 61 cases, 57 (93.44%) came with history of fever, 46 (75.40%) with altered sensorium, 41 (67.21%) with new onset seizures, 13 (21.31%) with limb weakness & 4 (6.55%) with sudden onset blindness of one or both eyes at the time of admission.

Table 2: Clinical presentation of cases

Clinical presentation	Number (n = 61)	Percentage
Fever	57	93.44%
Altered sensorium	46	75.40%
Seizures	41	67.21%
Limb weakness	13	21.31%
Blindness	4	6.55%

4. CLINICAL DIAGNOSIS –

Out of 61 cases, 9 cases (14.75%) were diagnosed as meningitis, 11 cases(18.03%) as acute disseminated encephalomyelitis, 4 cases(6.55%) as Neuromyelitis optica spectrum disorder (NMOSD), 31 cases (50.81%) as autoimmune encephalitis while 6 cases (9.83%) were diagnosed of others not mentioned above.

Table 3: Clinical diagnosis

Clinical diagnosis	Cases (n = 61)	Percentage
Meningitis	9	14.75%
ADEM	11	18.03%
AE (Non-ADEM)	31	50.81%
NMOSD	4	6.55%
Others	6	9.8%

5. CSF ANALYSIS –

Out of 61 cases, there was positive CSF cell count in 26 (42.62%) of them. Positive CSF cell count was defined as presence of cells more than 5 per cu.mm. There was more of lymphocyte predominance - 35 (84.61%) than neutrophils - 4 (15.38%). 13 (21.30%) had abnormal CSF glucose, defined by CSF glucose concentration less than 45 mg/dl or more than 80 mg/dl whereas abnormal CSF protein was seen in 7 (11.40%) of cases, defined by CSF proteins of less than 15mg/dl or more than 60 mg/dl.

Table 4: CSF Analysis

CSF characteristics	***Cases***
Positive cell count	26
Lymphocyte predominance	22
Neutrophil predominance	4
Abnormal CSF glucose	13
Abnormal CSF protein	7

6. IMAGING –

Out of 61 cases, there were abnormal CT scan findings in 11 of them, while 23 had abnormal MRI findings & 8 had both CT and MRI scan abnormalities.

Table 5: Cases with abnormalities in imaging studies

Abnormal findings	Cases
CT	11
MRI	23
Both	8

Among all the sites that were seen affected in CT/MRI scans, the most commonly involved area was the cortex 14 (22.90%) & the least commonly affected area was the spinal cord in one case (1.6%).

Table 6: Site of abnormalities in imaging studies

Site of lesion	Cases (n=28)	Percent
Cortex	14	50%
Subcortex	6	21.4%
Basal ganglia	3	10.71%
Brainstem	2	3.27%
Cerebellum	2	3.27%
Spinal cord	1	3.56%

Out of 61 cases, demyelination was observed in 11 (18.03%) cases while meningeal enhancement was seen in 8 (13.11%) cases.

Table 7: Type of abnormalities in MRI

Types of abnormal findings	Cases
Demyelination	11
Meningeal enhancement	8

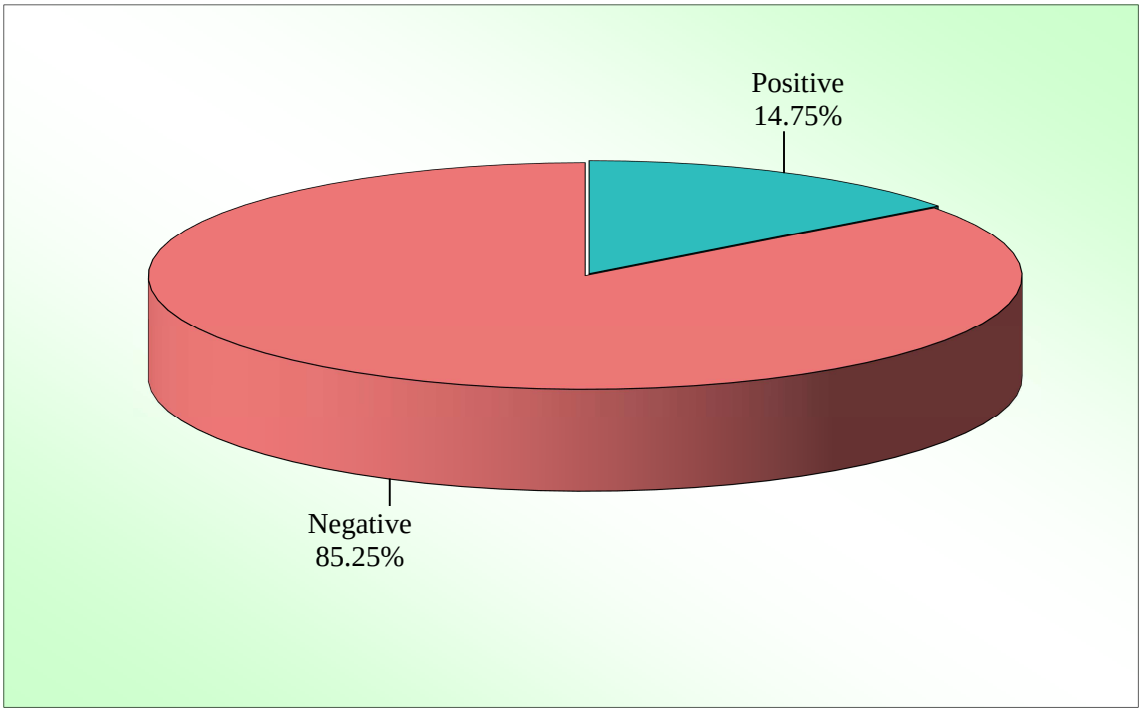
7. MOG SERO-POSITIVITY :

Out of 61 children with acute encephalitis syndrome, 9 (14.75%) turned out to be positive for myelin oligodendrocyte glycoprotein antibody & 52 (85.25%) were negative.

Table 8: MOG status

Status MOG	No of patients	% of patients
Positive	9	14.75
Negative	52	85.25
Total	61	100.00

