Association of Nuclear Factor kappa beta enhancer of activated B-cell (NF-KB) with Neuroinflammatory disease patients in Najaf / Iraq: (cross sectional study)

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Abstract
Background :Neuroinflammatory diseases are a broad category of diseases that affect brain function. Neurodegenerative disorders affect 37 million people worldwide (Karim et al., 2014) , Neurodegenerative disorders are characterized by the formation of distinct pathological changes in the brain, including extracellular protein deposits, cellular inclusions, and changes in cell morphology (Armstrong et al., 2005) including Alzheimer's disease (Sorbi & Ferrari, 2021) Parkinson disease (Tolosa et al., 2021), Epilepsy (Manford, 2017) , Wilson (Członkowska et al., 2018), stroke (Iadecola et al., 2020), multiple sclerosis (Kamińska et al., 2017) . NF-kappa B (NF-kB) transcription factors regulate cell proliferation, migration, and apoptosis. The etiology of cancer, autoimmune diseases, and inflammatory states all appears to rely on aberrant NF-kB activation (De Luca, 2020) . According to reports, NF-B is found in neurons where it is said to react to immunological and toxic stimuli, glutamate, and synaptic activity. However, because there are several different kinds of cells in the brain, it is challenging to carry out and interpret tests that precisely measure neuronal NF-B activity (Listwak et al., 2013) . Aim of the study: Study the Association of NF-kB with Neuroinflammatory disease patients. Methodology: Two-hundred people with neuroinflammatory disease (clinically diagnosed by neurology doctors) participated in the study. There were 120 girls and 80 men among the total of 200 patients, with the average age ranging from well under 20 to well over 80. The time frame for the investigation is November 2020 through May 2021, by using an enzyme-linked immunosorbent assay (ELISA), the levels of Nf-kB was measured. Results: the study results showed that out of the total 200 patients, 83 were positive Nf-kb (51 female, 32 male) while the rest 117 patient had negative Nf-kb (69 female, 48 male). Conclusions: The rise in NF-KB levels may be the result of neuro-tissue inflammation.
Keywords: NF-kB, neuroinflammatory disease, ELISA kit: Sunlong.

1. Introduction

Neuroinflammation refers to an inflammatory response that takes place inside the central nervous system. This systemic inflammation is caused by the production of cytokines, chemokine, reactive oxygen species, and secondary messengers. Endothelial cells, microglia and astrocytes found in the central nervous system, as well as immune cells coming from the periphery, are responsible for the production of these mediators ,These neuroinflammatory reactions have repercussions not just on the immune system but also on the body's physiology, biochemistry, and psychology (Wohleb & Godbout, 2013) the degree of neuroinflammation is determined by the nature of the main stimulus or injury, as well as its severity, duration, and progression (Jassam et al., 2017) Since the BBB blocks the entry of immune cells and humoral immunological components from the periphery, the central and periphery have been studied separately. Neurons, glial cells, and other immune cells work together as the central immune system. As reported by (Jeon et al., 2021) Stroke is a cerebrovascular disorder characterized by the sudden onset of symptoms and clinical signs , most prevalent type of all neuroinflammatory disease ,Ischemic stroke is the most common kind of stroke followed by Hemorrhagic stroke (Boursin et al., 2018) other neuroinflammatory disease includes Alzheimer's disease which is a genetic and sporadic neurodegenerative disease that causes an amnestic cognitive impairment in its prototypical presentation and non-amnestic cognitive impairment in its less common variants (Knopman et al., 2021) Meningitis is a serious condition that affects the central nervous system. It is an inflammation of the meninges, which is the membrane that surrounds both the brain and the spinal cord. Meningitis can be caused by bacterial, viral, or

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fungal infections (Kohil et al., 2021) Epilepsy is one of the most common and disabling neurologic conditions (Stafstrom & Carmant, 2015) An extremely life-threatening brain disorder (Schmidt & Schachter, 2014) Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that leads to neurodegeneration across the brain's gray and white matter (Lassmann, 2018) Neuroinflammation is associated with many neurological diseases, including ischemic stroke, traumatic brain injury, Alzheimer's disease (AD), and Parkinson's disease (PD) (Jiao & Gong, 2020) .

