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Evaluation of psychiatric characteristics in children of parents with multiple sclerosis

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ÖZ

Objective: *This study aims to investigate the psychiatric disorders in children with parental multiple sclerosis (MS) and to research the differences between without parental chronic disease.* ***Methods:*** *The children of the parents with MS diagnosis in the neurology department and the children of parents without chronic medical and psychiatric diseases were included in the study. Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version (K-SADS-PL) was applied to the children. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version (SCID-I-CV) was applied to parents with MS. Psychiatric characteristics of the parents and children were determined. The accompanying psychiatric disorders in children and adolescents with paternal MS and the clinical features affecting these disorders were analyzed.* ***Results:*** *Fifty children and adolescents with parental MS were included in the study group and 75 children and adolescents without a chronic disease in the parents were included in the control group. The mean age of children in the study group was 12.7±2.9 years and 58% were girls. 52% of the parents with MS were diagnosed with a psychiatric disorder. As a result of the evaluation, 54% of the children with parental MS were diagnosed with psychiatric disorder. The most common psychiatric diagnoses were anxiety disorders (30%), attention deficit and hyperactivity disorder (ADHD) (22%), and tic disorders (16%), respectively. The Expanded Disability Status Scale scores of the parents of children with psychiatric diagnoses were significantly higher than those of the children with no diagnosis.* ***Conclusion:*** *Children of MS patients have a high rate of psychiatric disorder. As the severity of MS increases, it is more common for children to be affected psychosocially. Children with parental MS should be follow-up for psychiatric disorders, especially for anxiety disorders and ADHD.* ***(Anadolu Psikiyatri Derg 2020; 21(5):515-522)***

Keywords: *multiple sclerosis, child and adolescent, psychiatric disorder, parental chronic illness*

Multipl skleroz hastalarının çocuklarının psikiyatrik özelliklerinin değerlendirilmesi

ABSTRACT

Amaç: *Bu çalışmada amacımız, multipl skleroz (MS) tanısı konan anne-babanın çocuklarında psikiyatrik bozuklukların incelenerek anne-babasında kronik hastalığı olmayan çocuk ve ergenlerle farklılıklarını araştırmaktır.* ***Yöntem:*** *Nöroloji polikliniğinde MS tanısıyla izlenen anne-babaların çocuklarıyla, kronik tıbbi ve psikiyatrik hastalığı olmayan anne-babaların çocukları çalışmaya alındı. Çocuklarla psikiyatrik görüşme yapılarak Okul Çağı Çocukları için Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi-Şimdi ve Yaşam boyu Şekli Türkçe uyarlaması (K-SADS-PL) uygulandı. MS'li anne-babalara DSM-IV Eksen I Bozuklukları için Yapılandırılmış Klinik Görüşme, Klinik Versiyonu (SCID-I-CV) uygulandı. Anne-baba ve çocukların psikiyatrik özellikleri belirlendi. Anne-babasında MS olan*

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çocuk ve ergenlerde eşlik eden psikiyatrik bozukluklar ve bu bozukluklar üzerine etkili olan klinik özellikler analiz edildi. ***Bulgular:*** *Çalışma grubuna anne-babasında MS olan 50 çocuk ve ergen, kontrol grubuna anne-babasında kronik hastalık olmayan 75 çocuk ve ergen alındı. Çalışma grubundaki çocukların yaş ortalaması 12.7±2.9 olup %58'i kızdı, kontrol grubunun yaş ve cinsiyet özellikleri benzerdi. Çalışma grubundaki olguların %78'inin annesi MS hastasıydı. MS'li anne-babaların %52'sine psikiyatrik bozukluk tanısı konuldu. Değerlendirme sonucunda MS'li anne-babaların çocuklarının %54'üne psikiyatrik bozukluk tanısı konuldu. Bu olgulara en sık konulan psikiyatrik tanılar sırasıyla anksiyete bozuklukları (%30), dikkat eksikliği hiperaktivite bozukluğu (DEHB) (%22), tik bozukluğu (16%) idi. Psikiyatrik tanı konanların anne-babalarının Genişletilmiş Engellilik Durum Ölçeği puan ortalaması, tanı konmayanlara göre anlamlı olarak yüksek bulundu.* ***Sonuç:*** *MS hastalarının çocuklarında yüksek oranda psikiyatrik bozukluk bulunmuştur. MS'nin ciddiyeti arttıkça, çocukların ruhsal-toplumsal yönden etkilenmesi daha fazla olmaktadır. MS'li anne-babaların çocukları, başta anksiyete bozuklukları ve DEHB olmak üzere psikiyatrik bozukluklar açısından izlenmelidir.* ***(Anatolian Journal of Psychiatry 2020; 21(5):515-522)***