Graph 2: Status MOG wise distribution of patients

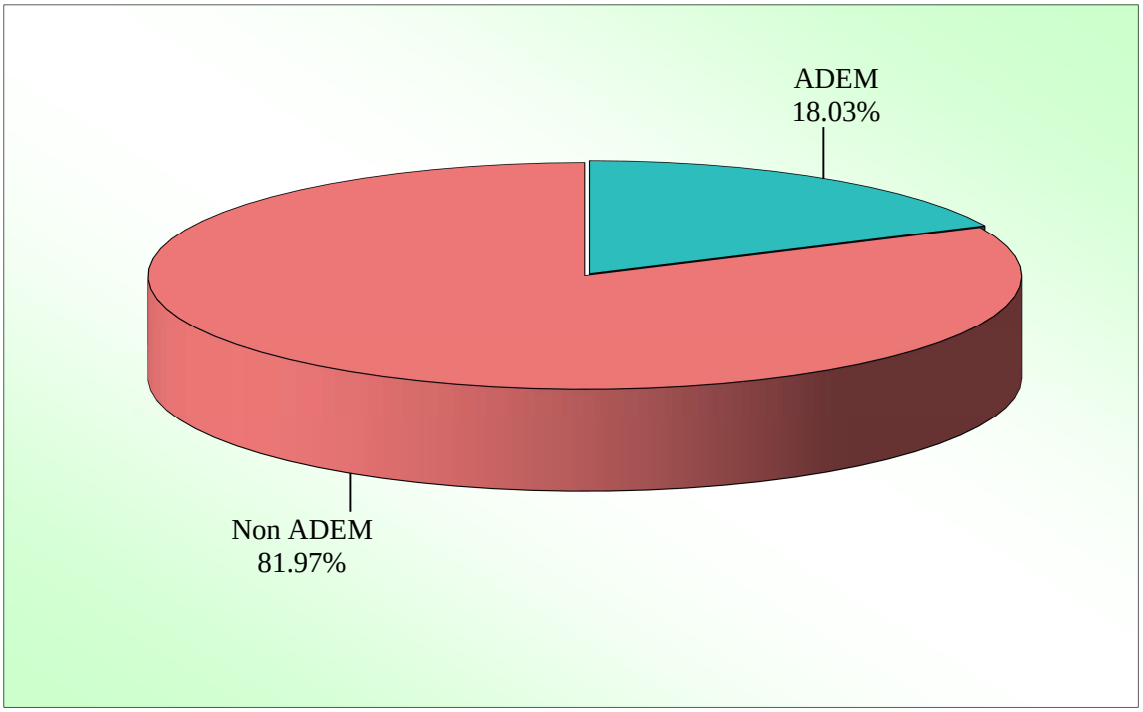


Out of 61 children acute encephalitis cases, 11 (18.03%) were diagnosed of ADEM & 50 (81.97%) were diagnosed of encephalitis other than ADEM.

Table 9: ADEM / Non ADEM wise distribution of patients

ADEM / Non ADEM	No of patients	% of patients
ADEM	11	18.03
Non ADEM	50	81.97
Total	61	100.00

Graph 3: Status ADEM / Non ADEM wise distribution of patients



Presentation of MOG positive cases –

Out of all MOG POSITIVE cases, the most common age of presentation was above 11 years – 5 (55.55%) & males - 5 (55.55%) were more involved than females. There was abnormal CSF findings in 6 (66.67%) of cases & MRI scan abnormalities in 5 (55.56%) of MOG positive cases.

Table 10: Presentation of MOG Positive cases

Characteristics		Cases (n=9)	Percentage
Age	1 – 5 years	0	0
	6 – 10 years	4	44.45%
	> 11 years	5	55.55%
Gender	Male	5	55.55%
	Females	4	44.45%
CSF findings	Normal	6	66.67%
	Abnormal	3	33.33%
MRI findings	Normal	5	55.55%
	Abnormal	4	44.45%

Out of 9 cases which were POSITIVE for MOG antibody, 5 (55.56%) were ADEM while 4 (44.44%) were encephalitis other than ADEM. And out of 52 cases which were NEGATIVE for MOG antibody, 6 (11.54%) were ADEM & 46 (88.46%) were non ADEM cases.

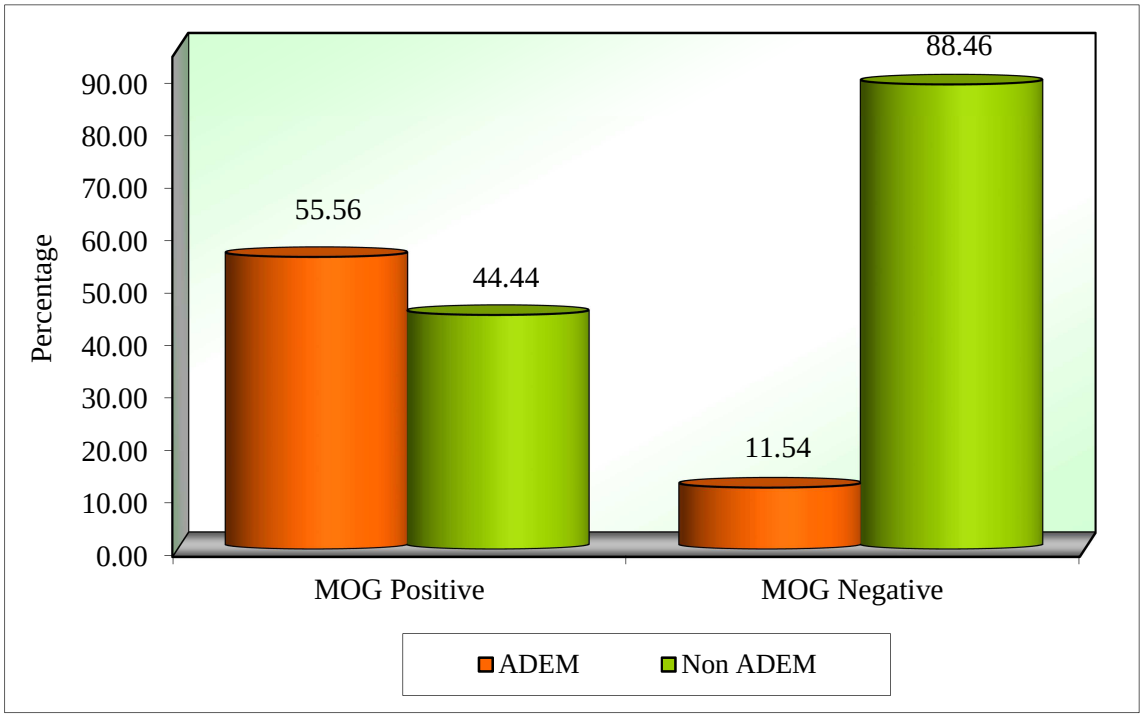
There was statistical significance in correlation between MOG sero-positivity & type of encephalitis.

Table 11: Association between ADEM & MOG sero-positivity

ADEM	MOG Positive	%	MOG Negative	%	Total	%
ADEM	5	55.56	6	11.54	11	18.03
Non ADEM	4	44.44	46	88.46	50	81.97
Total	9	100.00	52	100.00	61	100.00
Chi-square=10.0570, p=0.0020*						

*p<0.05

Graph 4: ADEM vs MOG sero positivity



Comparision between ADEM MOG & NON ADEM MOG cases –

All the typical characteristics of acute encephalitis syndrome – fever, altered sensorium, seizures, CSF abnormalities, MRI abnormalities were more seen in ADEM MOG group than NON ADEM MOG group although there were more recovery rate in NON ADEM MOG group than ADEM MOG group.

Table 12: Comparison between ADEM MOG & Non ADEM MOG cases

Characteristics	ADEM MOG (n =5)	Percentage	NON ADEM MOG (n=4)	Percentage
Fever	5	100%	3	75%
Altered sensorium	5	100%	2	50%
Seizures	4	80%	3	75%
CSF abnormalities	3	60%	2	50%
MRI abnormalities	5	100%	3	75%
Outcomes (MRS </= 2 at 1 month)	4	80%	4	100%

Comparision between MOG POSITIVE and MOG NEGATIVE cases –

Out of all the cases, MOG POSITIVE cases had more altered sensorium & seizures at presentation than MOG negative group. Abnormal CSF & MRI findings were also more common in MOG positive group than MOG negative group while there was no difference observed with respect to recovery rates.

Table 13: Comparison between MOG Positive & MOG negative cases

Characteristics	MOG Positive	% of cases	MOG Negative	% of cases	Total	% of cases
Fever	8	88.88%	49	94.20%	57	93.44%
Altered sensorium	7	77.99%	39	75.00%	46	75.40%
Seizures	7	77.99%	34	65.38%	41	67.21%
GCS < 10	3	33.33%	13	25%	16	26.22%
Abnormal CSF findings	5	55.55%	12	9.60%	17	27.86%
Abnormal CT/MRI findings	8	88.88%	17	32.60%	25	40.98%
Outcome (MRS </=2 at 1 month)	8	88.88%	45	86.50%	53	86.88%

Follow up MRI –

MRI scan was repeated in 17 cases at follow up of 1 month. Out of 17 cases, 12 (70.58%) had abnormal findings.