The nuclear factor kappa B (NF-B) family of transcription factors regulates the expression of crucial regulatory genes for immunity, inflammation, death, and cell proliferation and plays a crucial function as stresses in the cellular environment. The cytoplasmic NF-B protein can be triggered by a variety of biological events (Zinatizadeh et al., 2021) nuclear factor kappa-B is one of the primary inflammatory pathways in autoimmune disease (Barrow, 2021) NF-B 1 (p50/p105), NF-kB2 (p52/p100), RelA (p65), RelB, and c-Rel are the five characterized members of the NF-B family. A canonical pathway and a non-canonical pathway 369 each have a role in activating NF-B (Erasanambati et al., 2016) NF-B proteins are made up of precursor molecules (p105 and p100, commonly known as NF-B1 and NF-B2, respectively) and additional proteins that are produced when the two precursors are proteolyzed to remove their C-terminal ankyrin repeats (p50 and p52). Only the NF-B factors p65 , RelB, and c-Rel, which have a transactivation domain, may heterodimerize with P50 and p52 to control transcription (De Luca, 2020) NF-B controls and promotes B cell differentiation and maturation by controlling the growth of lymphoid organs that contain B cells. Second, the BCR recognizes NF-B as an essential factor in B-cell survival, which controls the rate of secondary lymphoid regeneration, which has a major impact on lymphocyte activation (Courtois et al., 2015) According to reports, NF-B is found in neurons where it is said to react to immunological and toxic stimuli, glutamate, and synaptic activity , neuronal NF-kB signaling suggest that the functional role of NF-kB in neurons is distinctly different than in other cells (Listwak et al., 2013) The triggers for neuronal NF-kB activation are unique as well. Early studies proposed that a major activator is not cytokines or physical stressors, but rather glutamate and its analogs (Guerrini et al., 1995) Astrocyte-mediated inflammation and oxidative stress elicit cerebral ischemia-reperfusion (IR) injury after stroke. Nuclear factor (NF)-κB activates astrocytes and generates pro-inflammatory factors (Liu et al., 2019) .

The overarching goal of this investigation is to determine if a link exists between NF-B (nuclear factor kappa light chain enhancer of activated B cells) in individuals with neuroinflammatory diseases.

2. Materials and Methods

Patients: Two-hundred people with neuroinflammatory disease (clinically diagnosed by neurology doctors) participated in the study. There were 120 girls and 80 men among the total of 200 patients, with the average age ranging from well under 20 to well over 80. The time frame for the investigation is November 2020 through May 2021. Patient's illnesses, including hypertension (high blood pressure) and diabetes (diabetes mellitus), as well as demographic information (name, gender, age, smoking history (yes/no), type of heart disease, and laboratory examination (WBC, PLT, Lymphocytes) these questions on the questionnaire were asked of each patient. patients with Congenital neurological disorders, Nerve damage from an accident, covid19 were excluded in this study.

Material: the tools used in this search included disposable gloves, disposable pipette tips, plastic EDTA tubes, sterile syringes 5 ml, disposable glass gel serum tubes, Eppendorf Tubes –Sterile, alcohol for sterilization, cotton, deep freezer, filter paper, Tourniquet, computer, centrifuge and incubator. and the following equipment's were used in our study: CBC for detection (WBC, PLT, Lymphocytes), ELISA automated washer, ELISA kit (NF-kB) Sunlong (CHINA) # No. SL1288Hu, ELISA printer, ELISA reader.

Methods: After gaining both verbal and written agreement from the participants, blood samples were collected. The research plan has been given the go light by the Kufa College of Medicine's ethics board, Vein blood samples (5 ml) were also included in order for CBC. We used alcohol (70% strength) to disinfect the area before collecting blood. Swatches were separated and placed in individual gel tubes. It takes about an hour for blood to coagulate at room temperature before it can be utilized to generate serum. After being centrifuged at 3000 rpm for 15 minutes, the serum was split into fresh plain tubes for FBS, urea, and creatinine tests, as well as immunological assays (NF-kappa), and then refrigerated at (-20 °C) until analysis.

