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Autism spectrum disorder referrals to a rural hospital in the past two years – a retrospective evaluation

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ABSTRACT

Objective: In addition to the core symptoms of Autism Spectrum Disorder (ASD); symptoms such as aggression, self-harm, impulsivity, hyperactivity, anxiety, and mood problems are also often present. Medication use is frequent and studies report that 27-40% of ASD patients use at least one psychotropic medication. We aimed to examine the clinical and sociodemographic features and treatment modalities of ASD patients who were referred to a rural hospital in the last two years.

Material and Methods: Age, gender, mean diagnosis age (MDA), type of ASD, psychiatric symptoms, medication (if they use one) types, and doses were recorded for 200 children with ASD (who were referred between August 2018 – August 2020) were retrospectively evaluated. Also, patients who were diagnosed with "childhood autism (CA)" and "other ASD diagnoses" were compared.

Results: The majority of the patients were male, the MDA value of the all patients was 4.56 (±2.2) years and there were no significant differences between groups regarding MDA (p = 0.053). Most frequently seen psychiatric symptoms were behavioral (33%) and attention problems (21%) and 52.5% of patients (n=105) were using at least one psychotropic medication. Patients with CA had higher rates of psychotropic medication use (p=0.010) and the most frequently used medication group was antipsychotic drugs (92.4%).

Conclusion: Treatment approaches utilized in rural hospitals are in line with the universal trends. However, considerably higher MDA compared to previous studies show that; to provide early diagnosis and better prognosis for ASD patients who live in rural areas, new interventions should be promoted by the local and/or general authorities.

Keywords: Autism spectrum disorder; early diagnosis; prognosis; treatment

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INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that is defined by difficulties in social communication/interaction and repetitive and restricted behaviors and interests (1). Studies with large samples indicate that ASD has a prevalence of 1-2% in the general population (2). Although some social and communicational problems might be present before the diagnosis; ASD specific symptoms generally occur around the age of three and mean diagnosis age (MDA) is reported to be 3.1 years (3, 4). ASD is one of the major psychiatric diagnosis with gender dominance; it is more frequently seen in males and male/female ratio among general population is almost four (5).

In addition to the core symptoms of ASD (disturbances in social communication/interaction, repetitive/restricted behaviors and interests); symptoms such as aggression, self-harm, impulsivity, hyperactivity, anxiety and mood problems are also often present (6). With mental retardation being the most common comorbid psychiatric diagnosis; these children generally have other psychiatric comorbidities such as anxiety disorders, conduct disorder, attention deficit and hyperactivity disorder (ADHD) and sleep disorders (3).

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Medication use towards comorbid psychiatric symptoms and/or diagnoses is frequent among children with ASD diagnosis and studies report that 27-40% of these patients use at least one psychotropic medication (7). In the light of these findings; we aimed to retrospectively examine the clinical and sociodemographic features and treatment modalities of ASD patients who were referred to a rural hospital in the last two years.

MATERIALS AND METHODS

Participants: In this study; clinical, sociodemographic and treatment-related characteristics of 200 children with ASD diagnosis who were referred to Children and Adolescent Psychiatry Out-patient Unit of Rize Training and Research Hospital between the dates of August 2018 – August 2020 were retrospectively evaluated. There were no exclusion criteria and only patients who were under age of 18 and were referred to our department between the indicated dates were included. Age, gender, age of diagnosis, type of ASD, psychiatric symptoms, medications (if they use one) and doses of the medications were recorded for each individual. Furthermore, patients who were diagnosed with Childhood Autism (CA [F84.0]) and "Other ASD Diagnoses (OAD)" [which includes Atypical Autism (F84.1), Rett's Syndrome (F84.2), Other Childhood Disintegrative Disorder (F84.3), Overactive Disorder Associated with Mental Retardation and Stereotyped Movements (F84.4), Asperger's Syndrome (F84.5), Other Pervasive Developmental Disorders (F84.8), Pervasive Developmental Disorder – Unspecified (F84.9)] according to International Statistical Classification of Diseases and Related Health Problems 10th Edition were compared regarding their gender, medication and age of diagnosis (8). The study was conducted in accordance with the ethical guidelines, including the World Medical Association (1975) Declaration of Helsinki 2008, and the legal requirements of the Ethics Committee of the institution it was conducted in (approval no: 2020/213).

Statistical Analysis: The data was analyzed using Social Sciences software version 21.0 (9). A definitive analysis of categorical data was conducted and results were reported as frequencies and percentages. Categorical data were compared with Chi-square test (Fisher's Exact Chi-square test if needed). Kolmogorov-Smirnov test was used to determine if continuous data fitted normal distribution or not.

Mean (± standard deviation [SD]) values were given for normally distributed variables and median (interquartile range [IQR]) values were given for non-normally distributed variables. Continuous variables between dichotomous groups were compared with Independent T-test (if normally distributed) or Mann-Whitney-U test (if non-normally distributed). The value of $p < 0.05$ was accepted as statistically significant.

