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RESEARCH ARTICLE

INTERVENTIONS AFFECTING PROGNOSIS AND QUALITY OF LIFE IN PEDIATRIC MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW

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Abstract

Introduction: Multiple sclerosis, autoimmune disease of the central nervous system primarily affecting young adults. The number of individuals suffering from multiple sclerosis under the age of 18 is gradually increasing. Early interventions in the form of pharmacotherapy have proven to be beneficial in reducing the severity of disease and thereby preventing disability. Furthermore, cognitive impairment affecting working memory, attention, and other domains is concerning in children.

Methodology: We identified papers by searching various electronic databases (PubMed, Google Scholar, Europe PMC, Scopus, Web of Science). Search terms included: Pediatric multiple sclerosis OR pediatric MS AND interventions AND prognosis OR disease progression OR disability OR quality of life OR QoL. Papers were included in this review if they were published in English, referenced interventions and their effects on quality of life of the patients, and included pediatric-onset multiple sclerosis as a primary population. Results: Seventeen papers were identified via the literature search that addressed interventions made in the field of pediatric multiple sclerosis and their effects on the quality of life of the patients. The current study extracted data from a diverse range of articles focusing on various aspects of pediatric-onset multiple sclerosis (POMS) treatment, outcomes, and associated factors. The data provided valuable insights into the clinical characteristics, treatment approaches, and quality of life considerations for POMS patients.

Discussion: Interventions include first line drugs (interferon beta-1a and glatiramer acetate) and disease modifying therapies like fingolimod, teriflunomide, natalizumab and rituximab. Potential modifiable factors like breastfeeding, vitamin D levels, exercise and diet were identified. CSF Neurofilament levels and various inflammatory genes are helpful in diagnosis.

Conclusion: The data extraction from diverse studies on POMS shed light on various treatment approaches, disease progression markers and psychosocial factors. The findings underscore the importance of early

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intervention, tailored treatment strategies, and multidisciplinary care to enhance outcomes for pediatric MS patients.

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Introduction:-

The aim of this systematic review is to identify and analyze the effectiveness of interventions, such as pharmacological treatments, physical therapies, and psychosocial interventions, ultimately providing valuable insights for healthcare professionals and policymakers in optimizing the care and well-being of young patients with multiple sclerosis.

Multiple sclerosis is an autoimmune disease of the central nervous system primarily affecting young adults before 40 years of age, with a worldwide prevalence of over 2.8 million.[1] Presently, the number of individuals suffering from multiple sclerosis under the age of 18 is gradually increasing. A different term is coined for this group of patients: pediatric onset multiple sclerosis (POMS), which affects approximately 0.027% of the population. The appearance of symptoms is fairly rare in the early age group.[2] POMS has a multifactorial pathogenesis encompassing environmental, nutritional, and lifestyle factors.[3] The course of disease in POMS is comparatively faster than that in adult patients. The rate of permanent disability in children occurs a decade earlier for disease progression than that in adult-onset MS.[4]

Early interventions in the form of pharmacotherapy have proven to be beneficial in reducing the severity of disease and thereby preventing disability. Highly effective disease-modifying treatments (HETs), for example, fingolimod, and medium-efficacy drugs such as teriflunomide are some of the approved drugs, and other disease-modifying therapies, such as B-cell therapies and immunomodulators, are under trial to prove their efficacy so that the quality of life of such patients can be improved.[5,6]

Although the physical deficits are comparatively low in POMS in contrast to the adult population due to early diagnosis and interventions, exercise can have a positive impact on fatigue, which is a more worrisome problem for them.[7]

Furthermore, cognitive impairment affecting working memory, attention, and other domains is concerning in children. Rehabilitation in the form of computerized assessments and programs may aid their day-to-day lives along with their academics.[8] Moreover, psychosocial care for both patients with POMS and their parents can help improve health-related quality of life with the help of counseling, computerized interventions, and informative resources.[9]

This study will help in strengthening knowledge of different intervention modalities and their impact on the quality of life in pediatric onset multiple sclerosis patients, in such a way that these children do not feel like a burden on their parents and families and have a more positive outlook on their lives. Since the existing literature on this topic is scarce, this review will help in commemorating all the essential points and curating a holistic management plan for patients.