Ethical Approval: After gaining both verbal and written agreement from the participants, blood samples were collected. The research plan has been given the go light by the Kufa College of Medicine's ethics board.

Statistical Analysis: Data were entered, managed, and analyzed using version 24 of the software for the social sciences, with variables shown as means, standard deviations,

frequencies, and percentages. The assumption of normality for all continuous variables was tested. One way to assess the significance of a link between two category variables is by use of the Chi-square test. Welch's t-test is used to evaluate lab variables and parameters. The relationship between demographic, clinical, and laboratory data is compared using bivariate Pearson correlation and spearman correlation. All statistical analyses were performed at a 5% threshold of significance. Excel and Word 2016 were used to create the tables and figures, and an explanatory paragraph was included.

3. Results

Distribution of neuroinflammatory disease according to age groups

Figure 1 explained the distribution of neuroinflammatory disease according to age groups. the table reveled that the highest age group was (61-80) with a total number 60 (30%), followed by age group (41-60) with total number 59 (29.5%) and age group (21-40) with total number 47 (23.5%), and age group (>80) with total number (14) (7%). The significance level was set at 0.05, hence a p-value of 0.17 was considered to be insignificant

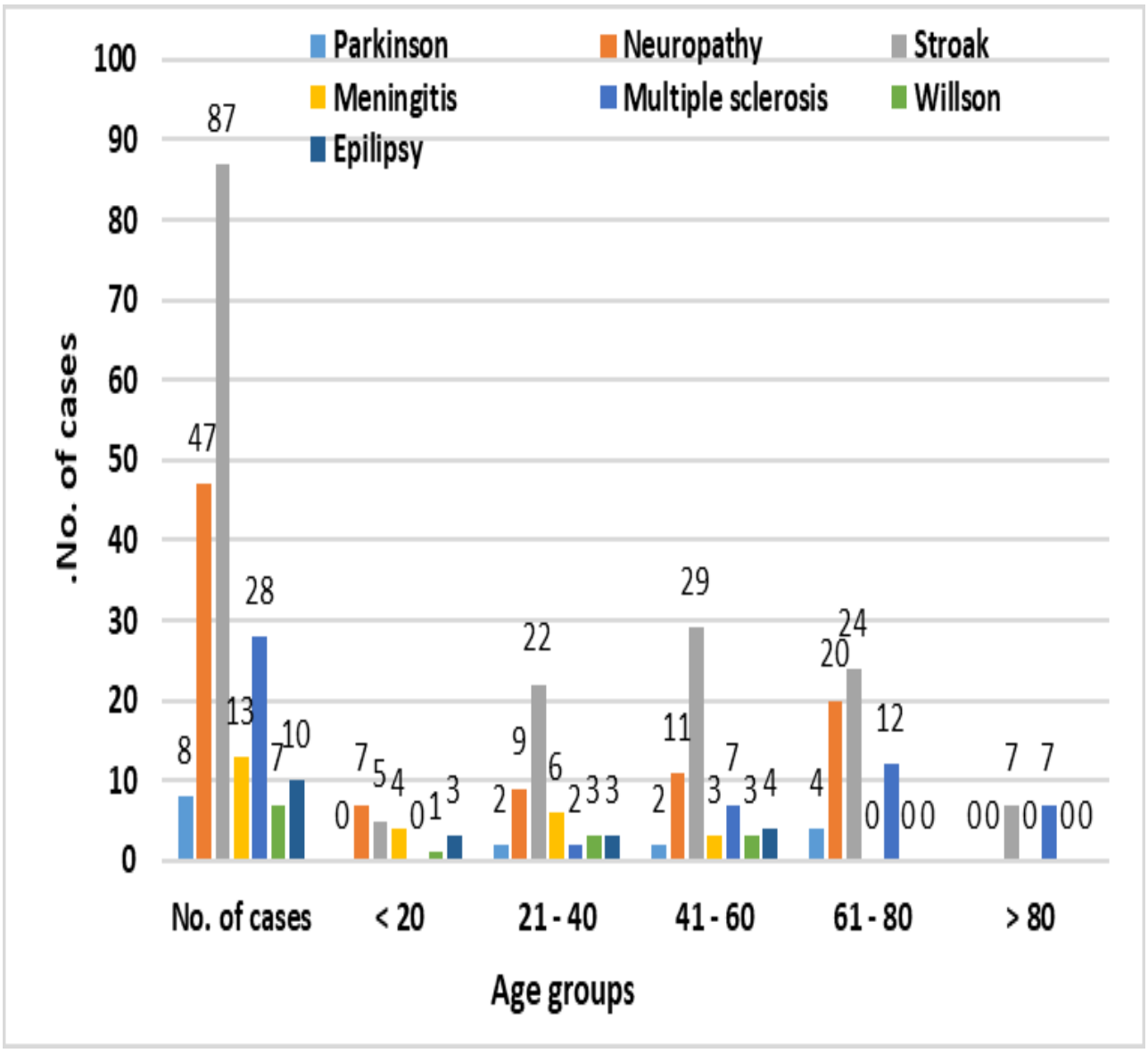

Figure 1: Distribution of neuroinflammatory disease according to age groups

Distribution of neuroinflammatory disease according to sex

Figure 2 explains the distribution of neuroinflammatory disease according to gender. the table revealed that out of 200 patients (cross sectional study) 120 were females and 80 males , stroke =87, 59(68%) females and 28 (32%) males , MS = 28 , females 15 (53.6%) , males 13 (46.4%) , Neuropathy =47, 24 (51%) for male and 32(49%), Meningitis = 13 , 7 (53.8%) females , 6 (46.2%) males , Epilepsy 10 , 7 (70.0%) females , 3 (30.0%) males , Parkinson = 8 , 6 (75.0%) females , 2 (25.0%) males) = , Wilson =7 , 4 (57/1%) females , 3 (42.9%) males .At p-value = 0.398 (p-value >0.05 statistically was not significant