RESULTS

Total of 114 patients (57%) had CA diagnosis, whereas number of patients with OAD was 86 (43%). The majority of the patients were male and they constituted 80.5% (n=161) of total ASD group. Ages of examined individuals were between 1 and 17 and mean age was 8.12 (±3.8) years. Ages of patients with CA diagnosis were between 1 and 11 and mean age was 8.67 (±3.8) years; while ages of patients with OAD were between 1 and 17 and mean age was 7.4 (±3.8) years. The MDA of all patients was 4.56 (±2.2) years, of patients with CA diagnosis was 4.3 (±1.8) years and of patients with OAD was 4.91 (±2.6) years (Table 1).

There were no statistically significant difference between CA and OAD groups regarding their MDA ($p = 0.053$, Independent T-test, Table 2). Most frequently seen psychiatric symptoms were behavioral (33%) and attention problems (21%) and 52.5% (n=105) of children with ASD were using at least one psychotropic medication. Gender, diagnosis type, medication, and psychiatric symptom characteristics of individuals included in our study were elaborated in Table 1.

Even though there were no significant differences between CA and OAD groups regarding their genders ($p=0.394$, Independent T-test); patients with CA diagnosis had higher rates of psychotropic medication use ($p=0.010$, Independent T-test, Table 2). The most frequently used medication group was antipsychotic drugs (92.4%), and most frequently chosen antipsychotics were risperidone (%46.7) and aripiprazole (35.2%).

In addition to antipsychotics, methylphenidate (MPH) was the second frequent drug choice and all of the medication treatments seen among our sample group and their mean doses were summarized in Table 3.

Table 1: Sociodemographic and clinical characteristics of the study sample

		Total *(n=200, 100%)*	Childhood Autism (F84.0) *(n=114, 57.0%)*	Other Autism Diagnoses* *(n=86, 43%)*
	Age	8.12±3.8	8.67±3.8	7.40±3.8
	Age of Diagnosis	4.56±2.2	4.30 ±1.8	4.91±2.6
Gender	**- Male**	161 (80.5%)	93 (81.6%)	68 (79.1%)
	- Female	39 (19.5%)	21 (18.4%)	18 (20.9%)
Medication Use	**- Yes**	105 (52.5%)	69 (60.5%)	36 (41.9%)
	- No	95 (47.5%)	45 (39.5%)	50 (58.1%)
Medication Reason	**Behavioral Problems**	66 (33.0%)	46 (40.4%)	20 (23.3%)
	Stereotypical Movements	17 (8.5%)	10 (8.8%)	7 (8.1%)
	Attention Problems / Hyperactivity	42 (21.0%)	24 (21.1%)	18 (20.9%)
	Fears / Anxiety	4 (2.0%)	2 (1.8%)	2 (2.3%)
	Agression	8 (4.0%)	7 (6.1%)	1 (1.2%)
	Sleep Disturbances	9 (4.5%)	7 (6.1%)	2 (2.3%)

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Table 2: Comparison of age, gender and medication status between diagnostic groups.

	Number of Cases			Mean (±SD)				
	CA *(n=114)*	OAD* *(n=86)*	p[a]	CA *(n=114)*	AA and Others* *(n=86)*	t	df	p[b]
Gender								
- Male	93	68	0.394					
- Female	21	18						
Medication Use								
- Yes	69	36	**0.010**					
- No	45	50						
Age of the Diagnosis				4.30±1.76	4.91±2.64	-1.9	198	0.053

CA, childhood autism (F84.0); OAD, Other Autism Diagnoses; SD, standart deviation. * (Atypical Autism [F84.1], Rett's Syndrome [F84.2], Other Childhood Disintegrative Disorder [F84.3], Overactive Disorder Associated with Mental Retardation and Stereotyped Movements [F84.4], Asperger's Syndrome [F84.5], Other Pervasive Developmental Disorders [F84.8], Pervasive Developmental Disorder – Unspecified [F84.9])
a Chi-Square test, statistically significant p values are written in bold. **b** Independent T-test, statistically significant p values are written in bold.

Table 3: Psychotropic medication profile in the study sample.

