Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

Journal of University Studies for inclusive Research
Vol.2 , Issue 13 (2021), 2365 - 2394
USRIJ Pvt. Ltd.,

CSF Analysis as a Predictive Value to Developing Seizure in Multiple Sclerosis Patients

Sawsan Haidar

Department of Pathology & Laboratory Medicine, King Abdulaziz Medical city, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

Tarig Karar

Clinical Laboratory Department, College of Applied Medical Sciences, King Saud bin Abdulaziz University for Health Sciences ,King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

Abstract

Background: Cerebrospinal fluid is a clear liquid that is around the organs of the central nervous system. CSF dissection acts as a valuable procedure in investigating a number of inflammatory and degenerative neurological diseases. In particular disorders in a detailed pathogenesis associated with MS, individual biomarkers which taken singly, are likely to reflect isolated components of ongoing neuro inflammation and neuro degeneration and most of the investigated MS biomarkers are currently unsuitable for predicting disease progression.

Aim: The aim of this study was to Comparing the CSF analysis between Multiple Sclerosis with seizure and Multiple sclerosis without seizure, to find the CSF works as predictive value to develop seizure in multiple sclerosis patients.

Method: It is a cohort retrospective study and it will be conducted at different hospitals. The sample would be convenient sample from different hospitals. These patients will be divided into two group MS patients and MS patients with epilepsy. Elevation of IgG levels within the cerebrospinal liquid (CSF) of patients with incendiary infections of the central nervous system (multiple sclerosis [MS], neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis) is due to nearby central apprehensive framework (CNS) synthesis of IgG. The two most commonly used diagnostic research facility tests for MS are CSF record and oligoclonal banding.

Result: The presence of IgG in the CSF indicates an increase. There was an increase in CSF in 41.20 percent of patients with MS+ seizures and 58.80 percent of patients with normal IgG levels. IgG levels were normal in 33.30 % with MS who did not have seizures, and normal in 66.70 %.Oligoclonal bands showed that 65.40 % of patients with MS+seizure had positive bands, while 34.60 % had negative bands, and 33.30 % of patients with MS without seizure had positive bands, while 66.70 % had negative bands.

Conclusion: The frequency of CSF, IgG level, CSF, and Oligoclonal bands were all found to be high in the study. The number of lymphocytes in patients with MS+seizures and patients with MS without seizures in Saudi Arabia rose. This study's findings can be interpreted as CSF having a predictive value for the development of seizures in Multiple Sclerosis.

CHAPTER ONE

INTRODUCTION & LITERATURE REVIEW

1.Introduction:

Cerebrospinal fluid is a clear liquid that is around the organs of the central nervous system. CSF dissection acts as a valuable procedure in investigating a number of inflammatory and degenerative neurological diseases. In particular disorders in a detailed pathogenesis associated with MS,

individual biomarkers which taken singly, are likely to reflect isolated components of ongoing neuro inflammation and neuro degeneration and most of the investigated MS biomarkers are currently unsuitable for predicting disease progression (Albert et al. 2013).

Multiple sclerosis is a common central nervous system inflammatory disease that causes severe cognitive and physical disability **(Ghasemi et al. 2017).** It is considered a primary causal factor of disability among youths **(Trapp and Nave, 2008).** The incidence and prevalence of MS vary between countries, with higher rates reported in northern geographical regions. Most studies suggest that the prevalence of MS is increasing over the last decades. The cause of MS is not yet well known, but several factors are thought to contribute to MS susceptibility. It is likely that the disease develops through an interplay of several factors such as genetics, environmental factors and epigenetic **(Ringh, 2019).** Epidemiological studies show that patients with multiple sclerosis are three to six times more likely to have epilepsy. The incidence has increased over time since the multiple sclerosis was diagnosed **(Lund et al. 2014)**

It is founded that epilepsy is more common in multiple sclerosis (MS) patients than in the general population, occurring in 2-3% of patients. The nature of convulsions may be either tonic colonic in nature or partial complex. In these individuals, seizures most likely result from lesions present in the cerebral cortex and subcortical white matter **(Najafi et al. 2013).**

As there is limited research published to find the pathogenesis and the triggering factors for seizure attacks in MS patients (MS-S). The aim of this research is to find if there is any relation between CSF analysis values in MS patients and MS patients with epilepsy.