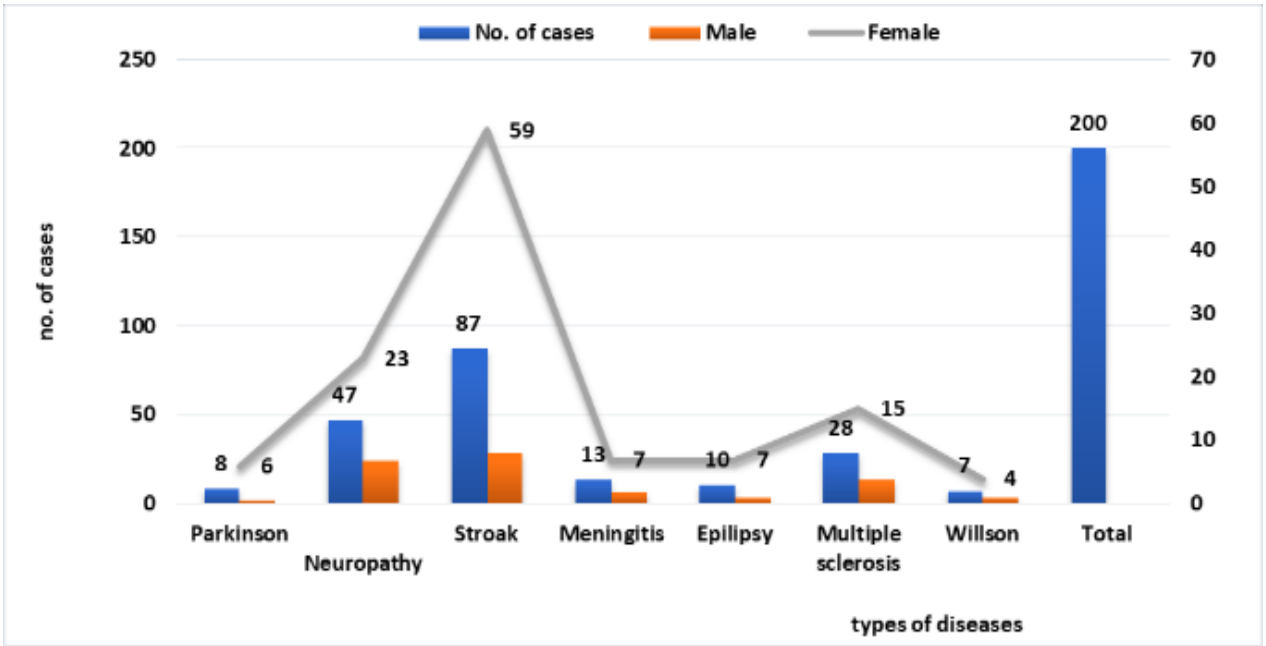

Figure 2: Distribution of neuroinflammatory disease according to sex

Seropositivity of NF-Kb in neuroinflammatory diseases

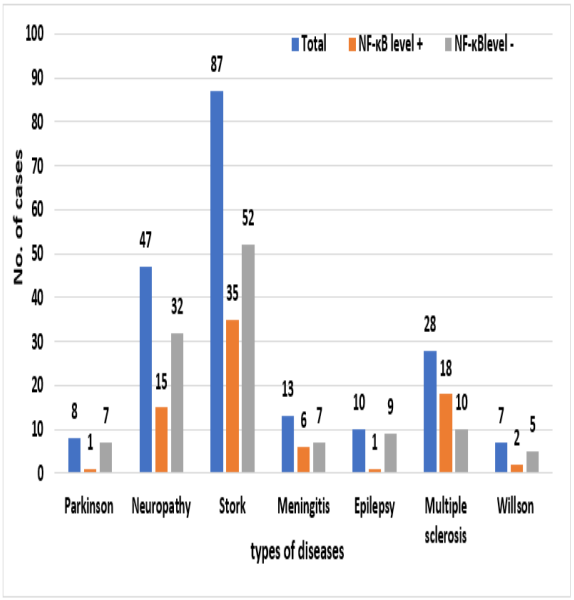

Figure 3: seropositivity of NF-Kb in neuroinflammatory diseases

Figure 3 revealed the seropositivity of NF-Kb among neuroinflammatory disease patients. As we can see in this table, in regard to the total number of Parkinson disease cases (8) the results of NF-κB were (1) positive and (7) negative in Neuropathy total disease cases (47) the results of NF-κB were (15) positive and (32) negative in stroke total disease cases (87) the results of NF-κB were (35). positive and (52) negative in meningitis total disease cases (13) the results of NF-κB were (6) positive and (7) negative in epilepsy total disease cases (10) the results of NF-κB were (1) positive and (9) negative in MS total disease cases (28) the results of NF-κB were (18) positive and (10) negative in Wilson total disease cases (7) the results of NF-κB were (2) positive and (5) negative at a P Value = 0.001

Correlation between the levels of white blood cells, platelets and lymphocytes according to the results of nuclear factor kappa: A statistical comparison by chi-square method