Table 14: Follow up MRI cases

MRI Findings	Number
Normal	5
Abnormal	12

Treatment given :

Out of 61 cases, 53 (86.88%) received antibiotics during hospital stay, 32 (52.45%) of them also received antiviral. 51 (83.60%) received anti seizure medications while 54 (88.52%) received pulse methyl prednisolone therapy. Only 2 (3.20%) received immunoglobulin while 3 (4.91%) received rituximab infusion.

Table 15: Modalities of treatment

Modalities	Number	% of cases
Antibiotics	53	86.88%
Antiviral	32	52.45%
Anti seizure medications	51	83.60%
Methyl prednisolone	54	88.52%
ivig	2	3.20%
Rituximab	3	4.91%

Table 16: Comparison of MOG sero-positivity with number of antibiotics, duration of antibiotics & number of ASM

Variables	MOG Positive		MOG Negative		t-value	p-value
	Mean	Std.Dev.	Mean	Std.Dev.		
Number of antibiotics	1.89	1.69	2.38	1.09	-1.1401	0.2590
Duration of antibiotics	5.25	3.54	5.80	2.30	-0.5746	0.5679
Number of ASM	2.00	1.00	2.45	1.02	-1.2152	0.2294

Graph 5: Comparison of MOG sero positivity with mean number of antibiotics, duration of antibiotics and Number of anti seizure medications

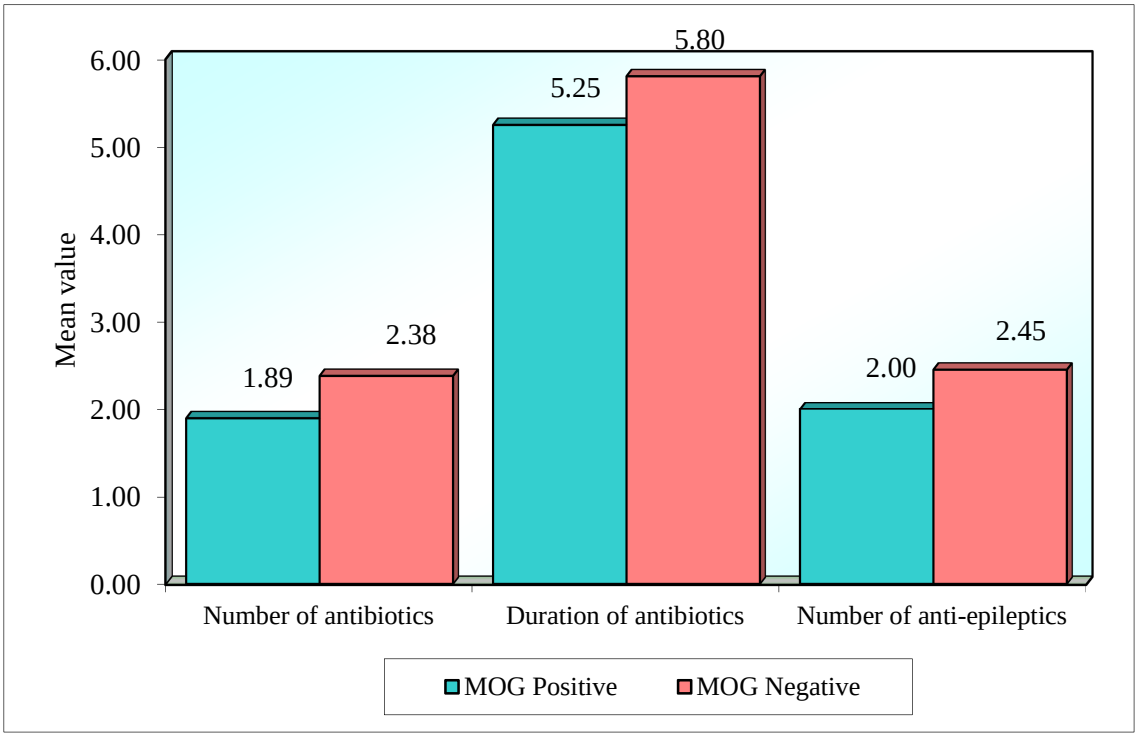


Table 17: Comparison of ADEM MOG cases & Non ADEM MOG cases with number of antibiotics, duration of antibiotics & number of ASM

Variables	ADEM MOG		Non ADEM MOG		t-value	p-value
	Mean	Std.Dev.	Mean	Std.Dev.		
Number of antibiotics	1.67	1.84	2.73	1.42	-1.2354	0.2784
Duration of antibiotics	5.76	3.79	6.94	3.14	-0.6123	0.4534
Number of ASM	3.00	2.00	2.45	1.36	-1.3124	0.2065

Table 18: Comparison of MOG sero-positivity with duration of stay, condition at discharge & 1 month after discharge

Variables	MOG Positive		MOG Negative		t-value	p-value
	Mean	Std.Dev.	Mean	Std.Dev.		
Duration of stay	7.44	4.25	7.77	3.36	-0.2576	0.7976
Condition at discharge (mrs)	2.00	1.00	2.06	1.13	-0.1487	0.8823
F/U 1month (mrs)	1.11	0.93	0.94	1.17	0.4156	0.6793

Graph 6: Comparison of MOG sero positivity with mean Duration of stay, Condition at discharge (mrs) and F/U 1month (mrs)

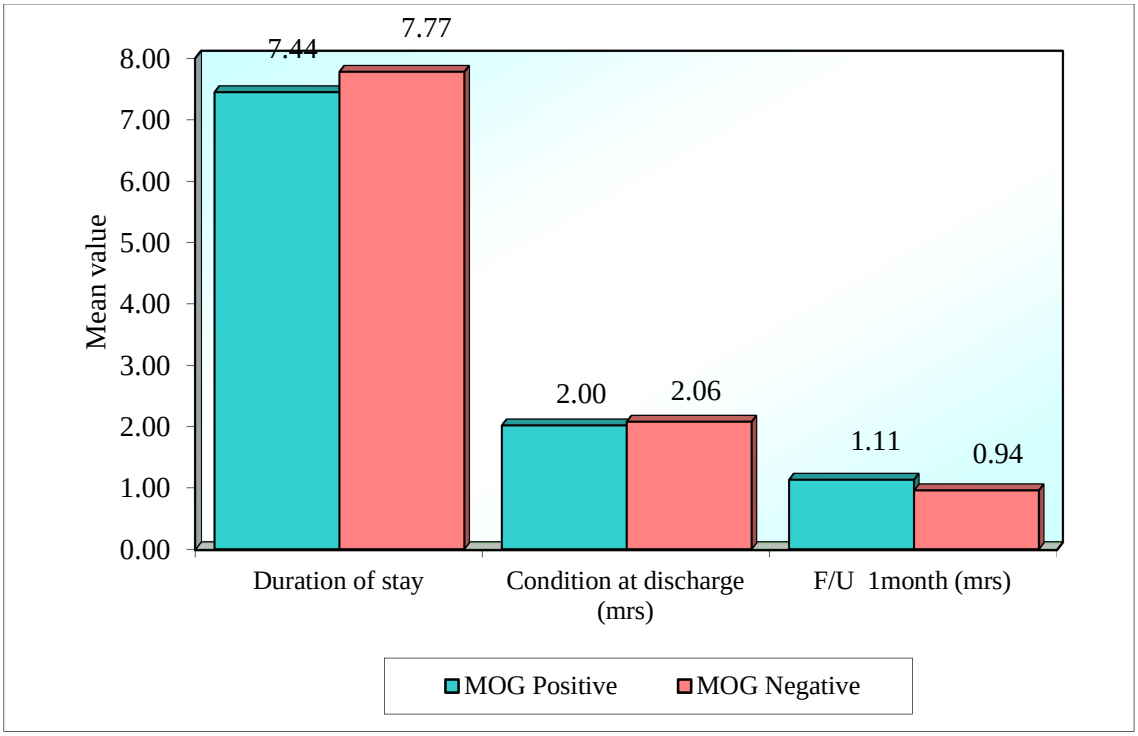


Table 19: Comparison of ADEM MOG & Non ADEM MOG cases with number of antibiotics, duration of antibiotics & number of ASM