1.1 Objective:

Our study objective is Comparing the CSF analysis between Multiple Sclerosis with seizure and Multiple sclerosis without seizure, to find the CSF works as predictive value to develop seizure in multiple sclerosis patients.

1.2 Literature review:

Multiple sclerosis (MS) disease is diagnosed on the basis of clinical presentations such as magnetic resonance imaging (MRI) of the brain and examination of the cerebrospinal fluid (CSF). MS presents in patient aged from 20 to 45 years. The cause of MS is idiopathic, but it involve a combination of genetic susceptibility and a nongenetic triggers such as a virus, metabolism, or environmental factors, that together result in a self-sustaining autoimmune disorder that leads to recurrent immune attacks on the CNS **(Cree, 2007).**

MS diagnosis is depending on McDonald criteria. It provides recommendations on the diagnosis of MS.

Figure1**. Shows McDonald criteria for MS diagnosis (**Saguil **et al. 2014).**

Table 4. The 2010 McDonald Criteria for Diagnosis of MS

Clinical presentation	*Additional data needed for MS diagnosis*
≥ 2 attacks*; objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack†	None‡
≥ 2 attacks*; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)§; or Await a further clinical attack* implicating a different CNS site
1 attack*; objective clinical evidence of ≥ 2 lesions	Dissemination in time demonstrated by: Simultaneous asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack*
1 attack*; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)§; or Await a second clinical attack* implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack*
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria§:

Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

Epilepsy is a highly disabling neurological disorder characterized by recurrent epileptic attacks **(Chang and Lowenstein, 2003).** Epilepsy has previously been reported in 3.2 to 3.6% of the Norwegian MS patients. The cause of the increased presence of epileptic fits among patients with MS is idiopathic, but it is can be related to epileptogenic role of cortical lesions. Although epilepsy can be the first symptom of MS, there is a study showed that some patients with active epilepsy got fits before other symptoms of MS. This may support the idea that the risk of epilepsy in MS increases with disease duration and number of lesions **(Calabrese et al. 2008).** Partial and complex seizures were described in MS studies. Some unusual seizure such as status epilepticus and musicogenic epilepsy, have also been found in MS patients **(Kelley and Rodriguez, 2009).**

Seizure can be the first manifestation of MS as mentioned in studies that reported that some patients have temporal lobe epilepsy, and another reported epilepsia partialis continua as the first clinical manifestation of MS. Although these presentations do occur, it is felt that epilepsy is rarely the

Symptom of MS **(Gambardella et al. 2003).**If there is effective non traumatic biomarkers for epilepsy can be evaluated prior to significant seizure attacks; it can reduce the risk of recurrent seizure attacks and improve the prognosis. So nowadays the exploration for biomarkers of

epileptogenesis has become one of the major focuses in epilepsy research studies **(Kubova et al. 2012).**

An important clinical test that clinicians use to monitor the CSF is the lumbar puncture (spinal tap) **(Cauley, 2015).** In this procedure, a long, hollow needle is typically inserted into the subarachnoid space of the lumbar spine just below where the spinal cord ends (usually below L2). The needle can then be uncapped, and samples of CSF can be obtained. The CSF fluid can be examined clinically through a lumbar puncture. With a lumbar puncture, physicians can look for abnormalities in the CSF, which can be helpful when creating a differential diagnosis **(Shenoy and Lui, 2020)**.