Methodology:-

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used as a reporting guideline in this review. A systematic search was conducted by two independent authors (S) and (AN). We searched through electronic databases like PubMed, Google Scholar, Europe PMC, Scopus and Web of Science. We used keywords such as “pediatric multiple sclerosis”, “pediatric MS”, “disease progression” etc. to refine our search. The screening and selection of included articles were selected through specific inclusion and exclusion criteria’s with the help of Rayyan software. The inclusion criteria’s were - a) All the randomized controlled trials (RCTs), Observational studies (Cohort and Case-Control studies) were included, b) The language of the included studies was exclusively English, c) The population comprised of youth and adolescents up to 18 years of age with hx of multiple sclerosis, d) Studies which used multiple therapeutic interventions were included, f) Studies with outcomes associated with prognosis and quality of life in pediatric multiple sclerosis was selected. The exclusion criteria’s were - a) Case reports, case series, editorial letters and conference abstracts were excluded, b) Studies with population above 18 and above were excluded, c) Studies which used diagnostic techniques were not included, d) Studies with irrelevant

outcomes were excluded. The included studies were checked for biases through the Critical Appraisal Skills Program (CASP) checklist.

Figure 1:- PRISMA flowchart of the study selection.

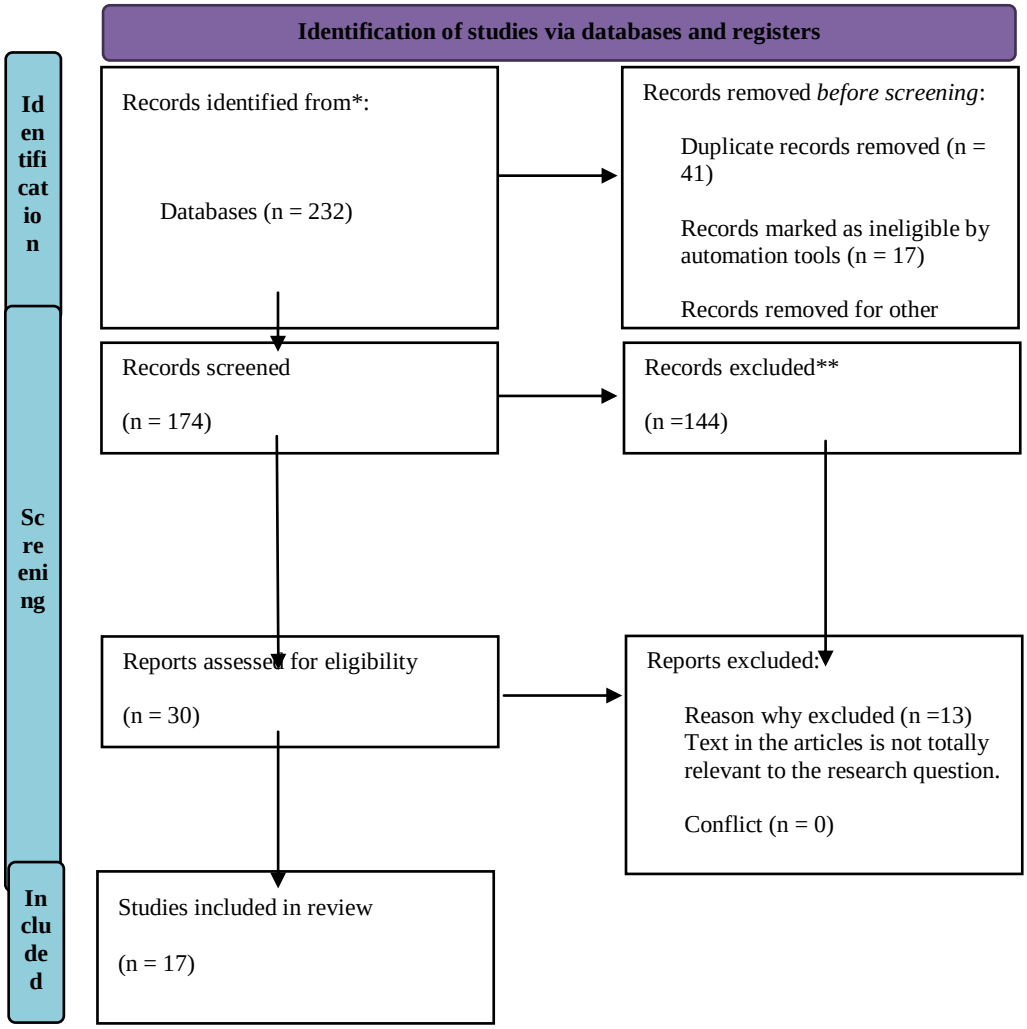

Table 1:- Characteristics of the study included.