Anahtar sözcükler: *Multipl skleroz, çocuk ve ergen, psikiyatrik bozukluklar, kronik hastalıklı anne-baba*

INTRODUCTION

In recent years, increases in the incidence of psychiatric disorders in children and adolescents have been reported in our country and the world.[1,2] It has been reported that psychosocial problems and psychiatric disorders are more common in children and adolescents with parental chronic disease.[3,4] Among these chronic diseases, cancer was the most investigated, and the rates of psychosocial disorder was found to be high in children of parents with severe cancers.[5]

Multiple sclerosis is a chronic, autoimmune and demyelinating central nervous system disease that causes neurological deficits especially in young adults.[6] MS is frequently seen in the 25-35 age range and is the most common non-traumatic disabling disease in young adults.[7] The etiopathogenesis of MS has not been fully elucidated, but it is a complex disease involving genetic, environmental and autoimmune factors.[8] Current evidence shows that the incidence of MS is increased.[6,9]

As it is seen in the age group where productivity is the highest, physical deficiencies that develop in individuals with MS often lead to job loss by disrupting one's functionality. However, changes in mood, personality, and cognitive functioning are among the most restrictive and disturbing symptoms for individuals diagnosed with MS, but patients and their families pay little attention to these problems.[10] The loss of functionality and psychological problems that develop with the disease in individuals with MS also affect the family of the person.

Most affected individuals have children under the age of 18 at the time of their diagnosis with MS. Disease and physical disabilities in the person may adversely affect their children. There is a limited number of data on psychiatric disorders in children of MS patients in the literature. There are no studies on this subject in our country. This study aims to investigate the psychiatric disorders in children with parental MS and to reveal the differences between children and adolescents without parental chronic disease.

METHODS

Study population

Our study was a cross-sectional study performed with the children of parents who applied to the Neurology outpatient clinic of Trakya University Faculty of Medicine between January 1st, 2019, and September 1st, 2019, diagnosed with MS according to the revised McDonald's criteria and followed for at least 1 year.[11]

Fifty children and adolescents between the ages of 6 and 18 who gave consent or whose parents provided consent on their behalf to participate in the study between these dates were included in the study. During the same time, 75 children and adolescents who applied to the pediatric outpatient clinic for routine control and who had no parental chronic medical illness and known psychiatric disorder were included in the control group. Approval of the study protocol was obtained from Trakya University Faculty of Medicine Scientific Research Ethics Committee numbered as TUTF-BAEK 2018/427.

Evaluation tools

Sociodemographic Data Collection Form: This form was developed by our clinic and filled out with accompany of families and physicians. The child's gender, developmental history, age, the number of siblings, grade, psychiatric illness history, medication history, family's monthly income, the age of parents, educational status, occupation, history of psychiatric disease and determinants of MS have been questioned using

this form.

Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version (K-SADS-PL): K-SADS-PL's Turkish version was applied to all cases.[12] The validity and reliability study of the scale was conducted for the Turkish sample.[13] K-SADS-PL is a semi-structured interview form used to determine current and lifelong psychopathologies in children and adolescents. K-SADS-PL was applied to all children and adolescents with and without parental MS who participated in the study.