Several analyses are possible on the contents of CSF obtained from a lumbar puncture. Since CSF would be transparent, the color is worth noting **(De Maria et al. 2019).**

In reviewing CSF biological role, it has molecules of potential prognostic significance for MS may be classified as follows: markers reveal immune activation as cytokines, some chemokines, some antibodies, complement factors and adhesion molecules.Markers of blood brain barrier disruption like matrix metalloproteinases and markers of demyelination as myelin basic protein, myelin oligodendrocyte glycoprotein, proteolytic enzymes and markers of oxidative stress and cytotoxicity as advanced oxidation protein products, total thiol, and markers of axonal/neuronal damage and gliosis as neurofilaments, tau, 14-3-3 protein, glial fibrillary acidic protein and markers of remyelination neural repair **(Albert et al. 2013).**

Some studies revealed that the Kininogen Level in the Cerebrospinal Fluid might serve as a potential biomarker of early epileptogenesis **(Zou et al. 2019).**

Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

CHAPTER TWO
METHOD and MATERIAL

2. Methodology:

It is a cohort retrospective study and it will be conducted at different hospitals Moreover, the ethical approval will be obtained from the Institutional Review Board (IRB) and it will be conducted in accordance with the ethical standards of the Helsinki Declaration of 1975 (as revised in 2000).

2.1 Study population:

The study includes patients diagnosed with MS and MS with epilepsy following at different hospitals.

2.2 Sample size and study design:

The sample would be convenient sample from different hospitals. These patients will be divided into two group MS patients and MS patients with epilepsy.

2.3 Inclusion criteria:

Diagnose with MS by MacDonald criteria.

2.4 Exclusion criteria:

Patients with other comorbidity correlated to MS with epilepsy or MS.

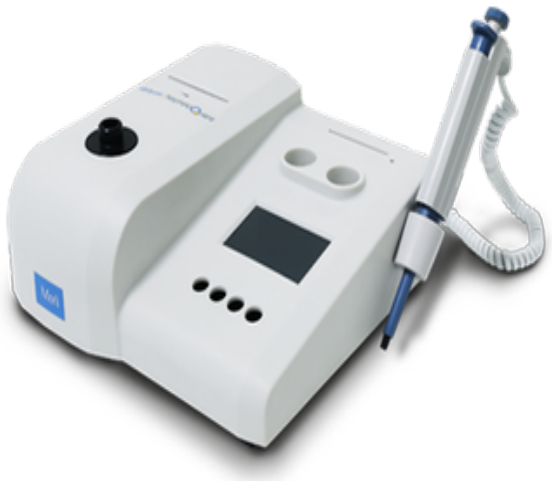
2.5 Materials:

Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

Cerebrospinal Fluid (CSF) IgG, Serum and Spinal Fluid:

Clinical Information:

Elevation of IgG levels within the cerebrospinal liquid (CSF) of patients with incendiary infections of the central nervous system (multiple sclerosis [MS], neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis) is due to nearby central apprehensive framework (CNS) synthesis of IgG. The two most commonly used diagnostic research facility tests for MS are CSF record and oligoclonal banding. The CSF file is the CSF IgG to CSF albumin proportion compared to the serum IgG to serum albumin proportion. The CSF list is, subsequently, an marker of the relative sum of CSF IgG compared to serum. Any increase within the list may be a reflection of IgG production within the CNS. The IgG union rate may be a numerical control of the CSF list information and can moreover be used as a marker for CNS inflammatory diseases.



Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

Method Name:

Nephelometry

Specimen Type:

CSF

Serum

Reference Values

CSF IgG: 0.0-4mg/dL

CSF lymphocytes:

By using flow cytometry this device works by laser counting cells as it helps us to read the result of lymphocyte.

Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

Specimen Type:

CSF
Blood
Serum

Reference Values

adult -62%
neonate 18-20%

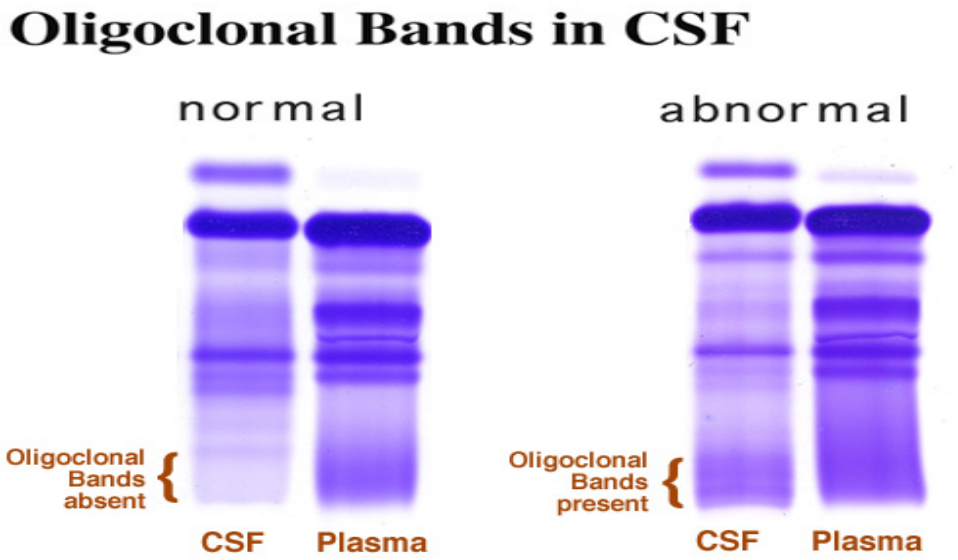
Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

Cerebrospinal Fluid (CSF) Oligoclonal Band Screen

Clinical Information:

An oligoclonal band could be a protein called an immunoglobulin. The CSF oligoclonal band screen looks for these groups in CSF. Their nearness proposes irritation of the central nervous system due to disease or another disease. If similar bands aren't present in blood, will have different sclerosis (MS).The test is also known as CSF oligoclonal banding or CSF immunofixation.

Interpretation the Oligoclonal Band resut:



2.6 Demographic and clinical information:

The information would be extracted from the patient's electronic medical record.

2.7 Clinical data:

The clinical data are CSF analysis, EEG finding, diagnosis and the course of the disease, type of seizure, medications, and Co-morbidities.

2.8 Statistical Analysis:

Data analysis would be done by statistical package for the social sciences (SPSS) and using simple statistical ratios consisting of frequency and percentages. A P-value to be significant, it would be less than 0.05.

2.9 Data management:

There would be a specific code for each participant for storage of data that will be secured by a password.

Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

CHAPTER THREE
RESULTS

3.Results:

3.1 Age

Fig.2 The frequency of study subject according to age group

The frequency of study participants by age group reveals that % of MS+ Seizure patients are over 25 years old, whereas 64.50 % of MS without seizure patients are over 25 years old and 35.50 % are under 25.

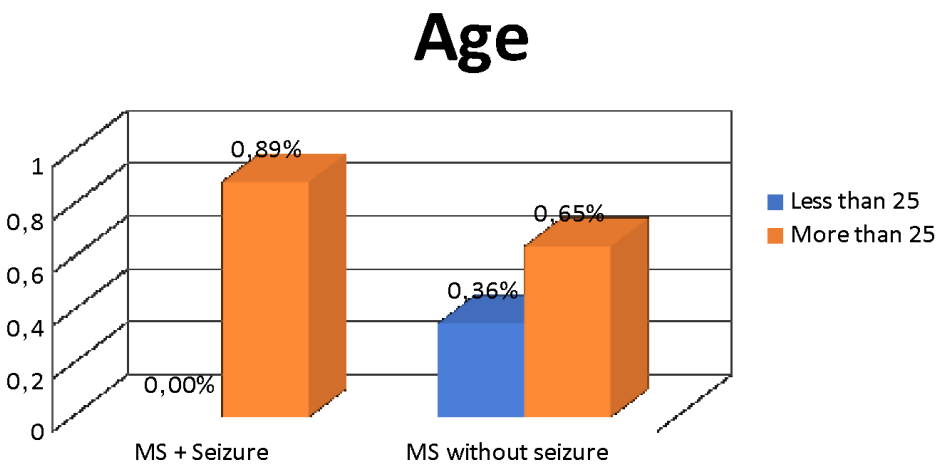


Fig.2

3.2 CSF IgG level

Figure: 3 shows the frequency of research subjects based on CSF. The amount of IgG in the body. According to CSF, the frequency of study subjects. The presence of IgG in the CSF indicates an increase. There was an increase in CSF in 41.20 percent of patients with MS+ seizures and 58.80 percent of patients with normal IgG levels. IgG levels were normal in 33.30 % with MS who did not have seizures, and normal in 66.70 %.