Authors, Year	Year	Key Findings
Filipe Palavra et al.	2021	- ARR decreased from 1.31 to 0 after 12 months of natalizumab treatment. - No relapses in first year for patients treated at least 12 months.
J Burman et al.	2017	- HSCT is a promising alternative for children failing standard therapy. - Long-term side effects include herpes zoster reactivation and thyroid disease.
J. Nicholas Brenton et al.	2017	- Breastfeeding is associated with lower risk of pediatric MS. - Breast milk contains immunologic factors. - Non-breastfed children had higher risk of POMS.
Lara A. Pilutti et al.	2017	- Exercise training reduces fatigue and depressive symptoms in MS. - Some improvements in aerobic exercise training. - No change in certain domains of cognitive function.
Barbara Kornek et al.	2013	- Natalizumab reduces relapse rates and disability progression. - Some patients developed high-titer neutralizing antibodies. - Risk of relapse after discontinuing natalizumab.

Monica Margoni et al.	2019	- Natalizumab maintains NEDA-3 plus status in up to 80% of patients. - Natalizumab is well-tolerated with no concomitant disease activity.
Angelo Ghezzi et al.	2015	- Natalizumab reduces relapse rates and new lesions. - Presence of anti-JCV antibodies varies in pediatric patients.
Akash Virupakshaiah et al.	2022	- Acylcarnitines and PUFAs associated with increased relapse risk. - Phosphatidylethanolamines associated with lower relapse risk.
David Jure Hunt and Anthony Traboulsee	2020	- Alemtuzumab improves EDSS scores and stabilizes disease. - Risk of secondary autoimmunity with alemtuzumab.
Kyla A. McKay et al.	2020	- First- and second-line DMT exposure associated with higher QoL. - Obesity and disability linked to lower QoL.
Julia O'Mahony et al.	2023	- MS Navigator program offers support for mental health. - Confidential questionnaires aid in identifying concerns.
PelinVurala et al.	2023	- Online exercise training improves physical functions and QoL. - Different exercise types offer different benefits.
Yara Dadalti Fragoso et al.	2015	- Fingolimod reduces relapses and disability progression. - Drug-induced bradycardia is a concern.
Elizabeth Morghen Sikes et al.	2018	- Vitamin D levels influence relapse rates. - Iron consumption and obesity linked to MS diagnosis. - Physical activity and diet impact MS symptoms.
Roos M van der Vuurst de Vries et al.	2019	- High CSF NfL levels predict CDMS diagnosis. - T1-hypointense lesions associated with higher NfL levels.
Cristina Fernandez-Carbonell et al.	2021	- Natalizumab and vitamin D treatments improve outcomes. - Intensive cognitive rehabilitation benefits cognitive deficits. - Physical activity and diet influence MS symptoms.
Eitan Shavit et al.	2022	- Overexpression of inflammatory genes in POMS. - HLA genes associated with pediatric MS onset. - Transcriptional levels influence disease severity.

Table 2:- CASP checklist for Systematic Review.

	(A) Are the results of the review valid?					**(B) What are the results?**		**(C) Will the results help locally?**	
	Question 1	**Question 2**	**Question 3**	**Question 4**	**Question 5**	**Question 6**	**Question 7**	**Question 8**	
Author, Year	**Did the review address a clearly focused question?**	**Did the authors look for the right type?**	**Do you think all the important, relevant studies were included?**	**Did the author's do enough to access the quality of the included studies?**	**If the results of the review have been combined, was it reasonable to do so?**	**What are the overall results of the review?**	**How precise are the results?**	**Can the results be applied to the local population?**	
	Score	**Score**	**Score**	**Score**	**Score**	**Score**	**Score**	**Score**	**TOTAL SCOR**

									E
Lara A. Pilutti et al. 2017	2	2	2	2	2	1	1	2	**18**
Julia O'Mahony et al. 2023	2	2	2	2	2	1	1	2	**18**
Elizabeth Morghen Sikes et al. 2018	1	2	1	2	2	2	1	2	**17**
Cristina Fernandez-Carbonell et al. 2021	2	2	2	2	2	2	2	2	**20**

Table 3:- CASP checklist for RCT.