Kurtzke Expanded Disability Status Scale: The expanded disability status scale is used for grading neurological disability. This scale is considered to be the standard for measuring disability in patients with MS. Patients are evaluated in scores ranging from 0 to 10, and higher scores indicate more serious disability.[14] Scoring consists of 20 digits from 0 to 10. EDSS steps are determined by combining the questioning and neurological examination findings based on 7 functional systems between 1.0 and 4.0. The EDSS score of MS patients was calculated by the researcher neurologist.

Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version (SCID-I-CV): It is a semi-structured interview form developed to evaluate psychiatric disorders in DSM-IV Axis I Disorders. This interview was conducted by adult psychiatrists with parents with MS. The reliability and adaptation of the Turkish version were made by Ozkurkcugil et al. When the reliability was examined, the percentage of agreement for all diagnoses was 98.1%, and the Kappa coefficient was 0.86.[15]

Statistical analysis

Data were analyzed by Statistical Package for Social Sciences (SPSS) version 17.0 for Windows (IBM, Armonk, New York, USA). Whether or not the distributions of continuous variables were normal was determined by the Kolmogorov-Smirnov test. Data were shown as mean±standard deviation for continuous variables. The number of cases and percentages were used for categorical data. Mean differences between groups were compared by Student's t-test, whereas the Mann-Whitney U test was applied for comparisons of the not normally distributed data. Categorical variables were analyzed by chi-square or Fisher's exact test, where applicable. Statistical significance was accepted as $p<0.05$.

RESULTS

Fifty children and adolescents with parental MS were included in the study group along with 75 children and adolescents whose parents had no chronic illness and known psychiatric disorder as the control group. In the study group, the mother of 78% (n=36) of the cases had MS. The diagnosis age of the parents was 32.6±6.9 years and median disease duration was 7 years (range: 2-22 years). The median attack number of MS cases was 2, while 78% had relapsing-remitting MS (RRMS), 20% had primary progressive and 2% had secondary progressive MS. The mean EDSS score of the parents with MS was 2.5±1.7. 32% of MS patients were receiving fingolimod, 26% interferon beta 1a antagonist, 26% glatiemaer acetate, 18% dimethyl fumarate, 16% interferon beta1b antagnosts, 16% octrelizumab, 8% sibudramine, 4% fampyridine, 4% teriflunomide, 4% inatalizumab, and 2% sphingosinphosphate treatment. 36% of parents with MS were using multiple MS drugs.

Regarding the educational level of mothers in the study group, 44% were primary, 36% high school, 20% university graduates, while 58.7% of the control group were primary, 28% high school and 10.7% university graduates. Regarding the educational level of the fathers of the study group, 36% were primary school, 30% high school, 34% university graduates, while 57.3% of the control group was primary, 28% high school, 14.7% university graduates.

The mean age of the children in the study group were 12.7±2.9 and 58% was girls. Age and gender characteristics of the control group were similar to the study group. The father's age of the children in the study group was significantly higher than the control group. Other demographic characteristics were similar to the control group (Table 1).

16% of the children with parental MS had a history of a psychiatric disorder before the evaluation and 54% of these cases were diagnosed with psychiatric disorder after the K-SADS-PL evaluation. The most common psychiatric diagnoses were anxiety disorders (30%), ADHD (22%), tic disorders (16%), obsessive-compulsive disorder (OCD) (8.0%) and depressive disorders (8.0%). The rate of psychiatric diagnosis was significantly higher in children with parental MS compared to the control group (54% vs. 16%, p=0.001). Anxiety disorder, ADHD, depressive disorders and tic disorder were higher in children with parental MS compared to the control group