As we can see in this table , the level of WBCs among NF-κB+ group was (high = 50 (70.4%) , normal = 23 (20.2%) , low = 6 (40.0%) and the their level among NF-κB - was (high = 21 (29.6%) , normal = 91 (79.8%) , low = 9 (60.0%) , while the level of platelets among NF-κB + group was (high = 51 (86.4%) , normal = 22 (16.2%) , low = 2 (40.0%) and their level among NF-κB - group was (high = 8 (13.6%) , normal = 114 (83.8) , low = 3 (60.0%)) and lastly the level of lymphocytes among NF-κB + group was (high = 59 (88.1%) , normal = 16 (13.8%) , low = 13 (76.5%)) and their level among NF-κB - group was (high = 8 (11.9%) , normal = 100 (86.2) , low = 4 (23.5%)) eventually resulting in a total number of cases with high WBCs in both positive and negative NF-κB groups was (71) , and a total number of normal WBCs was (114) , a total number of low WBCs was (15) , and total number of cases with high PLT in both positive and negative NF-kB groups was (59) , a total number of normal PLT was (136) , a total number of low PLT was (5) , and last the total number of high lymphocytes in both positive and negative NF-kB groups was (67) , a total number of normal lymphocytes was (116) , a total number of low lymphocytes was (17) at a P value = 0.0001.