		(A) Are the results of the review valid?						(B) What are the results?		(C) Will the results help locally?			
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8	Question 9	Question 10	Question 11	
	Author, Year	Did the trial address a clearly focused issue?	Was the assignment of patients to treatments randomized?	Were patients, health workers and study personnel blinded?	Were the groups similar at the start of the trial?	Aside from the experimental intervention, were the groups treated equally?	Were all of the patients who entered the trial properly accounted for at its conclusion?	How large was the treatment effect?	How precise was the estimate of the treatment effect?	Can the results be applied in your context? (or to the local population?)	Were all clinically important outcomes considered?	Are the benefits worth the harms and costs?	
		Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Total Score
1	PelinVurala et al. 2023	2	2	0	2	2	2	2	1	2	2	2	19

Table 4:- CASP checklist for cohort study

		(A) Are the results of the review valid?								(B) What are the results?			(C) Will the results help locally?			
		Question 1	Question 2	Question 3	Question 4	Question 5a	Question 5b	Question 6a	Question 6b	Question 7	Question 8	Question 9	Question 10	Question 11	Question 12	
	Author, Year	Did the study address a clearl	Was the cohort recruited in	Was the exposure accurately	Was the outcome accurately	(a) Have the authors identi	(b) Have theytakenaccount of the	(a) Was the follow up of	(b) Was the follow up of	What are the results of this	How precise are the results?	Do you believe the results?	Can the results be applied to	Do the results of this study	What are the implications of	

		y focused issue?	an acceptable way?	measured to minimize bias?	measured to minimize bias?	fied all important confounding factors?	confounding factors in the design and/or analysis?	subjects complete enough?	subjects long enough?	study?			the local population?	fit with other available evidence?	this study for practice?	
		Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Total Score
1	Filipe Palavra et al. 2021(10)	2	2	2	2	2	2	2	2	1	1	1	1	2	2	24
2	J Burman et al. 2017 (11)	2	2	2	2	2	2	2	2	2	1	1	1	2	2	25
3	Barbara Kornek et al. 2013	2	2	2	2	2	2	2	2	2	1	1	1	1	1	23
4	Monica Margoni et al. 2019	2	2	2	2	2	2	2	2	2	1	1	1	2	2	25
5	David Jure Hunt and Anthony Traboulsee et al. 2020	2	1	2	1	2	2	2	2	1	1	0	0	2	1	19
6	Roos M van der Vuurst de Vries et al. 2019	1	2	2	2	2	2	1	0	2	1	2	2	2	1	22
7	Kyla	2	2	2	2	2	2	2	2	1	1	2	2	2	2	26

	A. McKay et al. 2020															
8	Eitan Shavit et al. 2022	2	2	2	2	2	2	2	2	2	1	1	1	1	1	23
9	Angelo Ghezzi et al. 2015	2	1	2	2	2	2	2	2	1	1	2	2	2	2	25
10	Akash Virupakshaiah et al. 2022	2	2	2	2	2	2	2	2	2	1	2	2	2	2	27
11	Yara Dadalti Fragoso et al. 2015	2	2	2	2	2	2	1	0	2	1	1	1	1	1	20

Table 5:- CASP checklist for case control studies.

		(A) Are the results of the review valid?								(B) What are the results?		(C) Will the results help locally?		
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6a	Question 6b	Question 7	Question 8	Question 9	Question 10	Question 11	
	Author, Year	Did the study address a clearly focused issue?	Did the authors use an appropriate method to answer their question?	Were the cases recruited in an acceptable way?	Were the controls selected in an acceptable way?	Was the exposure accurately measured to minimise bias?	(a) What confounding factors have the authors accounted for?	(b) Have the authors taken account of the potential confounding factors in the design and/o	What are the results of this study?	How precise are the results? How precise is the estimate of risk?	Do you believe the results?	Can the results be applied to the local population?	Do the results of this study fit with other available evidence?	

								r in their analysis?						
		Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Total Score
1	J. Nicholas Brenton et al. 2017	2	2	2	2	2	2	2	1	1	2	2	2	22

Results:-

The first-line drug used to treat pediatric multiple sclerosis (MS) is interferon beta-1a.