Variables	ADEM MOG		Non ADEM MOG		t-value	p-value
	Mean	Std.Dev.	Mean	Std.Dev.		
Duration of stay	8.16	5.02	7.89	3.67	-0.2678	0.8768
Condition at discharge (mrs)	2.00	1.00	1.92	1.10	-0.1845	0.6739
F/U 1month (mrs)	1.34	0.89	0.91	1.23	0.6145	0.7124

Table 20: Comparison of MOG sero-positivity with all variables

Variables	MOG Positive		MOG Negative		t-value	p-value
	Mean	Std.Dev.	Mean	Std.Dev.		
Number of antibiotics	1.89	1.69	2.38	1.09	-1.1401	0.2590
Duration of antibiotics	5.25	3.54	5.80	2.30	-0.5746	0.5679
Number of antiepileptics	2.00	1.00	2.45	1.02	-1.2152	0.2294
Duration of stay	7.44	4.25	7.77	3.36	-0.2576	0.7976
Condition at discharge (mrs)	2.00	1.00	2.06	1.13	-0.1487	0.8823
F/u 1month (mrs)	1.11	0.93	0.94	1.17	0.4156	0.6793

Response to treatment :

Out of 61 cases, 35 (57.37%) had MRS score between 2-4, dropping to 23 (37.77%) at 1 month of follow up & to 16 (26.62%) at 3 months of follow up. 3 out of 61 cases died during course of treatment.

Table 21: Response to treatment by MRS score

Time of assessment	MRS (0 – 1)	MRS (2 – 4)	MRS (5 – 6)
Discharge	21	35	5
Follow up at 1 month	34	23	4
Follow up at 3 months	41	16	4

DISCUSSSION

A total of 61 cases were enrolled, who were above 1 month and less than 18 years of age who got admitted in pediatric emergency with history of acute onset of fever with altered sensorium with or without seizures. After thorough history, complete neurological examination, routine blood investigations, CSF analysis, CT/MRI scans were done. Possible infectious causes would be ruled out by CSF cell count, culture, gram staining and HSV PCR, and MRI features. Based on MRI findings, cases would be divided into demyelinating and non demyelinating cases. Serum for MOG antibody taken & tested through cell bases array. Almost all cases were given methyl prednisolone pulse therapy. Follow up of all cases were done at 1,3 & 6 months to assess the outcome & response between MOG positive & MOG negative encephalitis cases was assessed through modified Rankin scale.

In our study, total of 61 children were enrolled with the age distribution from 1 month of age till 18 years of age, out of which the majority 25 (40.98%) were in the age group of 11-18 years, followed by 19 (31.15%) in the age group of 1 – 5 years & 17 (27.87%) in the age group of 5 – 10 years. Mean age was 8.72 years & SD age being 4.87. Most of the studies done on AES backs this observation including the one done by Gitali Kakoti et al, where out of 140 AES children, 5–12 years age group had the highest 79 (56.4%) number of cases. Generally, infectious type like viral encephalitis tends to be more common in younger children while there's very less studies on age group differences with non infectious type involving autoimmune pathology. Our study showed that olden children were more affected by non infectious acute encephalitis syndrome than younger children in our region.

Out of 61 children who were enrolled in the study, 40 (65.57%) were females & 21 (34.43) were males. The females to males ratio in the study was 2:1. Conditions such as Neuromyelitis optica spectrum disorder (NMOSD), autoimmune encephalitis (AE), myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) which are antibody-mediated neurological diseases have mostly female predominance, affecting many women during childbearing age, as stated by Aysa Altintas et al. This may be related to female hormones involved with pregnancy in later part of the life.

Out of 61 cases, 57 (93.44%) came with history of fever, 46 (75.40%) with altered sensorium, 41 (67.21%) with new onset seizures, 13 (21.31%) with limb weakness & 4 (6.55%) with sudden onset blindness of one or both eyes at the time of admission. Fever was the most common presentation with respiratory system being most commonly affected system – 34 cases (59.60%), followed by GIT in 14 (24.56%) cases, Genito urinary in 5 (8.77%), skeletal in 2 cases (3.50%), eyes in 2 cases (3.50%). Most of the cases having fever backs up the theory of para infectious mechanisms in these cases where there are circulating autoimmune antibodies in the blood & this fever event breaks the blood brain barrier causing such wide spectrum of CNS symptoms. Most of the cases having fever at onset of their symptoms reiterates para infectious theory than post infectious one.

Out of 61 cases, 9 (14.74%) were diagnosed as meningitis, 11 (18.03%) as acute disseminated encephalomyelitis, 4 (6.55%) as Neuromyelitis optica spectrum disorder (NMOSD), 31(50.81%) as autoimmune encephalitis while 6 (9.83%) were diagnosed of others not mentioned above.

Out of 61 cases, there was positive CSF cell count in 26 (42.62%) of them. Positive CSF cell count was defined as presence of cells more than 5 per cu.mm. There was more of lymphocyte predominance - 35 (57.37%) than neutrophils - 4 (6.55%). 13 (21.30%) had abnormal CSF glucose, defined by CSF glucose concentration less than 45 mg/dl or more than 80 mg/dl whereas abnormal CSF protein was seen in 7 (11.40%) of cases, defined by CSF proteins of less than 15mg/dl or more than 60 mg/dl.

Out of 61 cases, there were abnormal CT scan findings in 11 of them, while 23 had abnormal MRI findings & 8 had both CT and MRI scan abnormalities.

Among all the sites that were seen affected in CT/MRI scans, the most commonly involved area was the cortex 14 (22.90%) & the least commonly affected area was the spinal cord in one case (1.6%).

Out of 61 cases, demyelination was observed in 11 (18.03%) cases while MRI contrast study was done in 18 cases where meningeal enhancement was seen in 10 (55.55%) cases.

Out of 61 children with acute encephalitis syndrome, 9 (14.75%) turned out to be positive for myelin oligodendrocyte glycoprotein antibody & 52 (85.25%) were negative.

Out of 61 children acute encephalitis cases, 11 (18.03%) were diagnosed of ADEM & 50 (81.97%) were diagnosed of encephalitis other than ADEM.

According to a 2008 study by Lotze TE, there are between 3 to 6 ADEM cases seen each year at regional medical institutions in the US, UK, and Australia. The

estimated incidence of ADEM in California is 0.4 per 100,000 people per year. Adults are less likely to get ADEM than children and adolescents do, and there doesn't appear to be a difference in the prevalence of ADEM between genders or among different racial or ethnic groups.

In our study group, out of 11 ADEM cases that were diagnosed, 9 cases (81.81%) had history of fever with some foci of infection few days prior to getting admitted in the hospital. This reiterates the assumption that any viral or bacterial infection precedes the inflammatory onslaught in 50 to 75 percent to cases of ADEM. 7 cases (63.63%) had altered sensorium & 6 cases (54.55%) had new onset seizures at time of presentation. Neurological symptoms and the inflammatory condition frequently appear a few weeks after the viral or bacterial disease.