Table 1. Demographic characteristics of study and control group

Variables	Study group (n=50) n	%	Comparison group (n=75) n	%	p
Age (Mean±SD)	12.7±2.9		12.1±3.0		0.22
Female gender	29	58.0	44	58.7	0.94
School class (Mean±SD)	7.4±3.3		6.9±2.8		0.52
Number of siblings (Mean±SD)	2.0±0.9		2.2±0.9		0.31
Number of people in the house (Mean±SD)	4.1±1.0		4.1±1.1		0.71
Mother's age (Mean±SD)	41.5±5.1		40.4±5.8		0.16
Father's age (Mean±SD)	44.5±5.5		41.2±5.7		**0.002**
Low socioeconomic status	13	26.0	20	26.7	0.93
Caesarian birth	26	52.0	41	54.7	0.88

Table 2. Distribution of psychiatric disorders in the study and control group

Variables	Study group (n=50) n	%	Comparison group (n=75) n	%	p
Anxiety disorders	15	30.0	4	5.3	**0.001**
Attention deficit and hyperactivity disorder	11	22.0	4	5.3	**0.009**
Tic disorder	8	16.0	2	2.7	**0.014**
Obsessive compulsive disorder	4	8.0	1	1.3	0.15
Depressive disorder	4	8.0	0	0	**0.024**
Oppositional defiant disorder	3	6.0	1	1.3	0.48
Elimination disorder	2	4.0	2	2.7	0.68
Conduct disorder	2	4.0	1	1.3	0.56

Table 3. Comparison of clinical characteristics of patients with and without psychiatric diagnosis in study population

Variables	with psychiatric diagnosis (n=27) n	%	without psychiatric diagnosis (n=23) n	%	p
Age (Mean±SD)	12.6±3.0		12.8±3.7		0.83
Gender, male	11	56.5	10	43.5	0.84
Gender, female	16	59.3	13	40.7	0.84
Mother's age (Mean±SD)	42.2±6.1		40.7±3.4		0.30
Father's age (Mean±SD)	45.6±5.9		43.2±4.5		0.11
Maternal multiple sclerosis	22	81.5	17	73.9	0.73
Parental psychiatric diagnosis	17	63.0	10	43.5	0.25
Parental multiple sclerosis duration (Mean±SD)	9.2±5.1		9.5±5.2		0.85
Expanded Disability Status Scale (Mean±SD)	2.9±21.9		1.9±1.24		**0.02**
Number of siblings (Median)	2.0		2.0		0.62

and no statistical difference was observed in terms of other psychiatric diagnoses (Table 2).

The characteristics of with and without psychiatric diagnoses in children of parents with MS were compared, no difference was found in terms of age, gender, mother-father's age, socioeconomic status and the duration of MS. The mean parental EDSS score of the cases with a psychiatric diagnosis was found to be significantly higher than those without a diag-

nosis (Table 3). 22% of the parents diagnosed with MS already had a psychiatric diagnosis. When SCID-I-CV was applied, a psychiatric disorder was determined in 52% of the cases. The most common diagnoses were depressive disorders in 32%, anxiety disorders in 24% and OCD in 16% of the cases. In the study group, there was no significant difference in the frequency of psychiatric diagnoses in children with and without a parental psychiatric diagnosis (Table 3).

In the study group, 45% (n=10) of the children with primary and lower maternal education level and 63% (n=17) of the children with high school and upper maternal education level were diagnosed with psychiatric diagnosis. There was no statistically significant difference between maternal education level and psychiatric disorder (p=0.39). There was a psychiatric disorder in 55.6% (n=10) of the children whose fathers have primary and lower education levels and 53.1% (n=17) of the children whose fathers have high school and upper education levels. There was no statistically significant difference between paternal education level and psychiatric disorder (p=0.86).

45.5% (n=5) of the children with paternal MS and 56.4% (n=26) of the children with maternal MS had a psychiatric diagnosis and no statistical significance was observed (p=0.73). The frequency of psychiatric diagnosis in children was compared according to parental MS subtypes, 56.4% (n=22) of children with parental RRMS and 45.5% (n=5) of other parental MS subtypes had a psychiatric disorder and no statistically significant difference was observed between the groups (p=0.73).