If the patient doesn't show any improvement with the first line treatment then disease modifying therapies may be considered as a possible intervention. DMTs include fingolimod, teriflunomide, natalizumab, rituximab etc.

In a retrospective study on the use of **Natalizumab** conducted in Portugal, the annual relapse rate (ARR) decreased from 1.31 events/patient/ year before treatment with natalizumab to 0 after 12 months of treatment and to 0.04 after 24 months. No relapses were observed in the first year in the group of patients treated at least for 12 months with natalizumab. There was one case of relapse after 13 months, and another one happened after nearly two years (1 year and 10 months). 13 adverse events (AEs) were observed in 6 patients during treatment, 8 that were possibly related to natalizumab, 2 that were probably related, and 2 that were unrelated to the treatment. This retrospective study shows that natalizumab treatment reduced disease activity in patients with POMS, with no concomitant relevant AEs, consistent with other published observational studies. Main risk concern associated with natalizumab treatment is progressive multifocal leukoencephalopathy (PML), and the presence of anti–JCV antibodies in serum is one of the risk factors for the development of PML. Despite carrying the greatest risk for PML among all DMTs, natalizumab's high efficacy makes it nonetheless superior to other DMTs in models of long-term morbidity and mortality. It has been suggested that extending the interval between natalizumab infusions may reduce PML risk.[10]Treatment with natalizumab was associated with reductions in mean annualized relapse rates (3.7 without treatment vs 0.4 with treatment; P - .001), median Expanded Disability Status Scale scores (2 without treatment vs 1 with treatment; P - .02), and mean number of new T2/fluid-attenuated inversion recovery lesions per year (7.8 without treatment vs 0.5 with treatment; P < .001).Two patients developed hightiter neutralizing antibodies against natalizumab and had to stop therapy.[14]

In another study conducted by the Italian registry a total of 66 clinical adverse events were observed in 36/101 patients. All of them were mild, did not cause drug discontinuation and, if necessary, were treated according to normal standard of medical care. Mild hematological abnormalities (below toxicity level 1) were observed in 15/101 cases: they were resolved spontaneously with no intervention. Ghezzi et al. conducted the study and the frequency of patient positive for anti-JCV antibody in his study was at baseline of 43% which was 14% lower than Moloia Lucia et al.[16]

Fingolimod is an efficacious and well-tolerated treatment for multiple sclerosis that reduces relapse rates, disability progression, new brain lesions, and loss of brain volume. The main concern regarding the use of fingolimod is drug-induced bradycardia during the first dose. Macular edema has been described as a potential complication from fingolimod use. In Fragoso et al. a patient developed genital herpes, and another patient experienced an isolated episode of upper airway viral infection, and a third patient had two episodes of UTI after treatment with fingolimod. Fingolimod significantly affected EDSS and improved the condition of this patient group (P = 0.05). In this study there were no drug-related complications and the majority of patients (94%; 16/17) showed no evidence of disease activity with regard to relapses, disability progression, or new lesions on MRI.[22]

Autologous hematopoietic stem cell transplantation (aHSCT) is a promising therapy for multiple sclerosis (MS), which has mainly been used in adults. A retrospective study is conducted and this is the first report of treatment with aHSCT for MS in children. The procedure was generally well tolerated and only one patient experienced unexpected serious adverse events. In the long term, well-known side effects are herpes zoster reactivation, which has been reported in 2.6–15% of patients, and thyroid disease with a prevalence of 4.0–8.4% post HSCT. AHSCT emerges as a hopeful option for children who do not respond well to conventional treatment, providing the benefits of rapid disease management and enhanced functionality in a significant proportion of patients. This single-session intervention presents the advantage of circumventing the potential negative effects linked to the ongoing use of disease-modifying drugs, which might otherwise impact academic performance and overall quality of life. However, it is important to note that AHSCT comes with the drawback of posing risks, including the potential occurrence of serious adverse events like hazardous infections, secondary autoimmunity, and reduced fertility.[11]