Out of all MOG POSITIVE cases, the most common age of presentation was above 11 years – 5 (55.55%) & males - 5 (55.55%) were more involved than females. There was abnormal CSF findings in 6 (66.67%) of cases & MRI scan abnormalities in 5 (55.56%) of MOG positive cases.

Out of 9 cases which were POSITIVE for MOG antibody, 5 (55.56%) were ADEM while 4 (44.44%) were encephalitis other than ADEM. And out of 52 cases which were NEGATIVE for MOG antibody, 6 (11.54%) were ADEM & 46 (88.46%) were non ADEM cases. There was statistical significance in correlation between MOG sero-positivity & type of encephalitis.

All the typical characteristics of acute encephalitis syndrome – fever, altered sensorium, seizures, CSF abnormalities, MRI abnormalities were more seen in

ADEM MOG group than NON ADEM MOG group although there were more recovery rate in NON ADEM MOG group than ADEM MOG group.

Out of all the cases, MOG POSITIVE cases had more altered sensorium & seizures at presentation than MOG negative group. Abnormal CSF & MRI findings were also more common in MOG positive group than MOG negative group while there was no difference observed with respect to recovery rates.

MRI scan was repeated in 17 cases at follow up of 1 month. Out of 17 cases, 12 (70.58%) had abnormal findings.

Out of 61 cases, 53 (86.88%) received antibiotics during hospital stay, 32 (52.45%) of them also received antiviral. 51 (83.60%) received anti seizure medications while 54 (88.52%) received pulse methyl prednisolone therapy. Only 2 (3.20%) received immunoglobulin while 3 (4.91%) received rituximab infusion.

Out of 61 cases, 35 (57.37%) had MRS score between 2-4, dropping to 23 (37.77%) at 1 month of follow up & to 16 (26.62%) at 3 months of follow up. 3 out of 61 cases died during course of treatment.

In this observational cross sectional study of 61 children with non infectious acute encephalitis syndrome, 9 (14.75%) cases had MOG antibodies. These antibodies were more prevalent in the demyelinating disorders (55.55%) than in the group with non demyelinating disorders (45.45%). Regarding the group of children with acute demyelinating diseases, our findings confirm the prevalence of MOG with new onset ADEM & relapsing CDEM.

When focussing on group of 9 children with MOG antibodies, the most common syndromes included ADEM, MOG spectrum disorder, relapsing CDEM, autoimmune encephalitis, varicella encephalitis, overlapping anti MOG & anti NMDAR encephalitis. Most of these cases presented with atypical symptoms or MRI findings. These findings are very important because this MOG antibody testing is rarely include in the diagnostic workup of patients suspected with encephalitis & many would've have been misdiagnosed and missed.

We didn't find any substantial difference between sex distribution in these MOG antibodies but with respect to age, they were seen in only older children (44 % in 6 – 10 years group & 56% in 10 years & above group, none in 1 – 5 years age group). CSF findings & MRI findings were normal in 66.66% & 55.55% of MOG positive cases respectively, making clinical suspicion & diagnosis of the conditions challenging.

The frequency of clinical relapses among 11 ADEM cases followed from time of presentation was 1 (9.09%). In other prospective studies focused on demyelinating disorders, the frequency of relapses ranged from 18% (18 of 99 patients) to 38% (25 of 65). 10 cases (90.90%) of ADEM had complete or almost complete recovery by the time of last follow up at 6 months. In the one chronic demyelinating disorder case which had multiple relapses, Rituximab was used to treat the relapse, just similar to those studies reported by others.

In our study, patients who became MOG antibody negative were less likely to develop relapses than those who remained sero-positive, as reported by Waters & colleagues.

STRENGTHS OF THE STUDY

- Our study was a prospective observational cross-sectional study.
- At our centre, we had pediatric neurologist guiding in diagnosis of suspected acute encephalitis syndrome cases as these cases could be missed due to very wide spectrum of clinical presentation.
- MOG antibody testing was done using cell based assay in all suspected cases of autoimmune encephalitis, this kind of study hasn't been done in this part of country. This study helps to know & compare prevalence of MOG antibodies with studies done in western countries.

LIMITATIONS OF THE STUDY

- The duration of this observational study was short, so we may have underestimated the prevalence of these MOG antibodies in our region, as well as missed any relapse due to shorter duration of follow up.
- The outcome of these cases was assessed with mRS score which is widely used in studies related to autoimmune encephalitis, but doesn't accurately assess the cognitive impairment.
- We were able to get less number of cases because of covid pandemic.
- We weren't able to do virological studies in the cases because of cost factor
- Radiological follow up scans couldn't be done in most of the cases.
- Repeat MOG antibody testing couldn't be done at successive follow ups.

CONCLUSION

- The MOG sero-positivity was found to be 14.75% in aseptic acute encephalitis syndrome cases in our cases.
- MOG seropositivity is associated with both demyelinating disorders & meningo - encephalitis presentation.
- It appears that there is a wider spectrum of MOG antibody-associated disorders in children than is currently thought to exist in our clinical practise. Early diagnosis of these disorders has significant clinical and prognosis ramifications.
- The findings of this study is important because 90% of the cases in the study had substantial recovery, illustrating the need of use of MOG antibody testing in all suspected cases of non infectious encephalitis syndromes.

SUMMARY

In our study, the age distribution was from 1 month - 18 years out of which, majority of the children i.e., 40.98% were in the age group of > 10 years, 27.87% patients were aged 6 - 10 years and 31.15% were aged 1 - 5 years. Mean age group was 10.79 years. Mean age was 8.72 years. This shows that most common age group seen in the study was above 10 years of age implying that older children were more affected than infants & younger children.

Out of 61 children who were enrolled in the study, 40 (65.57%) were females & 21 (34.43) were males. The female patients were double the number of male patients in our study group.

Out of 61 cases, 57 (93.44%) came with history of fever, 46 (75.40%) with altered sensorium, 41 (67.21%) with new onset seizures, 13 (21.31%) with limb weakness & 4 (6.55%) with sudden onset blindness of one or both eyes at the time of admission. Fever was the most common presentation with respiratory system being most commonly affected system.

Out of 58 cases who presented with seizures at the time of presentation, 70.49% had generalized seizures while 27.87% had focal seizures. Out of 9 MOG positive cases, most of them (88.90%) who had seizures were generalized type.

Out of 61 cases, there was positive CSF cell count in 26 (42.62%) of them. There was more of lymphocyte predominance - 35 (57.37%) than neutrophils - 4 (6.55%).

Out of 61 cases, there were abnormal CT scan findings in 11 of them, while 23 had abnormal MRI findings & 8 had both CT and MRI scan abnormalities. The most commonly affected areas of the brain was cortex, followed by subcortex & basal ganglia. More than half of the cases in the study group had normal CT/MRI findings, which makes suspicion & diagnosis of these cases even more challenging.

Out of 61 cases, 11 (18.03%) cases were diagnosed of ADEM, 31 (50.81%) cases were autoimmune encephalitis (Non ADEM), 9 (14.75%) cases were meningitis, 4 (6.55%) were NMOSD & 6 (9.83%) cases were others not mentioned above.