Table 4. Distribution of psychiatric disorders of children and adolescents in study population

Psychiatric diagnosis	Total (n=50) n	%	Children (n=18) n	%	Adolescent (n=32) n	%	p
Anxiety disorders	15	30.0	6	33.3	9	28.1	0.59
Attention deficit and hyperactivity disorder	11	22.0	5	27.8	6	18.8	0.49
Tic disorder	8	16.0	3	16.7	5	15.6	0.93
Obsessive compulsive disorder	4	8.0	2	11.1	2	6.3	0.62
Depressive disorder	4	8.0	0	0	4	12.5	0.28
Oppositional defiant disorder	3	6.0	1	5.6	2	6.3	0.92
Elimination disorder	2	4.0	1	5.6	1	3.1	0.68
Conduct disorder	2	4.0	1	5.6	1	3.1	0.68

Fifty cases in the study group were divided as children under 12 years (n=18) and adolescents at 12 years and older (n=32), and compared in terms of psychiatric profile; 50% of the children and 56.3% of the adolescents had psychiatric disorders and there was no significant difference between the two groups (p=077). There was no significant difference between children and adolescents in terms of psychiatric diagnoses (Table 4).

When the parents were diagnosed with MS, the children were median 3 years old. The cases were grouped as ≤3 years (n=26) and >3 years (n=24) when the parents were diagnosed, there was no significant difference between the two groups (50.0% vs. 58.3%, p=0.58) in terms of psychiatric diagnosis rates. In addition, there was no significant difference in the frequency and profile of psychiatric disorders between the cases with parents diagnosed in the antenatal period (n=14) and those diagnosed in the postnatal period (p>0.05).

DISCUSSION

Multiple sclerosis is an important public health problem affecting young adults, complicating their productive lives and putting a socioeconomic burden on society. MS mostly affects women and the female to male ratio is reported to be 3:1 in developed countries.[16] In our study, mothers of 78% of the cases had MS because MS is more common in women. In our study, RRMS type was found in 78% of the parents. In the studies, RRMS type constitutes approximately 80% of MS worldwide.[17] Therefore, the MS patient profile in our study reflects the usual MS patient profile.

It is reported that psychiatric disorders are frequently associated with MS patients.[18] In a recent study, 61% of MS patients had psychiatric disorders among which depressive symptoms

and anxiety disorders were most commonly detected.[19] In our study, a psychiatric disorder was found in 52% of the parents with MS, and depressive disorder, anxiety disorder and OCD were the most common comorbid psychiatric diagnoses. Psychiatric disorders accompanying MS patients worsen the quality of life and decrease functionality. Also, negative emotional state and psychosocial stress cause the worsening of MS.[20] Therefore, psychiatric disorders accompanying MS patients must certainly be treated.

One of the most important results of our study was the comorbid psychiatric disorder in 54% of children with parental MS. This rate is higher than both the control group and the prevalence of psychiatric disorders reported in the general population.[21] Parental chronic diseases cause various levels of financial and emotional stress in children. Malignancies are the parental chronic diseases of which the effects on children are most studied. Parental cancer, especially life-threatening, is associated with increased psychiatric disorders in children.[5] Among the neurological disorders, the most investigated chronic disease is a parental stroke. In a study, subclinical and clinical psychosocial problems were found in 54% of children and adolescents with parental stroke.[22] Similarly, psychiatric problems were found to be higher in children of parents with amyotrophic lateral sclerosis compared to those with healthy parents.[23]

The psychosocial effect of MS on the individual is well known. However, studies are limited in children and adolescents with parental MS. To the best of our knowledge, this is the first study in this field in Turkey. Steck et al. reported that parental MS affects children's behavior and that girls' deal with problems more easily than boys.[24] In the same study, it was reported that whether the mother or father having MS did not have an effect in behavioral problems in children. However, some other studies have reported that maternal MS is riskier on terms of psychosocial problems in children.[25,26] In our study, there was no difference in terms of psychiatric disorder between the cases with either maternal or paternal MS supporting the findings of Steck et al., but the frequency of psychiatric disorders was found to be similar in boys and girls.