Breastfeeding play as a modifiable, potentially protective factor for reducing the likelihood of developing MS as a child. Breast milk contains immunologic factors, including secretory IgA and considerable amounts of cytokines, such as interleukin-10 and transforming growth factor beta. When obese children were excluded from analysis, non–breastfed children still had almost four-fold increased risk of POMS (odds ratio = 3.89; 95% CI, 1.17 to 12.91; P = 0.027) compared with breastfed children after age at diagnosis, sex, and race were adjusted. Obesity in adolescence has been implicated as a risk factor for adult-onset multiple sclerosis and pediatric onset MS. Our study primarily assessed the association of breastfeeding as an infant upon risk of POMS and provides evidence of an association between breastfeeding as an infant and future risk of pediatric MS.[12]

Vitamin D levels were associated with relapse rate such that higher levels of vitamin D were associated with fewer relapses in POMS. Adequate vitamin D3 status was associated with a 34% decrease in subsequent relapse rates. Iron consumption below the recommended amount was associated with diagnosis of POMS. High body mass index or obesity as a risk factor for developing POMS. One of the papers reported that obesity was associated with a higher risk for developing POMS among girls than boys. Physical activity, particularly participation in strenuous exercise, was associated with smaller T2 lesion volumes in a sample of subjects with POMS. Those with POMS who engaged in higher levels of physical activity reported less fatigue, fewer sleep/rest fatigue symptoms, and lower relapse rates. POMS who participated in higher levels of physical activity reported less sleep/rest fatigue symptoms than those who did not achieve adequate levels of physical activity.[23]

Acylcarnitines and poly-unsaturated fatty acids (PUFAs) were significantly associated with an increased risk of relapse and worse baseline EDSS scores. On the other hand, phosphatidylethanolamines (PEs), plasmalogens, and primary bile acids were associated with a lower risk of relapse and lower baseline EDSS scores. In this cohort, we found that increasing levels of PEs and PCs were associated with lower relapse rates. Phosphatidylinositols, another class of phospholipids, were also trending in the same direction. Higher PE levels were also associated with lower EDSS scores while increasing levels of DAGs were associated with worse EDSS scores. These findings support the hypothesis of increased phospholipid turnover and suggest that it is associated with increased disease activity. In our study, the PUFA pathway consisted of both n3 and n6 PUFA metabolites, with the majority of them being of the n6 class. Thus, the direction of the relationship between this pathway and the clinical out- comes was mainly driven by the n6 component, higher levels of which were associated with more relapses and worse EDSS. Our results support the role of several lipid metabolic pathways in the course of MS. Lipid metabolites should be further investigated as biomarkers of disease activity and severity, as findings could lead to identifying new therapeutic targets.[17]

Two articles identified mentioned the role of **exercise** as another possible modifiable factor and its effect in disease progression.

Exercise training has a modest to moderate effect (g = 0.45) in alleviating fatigue symptoms in individuals with MS. It is also associated with a slight reduction (g = 0.36) in depressive symptoms and demonstrates an overall positive effect (g = 0.23) on the quality of life (QOL). However, there is a relative risk of adverse events (1.67 compared to controls) without surpassing levels reported in healthy populations. Notably, these benefits are predominantly established in the early, relapsing disease phase, or from diverse samples, making it challenging to ascertain whether exercise training's benefits are consistent across relapsing and progressive disease phases. Improvements are observed in aerobic exercise training for peak oxygen consumption, fatigue, depressive symptoms, walking endurance, and select cognitive functions, but no changes in certain biomarkers. Home-based exercises positively impact health-related quality of life in people with MS.[13]

Results of the other article indicate that OETP consisting of aerobic, strengthening, and balance exercises have positive effects on PwPOMS. Besides that, functional capacity, fatigue, and physical health were superior in the OETP group to the control group. In our study, at the end of the online exercise training program, a significant change was observed in the isokinetic muscle strength of both hamstring and quadriceps muscles, but no change was observed in the control group. In our study, there was a significant decrease in fatigue severity with the online exercise training program, but there was no change in the control group after 8 weeks. The significant change in the quality of life of children and parents in the OETP group may be related to decreased fatigue severity, increased self-confidence, and awareness of the positive effects of exercise in PwPOMS. Home-based exercises positively affected the health-related quality of life in PwMS.[21]