Out of 61 cases, 9 (14.75%) cases turned out to be MOG positive. Out of these 9 cases, 5 (55.55%) cases were ADEM, 1 (11.11%) was varicella encephalitis, 2 (22.22%) cases were autoimmune encephalitis & 1 (11.11%) was overlapping encephalitis. Out of 11 ADEM cases, 5 (45.45%) cases were positive for MOG. There was statistically significant correlation between MOG sero-positivity & ADEM cases.

There was no significant differences regarding sex, age groups, presentation, clinical findings & imaging studies between MOG positive & MOG negative cases. Focussing on MOG positive ADEM cases, they presented with fever (100% vs 75%), seizures (80% vs 75%), altered sensorium (100% vs 75%), CSF abnormalities (60% vs 50%), MRI abnormalities (100% vs 75%) compared to MOG negative ADEM cases. While there was full recovery (100% vs 80%)) in MOG negative ADEM cases compared to MOG positive ADEM cases.

There was no significant differences with respect to age, sex, clinical presentation between MOG positive & negative cases. CSF abnormalities (55% vs 9%) & MRI abnormalities 988% vs 32%) were more in MOG positive compared to MOG negative cases. But there was no difference in outcomes & recovery of cases between MOG positive & negative cases.

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ANNEXURE – I - INFORMED CONSENT FORM

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH

J.N. Medical College, Belagavi

Department of Paediatrics

"MYELIN OLIGODENDROCYTE GLYCOPROTEIN SEROPOSITIVITY IN CHILDREN WITH NON INFECTIOUS ACUTE ENCEPHALITIS SYNDROME"

Principal Investigator: Dr.

Co – investigator: Dr.

Introduction: You are being invited to participate in this study to find out **MYELIN OLIGODENDROCYTE GLYCOPROTEIN SEROPOSITIVITY IN CHILDREN WITH NON INFECTIOUS ACUTE ENCEPHALITIS SYNDROME**. Participation of your child will help us to know about the distinct form of auto antibody mediated encephalitis in children. During past decade, antibodies against MOG have been described in different subgroups of acquired demyelinating syndromes. Reports of children with clinical & radiological presentations in context of MOG are limited. The potential identification of novel MOG antibody associated disorders are important because of it's treatment & prognostic implications. The aim of this study is to know about presence of MOG antibodies in non infectious acute encephalitis syndrome & to know about prognosis &

outcome in MOG sero-positive encephalitis cases with MOG sero-negative encephalitis cases.

VOLUNTARY PARTICIPATION: You/your childs participation in this study in your voluntary decision. Whether to participate or not to participate will not affect your current or future relationship with the KLES DR. PRABHAKAR KORE Hospital and medical research centre, Belgaum. You are free to discontinue the participation in the study at any time for any reasons and you will not be paid any reimbursement for participation in the research

Possible Benefits: To know the presence of MOG antibodies in non infectious acute encephalitis syndrome & it's role in understanding the prognosis outcome in such cases

Possible Risks: There is no risk involved in this study.

Benefits from the study: We will know about presence of MOG antibodies, which will help to provide best treatment for the child.

Confidentiality: All the data collected will remain confidential and only aggregated data will be published. Your personal identity will not be revealed.

Withdrawal: Your participation in this study is purely voluntary. You may decide to participate or not. Even though you decide not to participate, you will not be deprived of the benefits of this study.

Costs of Participation: The cost of the study will be borne by the subjects if they can afford. If not, it will be borne by the researcher. It involves the cost of MOG antibody test. There will be no additional cost to you for participating in this study.

Payment of Participation: There will be no incentives to you for participating in this study.

Questions: If you have any questions regarding the study, you should contact Principal Investigator **Dr _____, PG 2020 MD admission batch,** Department of Paediatrics, J.N. Medical College, Belagavi, 590010.

Guide: Dr. _____, Paediatric Neurologist, Professor, Department of Paediatrics, J. N. Medical College, Belagavi, 590010.

If you have any questions about your rights as a study participant, you may contact **Dr.Harsha Hegde**, Chairman, Institutional Ethics Committee on Human Subjects' Research, J.N. Medical College, Belagavi - 590010, Ph. No 9480422500, Extn 4052, 4057.

Legal Rights: By signing this consent form; you are not waiving any of your Legal rights.

Consent statement:

"I volunteer and consent to participate in the study. I have read (or it has been read to me in the language known to me) the information sheet thoroughly. Full opportunity was given to me to ask questions. I am fully satisfied with the answers to the questions I wanted to ask. I hereby voluntarily agree to participate in this research project".

Name of the Participant	Signature of the participant or Left-Hand Thumb impression
Name of Investigator	Signature of investigator
Name of Witness	Signature of Witness
Date:	Place:

Assent (<18 years)

I have read the information in this form. After understanding all details about the study, I agree to give assent to be included as a volunteer in the study titled "**MYELIN OLIGODENDROCYTE GLYCOPROTEIN SEROPOSITIVITY IN CHILDREN WITH NON INFECTIOUS ACUTE ENCEPHALITIS SYNDROME"**

Name of the Participant	Signature of the participant or Left-Hand Thumb impression
Name of the Parent	Signature of the parent
Name of Investigator	Signature of investigator
Name of Witness	Signature of Witness

Date: _____ Place: _____

ANNEXURE – I - PROFORMA

TOPIC – Myelin oligodendrocyte glycoprotein sero-positivity in children with non infectious acute encephalitis syndrome

- Name –
- Age / Gender –
- Father's name –
- Address –
- Phone number –

- Complaints :
  - Fever –
  - Duration –
- Focus of fever :

Respiratory	GIT	Eyes	Skin	Urinary	Bones

- Seizures :
  - Generalized –
  - Focal –
  - Generalized and Focal –
  - Unknown onset –
  - Duration –
  - Frequency –
    - Day 1 –
    - Day 2 –
    - Day 3 –
    - Day 4 –
    - Day 5 –
    - Day 6 –
    - Day 7 –
    - Day 8 –
    - Day 9 –
    - Day 10 –
- Altered sensorium –
- Abnormal behavior :
  - Irritability –
  - Crying –
  - Hallucinations –
  - Others –
- Speech abnormalities –
- Others :
  - Hemiparesis –
  - Ataxia –
  - Autonomic dysfunction –

- Treatment given so far :
- Antibiotics - Dose Frequency Duration

1)			
2)			
3)			

- Antivirals –
- Anti epileptics –. Dose Frequency Duration

1)			
2)			
3)			

- Others –

- Examination :
  - GCS / MMSE -
  - Speech –
  - Abnormal behavior –
  - Cranial nerves :
    - 2^{nd} nerve –
    - Fundus –
    - 3^{rd}, 4^{th} & 6^{th} nerves –
    - Squint –
    - Extraocular movements –
    - 7^{th} nerve –
    - Facial nerve palsy –
    - Bulbar palsy –
    - 9^{th} 10^{th} nerve –

- Motor system examination : Tone Right Left

Shoulder		
Elbow		
Wrist		
Fingers		
Hips		
Knee		
Ankle		
Toe		

- Power – Right
  Left

Shoulder		
Elbow		
Wrist		
Fingers		
Hips		
Knee		
Ankle		
Toes		

- Deep tendon Reflexes : Right Left

Biceps		
Triceps		
Supinator		
Knee		
Ankle		

- Coordination –
- Signs of meningeal irritation –

- Provisional diagnosis :
  - Pyogenic meningitis –
  - Tubercular meningitis –
  - Viral meningitis –
  - ADEM –
  - Autoimmune encephalitis –
  - Others –
- Investigations –
  - Hb % -
  - Leukocytosis / leukopenia –
  - Platelet count –
  - Sodium/Potassium/Calcium/RBS –
  - Lumbar puncture :
    - Cell type –
    - Cell count –
    - Protein –
    - Sugar –
    - Lactate –
- CT / MRI findings :
  Abnormalities at
  - Cotrex –
  - Sub cortex –
  - Basal ganglia
  - Brain stem –
  - Cerebellum –
  - Spinal cord –