In many parental chronic diseases, the duration and severity of the disease have been associated with the frequency of psychosocial problems in children.[5,27] In their retrospective study, Razaz et al. found a high risk of early childhood developmental vulnerability in those with long-term exposure to parental MS.[28] In our study, psychiatric disorder rate was not different in children who exposed to parental MS at an early age and in those who exposed to parental MS for longer periods. However, the EDDS score indicating the severity of disability was significantly higher in the group with a psychiatric disorder. In light of these findings, our study suggests that the severity of parental MS rather than its duration is more related to the psychosocial problems of children.

Not surprisingly, anxiety disorders were the most common psychiatric disorder in children and adolescents with parental MS. Anxiety disorder has been reported frequently in children in many chronic diseases.[5,23] In the literature, anxiety and depressive disorders have been reported as the most common psychiatric disorder in children and adolescents with parental MS.[29,30] Although the rate of depressive disorder was relatively low in our study, it was significantly higher compared to the control group. In our study, depressive disorder was found in 32% of the parents with MS and in 8% of their children. In the literature, the prevalence of depressive disorder in pediatric population is about 3% and it is found to be higher in our study compared to the general population even though it is relatively lower than expected.[31] The reason for this lower-than-expected rate might be the absence of depressive disorder in the other parent that may have been protective for the development of the depressive disorder in the child. Since the depressive disorder is a disorder that disrupts functionality, it is often diagnosed early. In our study, the fact that some of the parents diagnosed with depressive disorder were diagnosed before the evaluation and recovered functionality with the help of treatment may also have an effect on the lower-than-expected rate of occurrence of depressive disorder in children.

One of the important findings of our study was the high rate of ADHD in children with parental MS (22%). There may be common pathophysiological reasons on the basis of these two disorders. MS is a disorder with a genetic transmission in which autoimmune, inflammatory and environmental factors play a role.[6] Approximately one in eight MS patients have a family history and up to 30% concordance has been reported in monozygotic twins.[26,32] Similar to MS, the etiology of ADHD is multifactorial. Studies have shown that ADHD has a genetic basis.[33] Also, there is a lot of current evidence that perinatal

factors, dietary characteristics, psychosocial factors, neurodevelopmental disorders and inflamemation may play a role.[34,35] Although a psychiatric disorder, ADHD is associated with other organic disorders.[36] In a recent study, ADHD symptoms were more common in adults with MS compared to controls.[37] In parallel, ADHD was reported more frequently in children of parents with immune components such as maternal rheumatoid arthritis, MS, asthma, diabetes, and hypothyroidism in a study from the longitudinal Norwegian registry.[38] This has been associated with prenatal increased inflammation. In light of this information, our study suggests that there may be common causes in the etiology of MS and ADHD.

Limitations of the study

The most important limitation of our study is the low number of patients. The use of single-center data may not reflect the whole country profile properly. The majority of the cases had maternal MS since MS is frequently seen in women. Our study will be a pioneer for performing multicenter prospective studies with a high number of cases. Our study will also suggests that studies targeting pathophysiological pathways that explain the association of ADHD and MS.

Conclusion

The results of our study show that children with parental MS have a high rate of psychiatric disorder. As the severity of MS increases, it is more common for children to be affected psychosocially. Children and adolescents with parental MS should be followed up for psychiatric disorders, especially anxiety disorders and ADHD, and preventive studies should be performed for these children.