Natalizumab (NTZ) maintains a NEDA-3 plus status (zero tolerance) in approximately 80% of pediatric MS patients over at least a 2-year period. Adverse events are generally well-tolerated, with only one case of moderate hypertension. No clinical relapses or increased disability are reported. The study concludes a high rate of NEDA-3 plus in pediatric MS patients treated with NTZ over a 2-year period.[15]

Cerebrospinal fluid (CSF) neurofilament levels are predictive for clinically definite MS diagnosis, particularly in children, suggesting more severe inflammation and early axonal damage than in adults. High CSF neurofilament levels are associated with T1-hypointense lesions, indicating axonal loss. CSF neurofilament emerges as a promising predictive marker for disease course in both adults and children with a first demyelinating event.[24]

In pediatric MS, there is overexpression of B-cell-related genes, highlighting the role of B cells, including CD38 positive memory cells, in distinguishing between pediatric and adult onset MS. HLA-DRB15 and A02 are strongly associated with pediatric MS onset. Higher transcriptional levels of genes involved in cell cycle, migration, and B-cell proliferation contribute to the more aggressive clinical course seen in pediatric MS.[26]

Intensive therapy, particularly with Natalizumab, proves beneficial for preserving cognitive function in pediatric MS patients. Additionally, 25(OH) D supplementation improves fatigue and quality of life scores. Intensive cognitive rehabilitation is effective in improving cognitive deficits and quality of life in adults with MS. Physical activity is beneficial for sleep issues and fatigue in children with pediatric-onset MS.[25]

Discussing the MS diagnosis with peers may aid in the psychosocial development and acceptance of children with MS. However, misinformation among peers can strain relationships. Specialized MS training for healthcare providers can provide families with essential information, while external resources such as the National MS Society's MS Navigator program can connect individuals with mental health providers. Confidential questionnaires may help identify mental health concerns, and providing accurate information through talking points can mitigate psychosocial distress.[20]

Discussion:-

The current study extracted data from a diverse range of articles focusing on various aspects of pediatric-onset multiple sclerosis (POMS) treatment, outcomes, and associated factors. The extracted data provided valuable insights into the clinical characteristics, treatment approaches, and quality of life considerations for pediatric MS patients. This discussion will interpret and contextualize the extracted data, highlighting key findings and their implications.

Treatment Approaches and Outcomes:

Several articles discussed the efficacy of different disease-modifying therapies **(DMTs)** for POMS. **Natalizumab**, a high-efficacy DMT, emerged as a promising option. The study by Kornek et al. (2013) demonstrated a reduction in relapse rates, disability progression, and new brain lesions following natalizumab treatment and discontinuation of the therapy led to the reoccurrence of relapse activity in 75 percent of the patients.[14] Similarly, Margoni et al. (2019) reported that **natalizumab** treatment maintained a no-evidence-of-disease-activity (NEDA-3 plus) status in a significant proportion of patients over a 2-year period, strongly supporting the use of natalizumab asa first choice treatment in the pediatric MS population.[15]

Fingolimod, another DMT, was also shown to be effective in reducing relapse rates and preserving cognitive function. The main concern regarding its use being the drug induced bradycardia during the first use. Overall the

drug showed significant improvement in EDSS(Expanded disability status scale) and no increase in disability since the start of treatment with fingolimod.(Fragoso et al.,2015).[22]

The findings from studies on autologous hematopoietic stem cell transplantation **(aHSCT)** as a treatment for POMS (Burman et al., 2017) and the potential benefits of **exercise training** (Pilutti& Edwards, 2017). aHSCT is a promising alternative for children failing standard therapy, with the advantages of immediate disease control and functional improvement in a majority of patients whereas it is associated with risk of serious adverse events, such as potentially dangerous infections, secondary autoimmunity and decreased fertility.[11]

Exercise training had a small to moderate effect in reducing symptoms of fatigue in people with MS, is associated with a small reduction in depressive symptoms in people with MS and one study also demonstrated a small overall positive effect of exercise training on quality of life in people with MS.[13] Results of a study by Vurala et al.(2023) indicate that online exercise training program consisting of aerobic, strengthening and balance exercises have positive effects on patients with pediatric onset multiple sclerosis and also lead to a significant decrease in fatigue severity. All these changes have a significant positive change in the quality of life of children and parents affected with POMS.[21]

These studies are indicative of new and alternative therapeutic avenues.