- EEG findings –
- Serum MOG antibody –
- CSF NMDA antibody –
- Treatment given :

▪ Antibiotics	Dose	Frequency	Duration
1)			
2)			
3)			
4)			

▪ Anti epileptics	Dose	Frequency	Duration
1)			
2)			
3)			
4)			

- Steroids –

- ivig –

- Supportive care –

- Condition on discharge :

▪ Modified Rankin score –

- Follow up :

	1 month	3 months	6 months
1) Sensorium			
2) Seizures			
3) Focal deficits			
4) Speech			
5) MRS (max 6)	/6	/6	/6
6) PCPC (max 6)	/6	/6	/6
7) FSS (max 30)	/30	/30	/30

▪ Repeat MRI findings -

SL NO	AGE (YEARS)	SEX	SEIZURES	ALTERED SENSORIUM	GCS AT ADMISSION (/15)	PROVISIONAL - ADEM / NON ADEM	CSF CELL COUNT	CSF CELL TYPE PREDOMINANCE	CSF PROTEINS	CSF GLUCOSE	CSF CULTURE	CT/MRI	SERUM MOG ANTIBODY	SERUM NMO ANTIBODY	NUMBER OF ANTIBIOTICS	DURATION OF ANTIBIOTICS	NUMBER OF ASM	STEROIDS	IVIG/RITUXIMAB	DURATION OF STAY	CONDITION AT DISCAHRGE (MRS)	F/U 1MONTH (MRS)
1	5	FEMALE	GENERALIZED	YES	7	NON ADEM	3	LYMPHOCYTES	11	81	NOGC	NORMAL	NEGATIVE	NEGATIVE	2	5	4	GIVEN	NOT GIVEN	7	2	1
2	9	MALE	GENERALIZED	NO	15	ADEM	6	LYMPHOCYTES	23	56	NOGC	NORMAL	POSITIVE	NEGATIVE	0	0	2	NOT GIVEN	NOT GIVEN	0	1	0
3	1	FEMALE	FOCAL	YES	14	NON ADEM	2					NORMAL	NEGATIVE	NEGATIVE	4	6	3	GIVEN	NOT GIVEN	9	2	1
4	14	FEMALE	GENERALIZED	YES	13	NON ADEM	60	LYMPHOCYTES	38	72	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	2	7	4	GIVEN	NOT GIVEN	7	2	1
5	14	MALE	GENERALIZED	YES	7	NON ADEM	5	LYMPHOCYTES	43	64	NOGC	NORMAL	NEGATIVE	NEGATIVE	3	5	3	GIVEN	NOT GIVEN	6	1	0
6	13	FEMALE	GENERALIZED	YES	14	NON ADEM	0		27	76	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	2	5	3	GIVEN	NOT GIVEN	8	3	1
7	9	FEMALE	GENERALIZED	YES	15	NON ADEM	0		18	57		ABNORMAL	NEGATIVE	NEGATIVE	2	7	2	GIVEN	NOT GIVEN	7	2	1
8	15	FEMALE	FOCAL	NO	11	ADEM	4	LYMPHOCYTES	29	74	NOGC	NORMAL	NEGATIVE	NEGATIVE	3	5	3	GIVEN	NOT GIVEN	5	1	0
9	2	FEMALE	GENERALIZED	YES	12	NON ADEM	3	LYMPHOCYTES	19	48	NOGC	NORMAL	NEGATIVE	NEGATIVE	2	6	3	GIVEN	NOT GIVEN	7	1	0
10	9	FEMALE	GENERALIZED	YES	9	NON ADEM	2					ABNORMAL	NEGATIVE	NEGATIVE	2	4	2	GIVEN	NOT GIVEN	10	1	1
11	15	MALE	ABSENT	YES	13	ADEM	3	LYMPHOCYTES	26	75	NOGC	NORMAL	POSITIVE	NEGATIVE	3	7	2	GIVEN	NOT GIVEN	7	2	1
12	14	FEMALE	FOCAL	YES	14	NON ADEM	30	POLYMORPHS	32	72	NOGC	NORMAL	NEGATIVE	NEGATIVE		5	1	GIVEN	NOT GIVEN	8	1	0
13	9	FEMALE	GENERALIZED	YES	15	NON ADEM	2	LYMPHOCYTES	45	61	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	2	7	5	GIVEN	NOT GIVEN	12	DEATH	
14	1	FEMALE	FOCAL	YES	12	NON ADEM	0		66	198		ABNORMAL	NEGATIVE	NEGATIVE	3		2	GIVEN	NOT GIVEN	7	1	0
15	15	FEMALE	GENERALIZED	NO	11	NON ADEM	0		34	65	NOGC	NORMAL	NEGATIVE	NEGATIVE	3	3	1	GIVEN	NOT GIVEN	4	3	0
16	15	FEMALE	GENERALIZED	YES	8	NON ADEM	3					NORMAL	NEGATIVE	NEGATIVE	2	5	3	GIVEN	NOT GIVEN	5	2	1
17	18	FEMALE	FOCAL	YES	14	NON ADEM	5	LYMPHOCYTES	47	36	NOGC	NORMAL	NEGATIVE	NEGATIVE	2	4	2	GIVEN	NOT GIVEN	9	1	0
18	14	FEMALE	GENERALIZED	YES	13	NON ADEM					NOGC	ABNORMAL	NEGATIVE	NEGATIVE		7		NOT GIVEN	NOT GIVEN	13	1	0
19	8	FEMALE	GENERALIZED	YES	12	NON ADEM	2				NOGC	NORMAL	NEGATIVE	NEGATIVE	2	6	2	GIVEN	NOT GIVEN	6	2	1
20	12	FEMALE	GENERALIZED	YES	11	NON ADEM	135	LYMPHOCYTES	21	65	NOGC	NORMAL	POSITIVE	NEGATIVE	4	7	2	GIVEN	GIVEN	14	1	0
21	2	FEMALE	GENERALIZED	YES	13	NON ADEM						NORMAL	NEGATIVE	NEGATIVE	2	3	2	GIVEN	NOT GIVEN	8	3	1
22	14	MALE	GENERALIZED	YES	13	ADEM	4	LYMPHOCYTES	25	46	NOGC	ABNORMAL	POSITIVE	NEGATIVE	0		1	GIVEN	NOT GIVEN	4	1	1
23	1	FEMALE	FOCAL	NO	10	NON ADEM	5	LYMPHOCYTES	34	74	NOGC	NORMAL	NEGATIVE	NEGATIVE	3	3	3	GIVEN	NOT GIVEN	7	1	0
24	4	FEMALE	GENERALIZED	NO	14	NON ADEM	0		17	67	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	1	2	2	GIVEN	NOT GIVEN	2	DEATH	
25	7	FEMALE	GENERALIZED	YES	14	NON ADEM	0		21	58	NOGC	NORMAL	POSITIVE	NEGATIVE	0	0	4	GIVEN	NOT GIVEN	8	2	1
26	1	FEMALE		YES	13	NON ADEM	7	LYMPHOCYTES	31	89	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	1	4	2	GIVEN	NOT GIVEN	5	1	0
27	5	MALE	FOCAL	YES	8	NON ADEM	16	LYMPHOCYTES	19	58		ABNORMAL	NEGATIVE	NEGATIVE	3	3	2	GIVEN	NOT GIVEN	4	3	2
28	6	MALE	FOCAL	YES	13	NON ADEM	27	POLYMORPHS	34	95	NOGC	NORMAL	NEGATIVE	NEGATIVE	2	5	2	GIVEN	NOT GIVEN	6	1	0
29	10	FEMALE	GENERALIZED	YES	14	NON ADEM	2	LYMPHOCYTES	26	71	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	1	4	3	NOT GIVEN	NOT GIVEN	5	2	1
30	14	FEMALE	GENERALIZED	YES	15	ADEM	3				NOGC	NORMAL	NEGATIVE	NEGATIVE	4	6	1	GIVEN	NOT GIVEN	23	3	0
31	11	MALE	GENERALIZED	YES	11	NON ADEM	76	LYMPHOCYTES	34	76	NOGC	ABNORMAL	POSITIVE	POSITIVE	3	10	1	GIVEN	NOT GIVEN	13	2	1
32	1	MALE	FOCAL	NO	13	NON ADEM	4					NORMAL	NEGATIVE	NEGATIVE	5	5	5	GIVEN	NOT GIVEN	7	5	4
33	5	FEMALE	GENERALIZED	YES	12	NON ADEM	4	LYMPHOCYTES	14	45	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	1	7	5	GIVEN	NOT GIVEN	9	5	5
34	4	FEMALE	GENERALIZED	YES	14	NON ADEM	3	LYMPHOCYTES	18	67	NOGC	NORMAL	NEGATIVE	NEGATIVE	2	4	2	NOT GIVEN	NOT GIVEN	5	1	1
35	8	FEMALE	GENERALIZED	YES	12	ADEM	0		23	89	NOGC	ABNORMAL	POSITIVE	NEGATIVE	2	6	3	GIVEN	NOT GIVEN	7	2	1
36	10	FEMALE	GENERALIZED	YES	9	NON ADEM	6	LYMPHOCYTES	11	47	NOGC	NORMAL	NEGATIVE	NEGATIVE	4	8	2	GIVEN	NOT GIVEN	8	2	0
37	3	MALE	FOCAL	NO	14	NON ADEM	17	POLYMORPHS	16	65	NOGC	NORMAL	NEGATIVE	NEGATIVE	3	5	2	GIVEN	NOT GIVEN	12	3	2
38	3	FEMALE	GENERALIZED	YES	15	NON ADEM	9	LYMPHOCYTES	24	59	NOGC	NORMAL	NEGATIVE	NEGATIVE	2	6	1	GIVEN	NOT GIVEN	9	2	1
39	4	MALE	GENERALIZED	YES	14	ADEM	34	LYMPHOCYTES	17	71	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	1	4		NOT GIVEN	NOT GIVEN	10	2	0
40	15	FEMALE		NO	8	NON ADEM	4	LYMPHOCYTES	19	108	NOGC	NORMAL	NEGATIVE	NEGATIVE	4	6	3	GIVEN	NOT GIVEN	13	2	1
41	6	FEMALE	FOCAL	YES	11	NON ADEM	0		31	36		NORMAL	NEGATIVE	NEGATIVE	2	4	2	GIVEN	NOT GIVEN	5	2	1