Authors' contributions: *M.A.A.: conceptualization, writing-original draft, data analysis, project administration; I.G.: supervision, review and editing; S.G.: data curation, investigation; B.D.Ş.: data curation, methodology; T.A.: data curation, editing.*

REFERENCES

1. *Olfson M, Druss BG, Marcus SC. Trends in Mental Health Care among Children and Adolescents. N Engl J Med 2015; 373(11):1079.*
2. *Altay MA, Bozatlı L, Demirci Şipka B, Görker I. Current pattern of psychiatric comorbidity and psychotropic drug prescription in child and adolescent patients. Medicina (Kaunas) 2019; 55(5):159.*
3. *Romer G, Bakmann C, Schulte-Markwort, Thomalla G, Riedesser P. Children of somatically ill parents: a methodological review. Clin Child Psychol Psychiat 2002; 7(1):17-38*
4. *Barkmann C, Romer G, Watson M, Schulte-Markwort M. Parental physical illness as a risk for psychosocial maladjustment in children and adolescents: epidemiological findings from a national survey in Germany. Psychosomatics 2007; 48:476-481*
5. *Chen R, Regodón Wallin A, Norén Selinus E, Sjölander A, Fall K, Valdimarsdóttir U, et al. Psychiatric disorders among children of parents with cancer: A Swedish register-based matched cohort study. Psychooncology 2018; 27(7):1854-1860.*
6. *Dobson R, Giovannoni G. Multiple sclerosis - a review. Eur J Neurol 2019; 26(1):27-40.*
7. *Kobelt G, Thompson A, Berg J, et al. New insights into the burden and costs of multiple sclerosis in Europe. Mult Scler 2017; 23: 1123-1136.*
8. *Ascherio A. Environmental factors in multiple sclerosis. Expert Rev Neurother 2013; 13:3-9*
9. *Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, et al. Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. Neurology 2014; 83:1022-1024.*
10. *Galeazzi GM, Ferrari S, Giaroli G, Mackinnon A, Merelli E, Motti L, et al. Psychiatric disorders and depression in multiple sclerosis outpatients: impact of disability and interferon beta therapy. Neurol Sci 2005; 26(4):255-262.*
11. *Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018; 17(2):162-173.*
12. *Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36(7):980-988*
13. *Gökler B, Ünal F, Pehlivantürk B, Kültür EÇ, Akdemir D, Taner Y. Okul çağı çocukları için duygulanım bozuklukları ve şizofreni görüşme çizelgesi şimdi ve yaşam boyu şekli Türkçe uyarlamasının geçerlik ve güvenirliği. Turk J Child Adolesc Ment Health 2004; 11:109-116.*