4. Discussion

The number of disease cases was higher in females than in males, but when a statistical analysis was performed, it was discovered that there are no significant differences between the sexes. This indicates that there is no possibility that females are exposed to these diseases more than males, which

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means that the samples that were obtained during that time period may have come into contact with the presence of the disease especially considering that the time it took to collect samples for this study was just three to four months. Age in general may play a major role in the presence of these diseases, as the results showed that age in general may have a close relationship with the presence of inflammatory diseases due to the patient's immune and physiological status and his use of various treatments and virus infections due to medical reviews and others. Additionally, the age group less than 20 years old was the least due to the smallness of these ages and the lack of possibility of exposure to a variety of diseases and viral infections. In addition, the case when distributing these ages to the sexes, there are no significant differences between them.

Table 1: Results of nuclear factor kappa B assays showing a correlation between white blood cell, platelet, and lymphocyte counts

NF-κB results Hematological levels	NF-κB Positive %	NF-κB Negative %	No. of cases %	P-value
High WBC	50(70.4%)	21(29.6%)	71	
Normal WBC	23(20.2%)	91(79.8%)	114	
Low WBC	6(40.0%)	9(60.0%)	15	
High PLT	51(86.4%)	8(13.6%)	59	
Normal PLT	22(16.2%)	114(83.8%)	136	0.0001
Low PLT	2(40.0%)	3(60.0%)	5	
High lymphocyte	59(88.1%)	8(11.9%)	67	
Normal lymphocyte	16(13.8%)	100(86.2%)	116	
Low lymphocyte	13(76.5%)	4(23.5%)	17	
p-value=0.0001(p-value ≤ 0.05 statistically was significant), X2=258.61 ,df=8				

According to Figure 1, the distribution of neuroinflammatory disease categories in the total cases of this study according to age groups indicated the following disorders: (Parkinson's disease, neuropathy, Stroke disease, meningitis disease, epilepsy disease, multiple sclerosis disease, and other Wilson disease). The greatest incidence rate was reported as a stroke at 43.5%, followed by multiple sclerosis at 14%, neuropathy at 23.5%, meningitis at 6.50%, epilepsy at 5%, Parkinson's at 4%, and lastly Wilson's disease at 3.5%. In addition, the findings of this research showed that the highest incidences of Parkinson's disease were found in patients who were in the age group (61-80), 50%, and in neuropathy (61-80), 72.2% and in Stroke (41-60), 44.8%. The results in Wilson (21-40) and (41-60) showed increases of 42.9% overall. The p-value of 0.05 was not statistically significant at 0.465, which means that the result is not significant.

Vaupel et al., 2003 refers to the fact that the proportion of elderly people in the adult population is expanding both in size and in number. (Di Benedetto et al., 2017) came to the conclusion that the most important aspect of dealing with this demographic change will be how people choose to use the additional years of their lives. However, this will only be beneficial to the individual and to society as a whole if people can continue to be active participants in daily life and work.

According to Müller and Pawelec (2014) and Di Benedetto et al. (2017), the older population should also take into account age-related physiological changes in the gastrointestinal tract, as well as age-related changes in lifestyle, dietary behavior, and reduced immunological function. According to Müller and Pawelec 2014, Di Benedetto et al., 2017, Tolppanen et al., 2015], it was shown that exercise can have a protective impact, even if it is started in advanced old age. This is encouraging news. Consuming foods rich in antioxidant compounds helps lower inflammation throughout the body, including neuroinflammation, which occurs naturally with age.