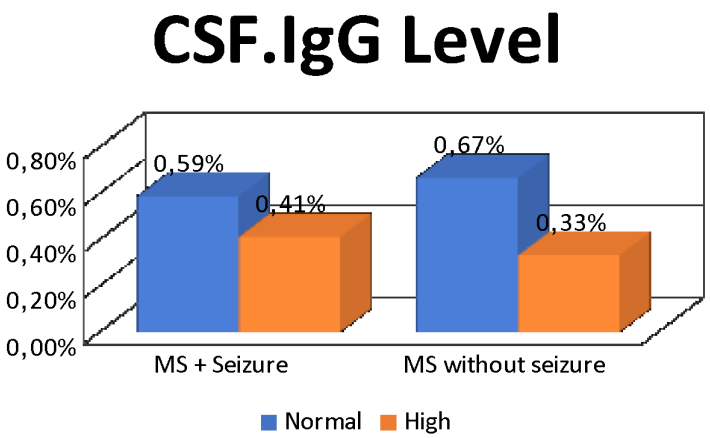


Fig 3

3.3 CSF Oligoclonal band

Figure 4 shows a study of frequency subjects based on CSF. Bands of oligoclonality

According to CSF, the frequency of study subjects.

Oligoclonal bands showed that 65.40 % of patients with MS+seizure had positive bands, while 34.60 % had negative bands, and 33.30 % of patients with MS without seizure had positive bands, while 66.70 % had negative bands.

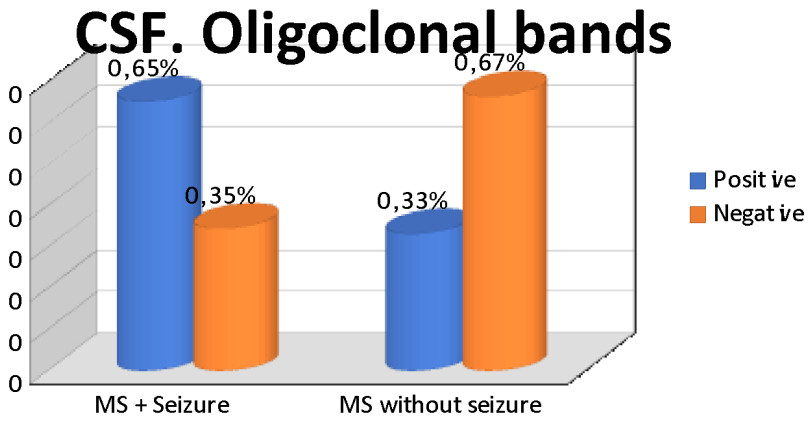


Fig.4

3.4 CSF lymphocyte

Fig. 5 According to CSF, the frequency of study subjects. Level of lymphocytes

According to CSF, the frequency of study subjects. Lymphocyte level reveals that all MS+seizure patients in this study had a high level of CSF lymphocyte, and 50% of MS patients without seizures have a high level of CSF lymphocyte, while the other 50% are normal.