14. *Kurtzke JF. Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS). Neurology 1983; 33(11):1444.*
15. *Özkürkcügil A, Aydemir Ö, Yıldız M, Danacı AE, Köroğlu E. DSM-IV eksen I bozuklukları için yapılandırılmış klinik görüşmesinin (SCID-I) Türkçe'ye uyarlanması ve güvenilirlik çalışması. İlaç ve Tedavi Dergisi 199; 12:233-236.*
16. *Orton S-M, Herrera BM, Yee IM,* Valdar W, Ramagopalan SV, Sadovnick AD, et al*. Sex ratio of multi-ple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006; 5:932-936.*
17. *Gupta S, Tewari A, Nair V. Multiple sclerosis: Indian perspective. API India Medicine Update; 2013, pp.547-551.*
18. *Marrie RA, Reingold S, Cohen J, Stuve O, Trojano M, Sorensen PS, et al. The incidence and prevalence of psychiatric disorders in multiple sclerasis: a systematic review. Mult Scler J 2015; 21(3):305-317.*
19. *Panda SP, Das RC, Srivastava K, Ratnam A, Sharma N. Psychiatric comorbidity in multiple sclerosis. Neurol Neurochir Pol 2018; 52(6):704-709.*
20. *Mohr DC, Hart SL, Julian L, Cox D, Pelletier D. Association between stressful life events and exacerbation in multiple sclerosis: A meta-analysis. BMJ 2004; 328:731.*
21. *Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry 2015; 56(3):345-365.*
22. *Visser-Meily A, Post M, Meijer AM, Maas C, Ketelaar M, Lindeman E. Children's adjustment to a parent's stroke: determinants of health status and psychological problems, and the role of support from the rehabilitation team. J Rehabil Med 2005; 37(4):236-241.*
23. *Calvo V, Bianco F, Benelli E, Sambin M, Monsurrò MR, Femiano C, et al. Impact on children of a parent with ALS: a case-control study. Front Psychol 2015; 6:288.*
24. *Steck B, Amsler F, Kappos L, Burgin D. Gender-specific differences in the process of coping in families with a parent affected by a chronic somatic disease (e.g. Multiple Sclerosis). Psychopathology 2001; 34:236-244.*
25. *Diareme S, Tsiantis J, Kolaitis G, Ferentinos S, Tsalamanios E, Paliokosta E, et al. Emotional and behavioural difficulties in children of parents with multiple sclerosis: a controlled study in Greece. Eur Child Adolesc Psychiatry 2006; 15(6):309-318.*
26. *Razaz N, Tremlett H, Boyce T, Guhn M, Marrie RA, Joseph KS. Incidence of mood or anxiety disorders in children of parents with multiple sclerasis. Paediatr Perinat Epidemiol 2016; 30(4):356-366.*
27. *Sieh DS, Meijer AM, Oort FJ, Visser-Meily JM, Van der Leij DA. Problem behavior in children of chronically ill parents: a meta-analysis. Clinical Child and Family Psychology Review 2010; 13:384-397.*
28. *Razaz N, Tremlett H, Boyce WT, Guhn M, Joseph KS, Marrie RA. Impact of parental multiple sclerasis on early childhood development: A retrospective cohort study. Mult Scler 2015; 21(9):1172-1183.*
29. *Marrie RA, Fisk J, Yu BN, Leung S, Elliott L, Caetano P, Warren S, et al. Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. BioMed Central Neurology 2013; 13:16.*
30. *Harirchian MH, Fatehi F, Sarraf P, Honarvar NM, Bitarafan S. Worldwide prevalence of familial multiple sclerosis: a systematic review and meta-analysis. Mult Scler Relat Disord 2017; 20:43-47.*
31. *Merikangas KR, He JP, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the 2001-2004 NHANES. Pediatrics 2010; 125(1):75-81.*
32. *Ristori G, Cannoni S, Stazi MA, Vanacore N, Cotichini R, Alfò M, et al. Multiple sclerosis in twins from continental Italy and Sardinia: a nationwide study. Ann Neurol 2006; 59:27-34.*
33. *Faraone SV, Biederman J, Monuteaux MC. Toward guidelines for pedigree selection in genetic studies of attention defi cit hyperactivity disorder. Genet Epidemiol 2000; 18:1-16.*
34. *Thapar A, Cooper M, Eyre O, Langley K. What have we learnt about the causes of ADHD? J Child Psychol Psychiatry 2013; 54:3-16.*
35. *Altay MA. Sleep disorders and attention deficit: a consequence of proinflammatory state? J Clin Sleep Med 2018; 14(6):1081.*
36. *Altay MA. Does attention deficit hyperactivity disorder have arrhythmia potential? Anadolu Psikiyatri Derg 2018; 19(6):624-630.*
37. *Alpua M, Turkel Y, Gunes HN, Oguzturk O, Dag E, Yoldas TK. Attention deficit/hyperactivity disorder in adults with multiple sclerosis. Int J Ment Health Psychiatry 2017; 3:3.*
38. *Instanes JT, Halmøy A, Engeland A, Haavik J, Furu K, Klungsøyr K. Attention-deficit/hyperactivity disorder in offspring of mothers with inflammatory and immune system diseases. Biol Psychiatry 2017; 81(5):452-459.*