Moreover, the study by Brenton et al. (2017) highlighted the association between **breastfeeding** during infancy and a lower future risk of POMS, non-breastfed children have almost four-fold increased risk of POMS compared with breastfed children after age at diagnosis, sex, and race were adjusted, suggesting a potential modifiable protective factor.[12]

Obesity in adolescence has been implicated as a risk factor for adult as well as pediatric onset MS.[12]

Quality of Life and Psychosocial Factors:
The impact of POMS on quality of life (QoL) and psychosocial well-being was another important aspect addressed in the extracted data. Factors influencing QoL included **physical activity levels, mood, and cognitive health.** The study by Fernandez-Carbonell et al. (2021) demonstrated that **cognitive rehabilitation** interventions had a positive impact on cognitive deficits and QoL in POMS patients. Intensive cognitive rehabilitation with a special emphasis on attention, processing speed, memory, and executive function has shown benefit on improving cognitive deficits and QoL in adults with MS, with brain changes demonstrated on functional MRI. Physical activity helps with sleep issues and fatigue in children with POMS. Although some studies found that low fat diets improved fatigue, QoL, depression and cognitive health.[25]

However, the study also emphasized the need for prompt evaluation and treatment of mood disorders in pediatric MS patients.It is likely that, for those in the pediatric age group, nonpharmacologic approaches will have the best outcomes.

Biomarkers and Disease Progression:
Several studies explored potential biomarkers associated with disease progression and severity in POMS. Notably, **CSF neurofilament** levels were predictive of clinically definite multiple sclerosis (CDMS) diagnosis in both children and adults (van der Vuurst de Vries et al., 2019). CSF neurofilament levels in children and adults with a first attack of suspected MS are predictive for clinically definite multiple sclerosis (CDMS) diagnosis. At the time of clinically isolated syndrome (CIS), CSF neurofilament levels in patients with a future CDMS diagnosis are higher in children than in adult patients. This underlines that not only inflammation is more severe in children but that children also have more axonal damage early in the disease course of MS than adult patients.[24]

Additionally, **age-related blood transcriptional regulators** were found to influence disease progression (Shavit et al., 2022). Significant inflammation in POMS has been shown to be based on over expression of well-known inflammatory genes such as IL3, CCL5, CXCR3, CD38 and IL19. HLA-DRB*15 and A*02 were strongly associated with POMS. Findings of the study of higher transcriptional levels of genes involved in cell cycle, cell migration and B cell proliferation in POMS, that promoted by transcriptional level of age associated genes and transcriptional factors allows better understanding of the more aggressive clinical course that defines the POMS.[26]

Limitations and Future Directions:
While the extracted data provided valuable insights, certain limitations were evident. Variations in sample sizes, study designs, and methodologies across different studies may influence the generalizability of the findings.

The data about the pathogenesis of POMS in the pediatric population is limited. Also, the sample size could be mentioned as a possible limitation in many of the studies. In the study by RM van der Vuurst de Vries et al., in order to prove an association of CSF NfL levels with EDSS, a longer follow-up period was needed since disability occurs later in the disease course especially in children and also access to advanced imaging techniques for quantification of neurodegeneration was not there. Therefore, short follow up period is another limitation in few studies.

Additionally, the limited number of longitudinal studies and clinical trials highlights the need for more robust research in the field of POMS. We believe there is an abundant opportunity for descriptive research on healthy behaviours in POMS ;validation research on appropriate methods for measuring them and the reliability of such measures; qualitative and cross- sectional research on predictors and consequences (e.g., reduced relapse rates and increased quality of life) of health behaviours in POMS.

Conclusion:-

In conclusion, the data extraction from diverse studies on POMS shed light on various **treatment approaches, disease progression markers, and psychosocial factors.** The findings underscore the importance of early intervention, tailored treatment strategies, and multidisciplinary care to enhance outcomes for pediatric MS patients. Future research should focus on addressing gaps in knowledge, conducting longitudinal studies, and investigating personalized treatment regimens for this unique population.

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No potential conflicts of interest among the authors.

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