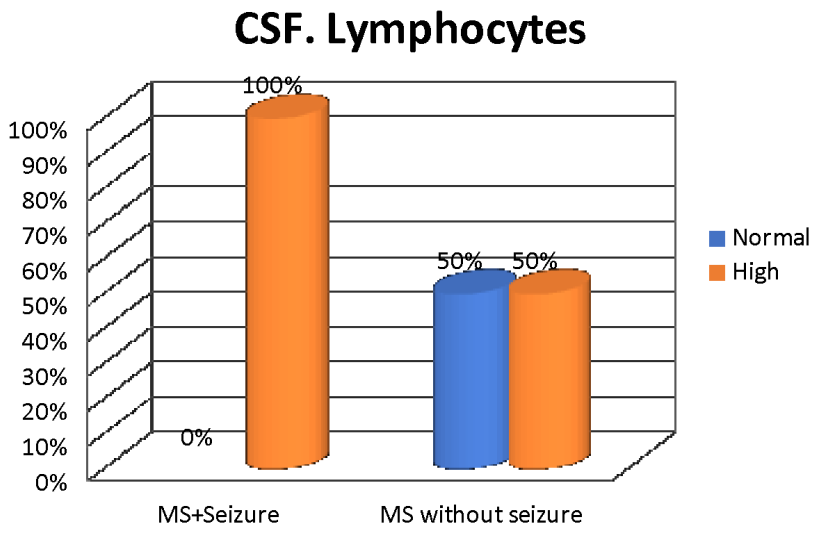


Fig. 5

Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة

CHAPTER FOUR DISCUSSION AND CONCLUSION

4.0 Discussion:

Multiple sclerosis (MS) is a common inflammatory disease of the central nervous system that causes significant cognitive and physical impairment. It is thought to be a main cause of impairment, and it affects adults more than children. The purpose of this study was to determine the predictive value of CSF analysis in patients with developing seizures in multiple sclerosis and patients with multiple sclerosis without seizures. The study was conducted in two populations of patients (over 25 years old and under 25 years old), with the population of patients over 25 years old having a higher

prevalence than the population of patients under 25 years old. CSF was tested for IgG levels. CSF and oligoclonal bands The study discovered a rise in IgG and CSF levels in lymphocytes. Lymphocyte levels are higher in MS+seizure patients than in MS patients without seizures.Furthermore, individuals with MS with seizures had a higher percentage of positive CSF oligoclonal bands than patients with MS without seizures. We may consider CSF analysis as a consideration value for diagnosing multiple sclerosis disease based on our data analysis. Patients diagnosed with multiple sclerosis were found to be between the ages of 20 and 40 in one of the earlier studies conducted by certain researchers. They are, however, idiopathic, and magnetic imaging is used to diagnose them. Other variables such as genetics or the environment might also play a role (Cree, 2007). Epilepsy has been recorded in 3.2 to 3.6 percent of Norwegian MS patients in the past. The higher prevalence of epileptic fits in MS patients is unknown, although it may be linked to the epileptogenic role of cortical lesions. Despite the fact that epilepsy can be the initial sign of MS, a research found that some individuals with active epilepsy had fits before experiencing other MS symptoms. This might back up the theory that the likelihood of seizures in MS patients increases as the disease progresses and the number of lesions increases (Calabrese et al. 2008). In MS investigations, partial and complex seizures were identified. MS patients have also been shown to experience certain atypical seizures, such as status epilepticus and musicogenic epilepsy (Kelley and Rodriguez, 2009).

4.1 Conclusion:

The frequency of CSF, IgG level, CSF, and Oligoclonal bands were all found to be high in the study. The number of lymphocytes in patients with MS+seizures and patients with MS without

seizures in Saudi Arabia rose. This study's findings can be interpreted as CSF having a predictive value for the development of seizures in Multiple Sclerosis. After completing the study and evaluating the data, we suggested caring for individuals with MS, seizure or not, because they require particular care. In the future, the rarity of the condition is a problem for future study to examine. as a result of this for prior research and studies, we find that the measurement of lymphocyte, IgG, and Oligoclonal bands are predictive ratios and not fixed for patients with multiple sclerosis and epilepsy.

There are many challenges that we faced while conducting this study:

- Multiple sclerosis with seizure is a rare disease.
- Unavailability of a large number of patients.
- Difficulty and accurate comparison between MS +seizure and MS without seizure patients.
- Difficulties in collecting samples.
- Less of availability of previous studies.
- Unavailability of much reference.

In the future, we recommend doing more study for better accurate result.

References:

Albert, G. 2013. Clinical, MRI, and CSF Markers of Disability Progression in Multiple sclerosis. *Disease markers*; 35. Available at: https://doi.org/10.1155/2013/484959

Calabrese M, et al. 2008 Extensive cortical inflammation is associated with epilepsy in multiple sclerosis. J Neurol; 255(4):581–6.

Chang BS, Lowenstein DH. 2003. Epilepsy.N Engl J Med; 349(13):1257-66.