The Acosta-Martinez, 2020 study indicated that the origins of the sex-related changes in microglia are far from apparent, with sex hormones being a prominent element whose effect has been well-established. In addition, a substantial function for sex hormones has been demonstrated. The effects of estrogen on immunological cells, particularly microglia, are profound. Both estrogen response elements positioned on the promoters of immune-function genes and receptor-induced intracellular signaling cascades regulate the production of immune mediators. There are significant differences in the incidence or prognosis of some neurological illnesses between the sexes. As an example, boys are disproportionately affected by autism, whereas women suffer disproportionately from depression, men from Parkinson's disease, and women from multiple sclerosis. In the event of a stroke, women experience a less favorable prognosis and a more abrupt decline in health than males. As a result, such disorders are difficult to treat and have diverse outcomes. Despite this, sexual orientation is rarely addressed in treatment choices.

Although the processes driving sex variations in illness development are poorly understood, there is a substantial correlation between the inflammatory states of men and women and their susceptibility to acquire certain diseases. Since neuroinflammation is involved in the development of many neurological diseases, it stands to reason that if the brain's inflammatory state is altered in any way during normal development, the risk of developing neurological and neurodegenerative diseases is increased. Since microglia play a crucial role in the onset and regulation of inflammation, sex variations in microglial activity may account for some of the documented differences in susceptibilities and

outcomes of neurological disorders between men and women. Understanding the processes behind sex differences should facilitate the development of more focused therapies with a greater success rate, particularly for illnesses in which sex differences are most pronounced. Multiple studies (e.g., Gaillard & Spinedi 1998, Klein 2000, McClelland & Smith 2011, McMillen 1979, Schuurs & Verheul 1990, Washburn et al 1965) show that females of many species, including humans, often have better immune responses and tolerance to illness than males. The reference here is to (Kivity & Ehrenfeld 2010, McCombe et al 2009). The increased prevalence of autoimmune diseases in females may be attributable to their stronger peripheral immune response.

Regarding the total number of Parkinson's disease cases 8 the results of NF-B were 1 positive and 7 negative in the total number of neuropathy cases 47 the results of NF-B were 15 positive and 32 negative in all stroke disease cases 87 NF-B results were 35 positive and 52 .negative , in all meningitis cases 13 NF-B results 6 were positive and 7 negative in epilepsy cases Overall 10 NF-B results were 1 positive and 9 negative in total MS cases 28 NF-B results were 18 positive and 10 negative in total cases of Wilson's disease 7 NF-B results were 2 positive and 5 negative in AFP p = 0.001. No discernible gap existed between the sexes. The toxic effect of chemotherapy has a major influence on the decline in immunity, leading to reactivation of the virus, which means both genders are vulnerable to infection. Further, the toxic effect of chemotherapy has a substantial influence on the reduction in immunity, therefore there is no significant age difference in exposure to viral infection and NF-kB. It has been shown that B cells are able to store energy by means of a combination of complementary cellular functionality and cell death. Through downregulation of both apoptotic pathways, the transcription factor NF-kB promotes cell survival. In the background is the activation and downregulation of NF-kB that is necessary for B cell rule entry.

Since NF-kB is activated during B cell maturation, (Zhang et al., 2017) hypothesized that it played a crucial role in B cell activation and development. Despite being proven correct, this severely understates NF-kB impact on living organisms. While the secondary NF-kB activation pathway has fewer activities than the primary route, it is essential for regulating immune-related processes such B cell maturation, peripheral lymphoid development, and thymic progression (Zinatizadeh et al., 2021). Immune system dysfunction is among the many symptoms of inherited illnesses associated with a breakdown in NF-kB signaling.

(Disis, 2010) demonstrated the significance of inflammation and NF-kB in cancer. On one side, the immune system uses NF-kB activation as a weapon against abnormal cells. Full NF-kB activation appears to go hand in hand with a high level of cytotoxic immune cell activity against cancer cells, and this appears to be especially true in acute inflammatory processes.

5. Conclusion

The rise in NF-KB levels may be the result of neuro-tissue inflammation, stroke was the most common neuroinflammatory diseases found in this investigation. In addition to that prevalence increases with age

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