42	6	FEMALE	GENERALIZED	YES	13	ADEM	23	LYMPHOCYTES	18	74	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	3	6	2	GIVEN	NOT GIVEN	7	1	0
43	9	MALE	GENERALIZED	NO	9	NON ADEM	9	POLYMORPHS	13	83	NOGC	NORMAL	NEGATIVE	NEGATIVE	1	10	4	GIVEN	NOT GIVEN	12	1	1
44	11	FEMALE	GENERALIZED	YES	13	NON ADEM	0		26	48		ABNORMAL	NEGATIVE	NEGATIVE	4	6	2	GIVEN	NOT GIVEN	8	2	1
45	5	MALE	FOCAL	YES	9	NON ADEM	25	LYMPHOCYTES	23	56	NOGC	NORMAL	NEGATIVE	NEGATIVE	1	14	3	GIVEN	NOT GIVEN	15	3	2
46	15	FEMALE	GENERALIZED	YES	10	NON ADEM	7	LYMPHOCYTES	17	74	NOGC	NORMAL	NEGATIVE	NEGATIVE	5	9	2	GIVEN	NOT GIVEN	9	3	2
47	7	MALE	GENERALIZED	NO	14	NON ADEM	4	LYMPHOCYTES	20	49	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	2		2	GIVEN	NOT GIVEN	5	2	0
48	1	MALE	GENERALIZED	NO	13	NON ADEM	6	LYMPHOCYTES	26	63	NOGC	ABNORMAL	POSITIVE	NEGATIVE	4	7	1	GIVEN	NOT GIVEN	8	3	2
49	4	MALE	GENERALIZED	YES	15	ADEM	0		35	41		NORMAL	NEGATIVE	NEGATIVE	1	7	1	NOT GIVEN	NOT GIVEN	8	5	5
50	6	MALE	FOCAL	YES	13	NON ADEM	65	LYMPHOCYTES	26	96	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	3	4		NOT GIVEN	NOT GIVEN	9	1	0
51	8	MALE	FOCAL	YES	11	NON ADEM	4	LYMPHOCYTES	19	50	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	2		2	GIVEN	NOT GIVEN	6	2	1
52	14	MALE	GENERALIZED	YES	12	ADEM	3	LYMPHOCYTES	13	63	NOGC	NORMAL	NEGATIVE	NEGATIVE	2	7	3	GIVEN	NOT GIVEN	7	1	0
53	13	MALE	GENERALIZED	YES	9	NON ADEM	11	LYMPHOCYTES	24	76	NOGC	NORMAL	NEGATIVE	NEGATIVE	3	8	1	GIVEN	NOT GIVEN	5	1	0
54	10	FEMALE	GENERALIZED	YES	13	NON ADEM	7	LYMPHOCYTES	25	55	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	1	4	2	GIVEN	NOT GIVEN	8	4	2
55	2	FEMALE	GENERALIZED	NO	14	NON ADEM	3	LYMPHOCYTES	28	83	NOGC	NORMAL	NEGATIVE	NEGATIVE	4	7	2	GIVEN	NOT GIVEN	6	3	1
56	16	FEMALE	GENERALIZED	YES	16	NON ADEM	0		16	92	NOGC	NORMAL	NEGATIVE	NEGATIVE	1	4	3	GIVEN	NOT GIVEN	5	1	0
57	12	MALE	GENERALIZED	NO	13	NON ADEM						ABNORMAL	NEGATIVE	NEGATIVE	3	6	2	GIVEN	NOT GIVEN	7	2	1
58	12	FEMALE	FOCAL	YES	14	NON ADEM	4		25	49	NOGC	ABNORMAL	NEGATIVE	NEGATIVE	1	13	3	GIVEN	NOT GIVEN	8	4	2
59	13	MALE	GENERALIZED	YES	13	NON ADEM	19		38	37	NOGC	NORMAL	NEGATIVE	NEGATIVE	2	7	1	GIVEN	NOT GIVEN	6	2	1
60	11	FEMALE	GENERALIZED	YES	12	NON ADEM	6	LYMPHOCYTES	24	58	NOGC	NORMAL	NEGATIVE	NEGATIVE	3	6	3	GIVEN	NOT GIVEN	5	1	1
61	11	FEMALE	GENERALIZED	YES	13	ADEM	5	LYMPHOCYTES	25	57	NOGC	ABNORMAL	POSITIVE	NEGATIVE	1	5	2	GIVEN	NOT GIVEN	6	4	3