Cree B. 2007. Multiple sclerosis. In: Brust JCM, editor. Current Diagnosis and Treatment in Neurology. *New York: Lange Medical Books/McGraw-Hill Medical.*

Gambardella A, Valentino P, Labate A, et al. 2003. Temporal lobe epilepsy as a unique manifestation of multiple sclerosis. Can J Neurol Sci; 30(3):228–232.

Ghasemi N, Razavi S, Nikzad E. 2017. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy. *Cell Journal (Yakhteh)*;19(1):1.

Goldenberg M. M. (2012). Multiple sclerosis review. *P & T :a peer-reviewed journal for formulary management*, *37*(3), 175–184.

Kelley, B. J., & Rodriguez, M. (2009). Seizures in patients with multiple sclerosis: epidemiology, pathophysiology and management. *CNS drugs*, *23*(10), 805–815. https://doi.org/10.2165/11310900-000000000-00000

Kubova, H., Lukasiuk, K., & Pitkänen, A. (2012). New insight on the mechanisms of epileptogenesis in the developing brain. *Advances and technical standards in neurosurgery*, *39*, 3–44. https://doi.org/10.1007/978-3-7091-1360-8_1

Langenbruch L, Krämer J, Güler S, Möddel G, Geßner S, Melzer N, Elger CE, Wiendl H, Budde T, Meuth SG, Kovac S. 2019. Seizures and epilepsy in multiple sclerosis: epidemiology and prognosis in a large tertiary referral center. *Journal of neurology*. ;266(7):1789-95.

Lund C, Nakken KO, Edland A, Celius EG.2014. Multiple sclerosis and seizures: incidence and prevalence over 40 years. *Acta Neurologica Scandinavica*; 130(6):368-73.

Najafi, M. R., Chitsaz, A., & Najafi, M. A. (2013). Jacksonian seizure as the relapse symptom of multiple sclerosis. Journal of research in medical sciences : *the official journal of Isfahan University of Medical Sciences*, 18(Suppl 1), S89–S92.

Ringh, M. 2019. Epigenetics in health and disease: on smoking, multiple sclerosis, and rheumatoid arthritis disease states. *Karolinska Institute.*

Saguil, A. et al. 2014. Multiple sclerosis: Aprimary care perspective. *American Family Journal.* 1;90(9):644-652.

Trapp BD, Nave KA. 2008. Multiple sclerosis: an immune or neurodegenerative disorder? .Annu. Rev. *Neurosci.*.21;31:247-69

Javed, K., Reddy, V., & Lui, F. (2020). Neuroanatomy, Choroid Plexus. In *StatPearls*. StatPearls Publishing.

Shenoy, S. S., & Lui, F. (2020). Neuroanatomy, Ventricular System. In *StatPearls*. StatPearls Publishing.

Kiroğlu, Y., Karabulut, N., Oncel, C., Yagci, B., Sabir, N., & Ozdemir, B. (2008). Cerebral lateral ventricular asymmetry on CT: how much asymmetry is representing pathology?. *Surgical and radiologic anatomy: SRA*, *30*(3), 249–255. https://doi.org/10.1007/s00276-008-0314-9

Özütemiz, C., & Rykken, J. B. (2019). Lumbar puncture under fluoroscopy guidance: a technical review for radiologists. *Diagnostic and interventional radiology (Ankara, Turkey)*, *25*(2), 144–156. https://doi.org/10.5152/dir.2019.18291

De Maria, L., Brinjikji, W., & Lanzino, G. (2019). Unruptured brain arteriovenous malformations and hydrocephalus: Case series and review of the literature. *Journal of clinical neuroscience: official journal of the Neurosurgical Society of Australasia*, *64*, 116–121.

Cauley K. A. (2015). Fluoroscopically Guided Lumbar Puncture. AJR. *American journal of roentgenology,* 205(4), W442–W450. https://doi.org/10.2214/AJR.14.14028

Hupp, S., & Iliev, A. I. (2020). CSF-1 receptor inhibition as a highly effective tool for depletion of microglia in mixed glial cultures. Journal of neuroscience methods, 332, 108537. https://doi.org/10.1016/j.jneumeth.2019.108537.