Total of cases that use medication *(n=105)*	Number (%)	Dose Range (mg/day)	Mean Dosage (±SD) (mg/day)
Risperidone	49 (46.7%)	0.25 - 4	1.20 (±1.01)
Aripiprazole	37 (35.2%)	20-Jan	4.93 (±4.52)
Quetiapine	3 (2.9%)	50 - 100	83.33 (±28.87)
Haloperidole	4 (3.8%)	0.5 - 16	5.63 (±7.20)
Olanzapine	3 (2.9%)	2.5 - 10	5.63 (±3.16)
Clozapine	1 (1.0%)	200	200.00 (±0.00)
Antipsychotic Total	97 (92.4%)	-	-
OROS-MPH	19 (18.1%)	Oct-54	28.42 (±14.97)
MPH	7 (6.7%)	10-May	7.86 (±2.67)
Atomoxetine	8 (7.6%)	Oct-80	38.25 (±22.74) ≈ 1.42 mg/kg/day *
ADHD Treatment Total	34 (32.4%)	-	-
Fluoxetine	6 (5.7%)	20-Feb	15.33 (±7.66)
Sertraline	1 (1.0%)	50	50.00 (±0.00)
SSRI Total	7 (6.5%)	-	-
Sodium Valproate	3 (2.9%)	500	500.00 (±0.00)
Carbamazepine	1 (1.0%)	400	400.00 (±0.00)
Mood Stabilisers Total	4 (3.8%)	-	-
Melatonin	3 (2.9%)	6-Mar	4.00 (±1.73)

SD, standart deviation; OROS, osmotic-controlled release oral delivery system; MPH, methylphenidate; ADHD, attention deficit and hyperactivity disorder; SSRI, selective serotonin re-uptake inhibitor. * Calculated according to mean age of study sample (8.12 years) and 50 percantile weight values of Turkish children for that particular age (27)

DISCUSSION

In this study, several sociodemographic and clinical features of children with ASD who were referred to a rural hospital child and adolescent out-patient unit were examined. It was found that; the majority of children with ASD were male, rates of CA diagnosis (57%) and OAD (43%) were almost similar, MDA of these patients who were under treatment in a rural hospital was fairly late (MDA = 4.56 [±2.2] years), around half of them used at least one psychotropic medication and most frequent psychiatric symptoms seen among these patients were behavioral and attention problems. ASD is a neurodevelopmental disorder that is more frequently seen in males and in line with this rates of male gender were significantly higher for all of the examined groups (total, CA, OAD) (5). In addition to this; with non-specific symptoms might be present before the age of three, ASD specific symptoms generally occur around that age period and patients are mostly diagnosed few months later the onset of these specific symptoms (MDA for ASD is reported to be around 3.1 years) (3, 4). In a recent study which was conducted in Ankara (capital city of Turkey); MDA was reported as 40.7 months (3.4 years) (10).

MDA which we found in our sample group is considerably greater than what both national and international studies reported. Sociodemographic characteristics of the city which this study was conducted in might explain this discrepancy: It is a fairly secluded city with low population and the socioeconomic and educational level of its population is quite low compared to major cities of Turkey. It can be postulated; that in cities further than the focus of central health care systems, patients might have difficulties in reaching out to a child and adolescent psychiatrist or families with lower socioeconomic/educational levels might overlook ASD specific symptoms which their children exhibit and do not seek help until it is quite late.

This situation should be particularly emphasized cause early diagnosis and intervention strategies are the major positive prognostic factors for ASD and necessary steps should be taken (such as proper facilitation of health care systems in small cities and psychoeducation of families living in these cities regarding early symptoms of ADS) in order to enable these (11,12).

Behavioral problems are seen in ASD account for the majority of the referrals to a child and adolescent psychiatry clinic (13). Disruptive behaviors such as irritability and aggression are common among children with ASD and they usually have negative impacts on the daily life of both child and family (14, 15). In a study done by Mazurek et al. (2013), behavioral problems at clinically significant levels were reported in 50% of ASD group (16). Similar to these results, we also found that behavioral problems were the most common psychiatric symptoms (33%) among individuals with ADS who were under follow-up in child and adolescent out-patient unit. In addition, attention problems were determined as the second most common psychiatric symptoms (21%) in our sample group. In fact, both genetic and epidemiologic studies underline that attention problems are frequent in autistic children and ASD and ADHD have high comorbidity rates, symptom overlaps and shared genetic and psychopathological mechanisms (17).

Regarding the relationship between psychiatric symptoms of ADS patients and drug prescriptions; Uğur and Göker (2018) found that 49.2% of children with ASD were using at least one psychotropic medication and among the patients who were using medication, behavioral problem scale (Aberrant Behavior Checklist and Autism Behavior Checklist) scores were significantly higher compared to patients who were not using any medications (10). CA can be taken into account as a more "severe" condition than OAD and behavioral problems among CA are expected to be more frequent. In this respect, higher rates of psychotropic medication we found in children with CA in our sample were in line with previous research done in this field. Our findings of antipsychotics (92.4%) and ADHD medications (32.4%) being the most frequently used medication groups in a disorder characterized by behavioral and attention problems are also anticipated. In a review done by Young and Robert (2015), antipsychotics are stated as the most commonly used drugs in patients with ASD (6). Antipsychotics, particularly risperidone and aripiprazole, extensively studied and found to have positive effects on irritability, hyperactivity and stereotypical symptoms (6). A recent study showed that, high dose (1.25-1.75 mg/day) risperidone treatment was more effective in reducing behavioral disturbances compared to low dose (0.125-0.175 mg/day) risperidone treatment (18). In our study, we also found that used risperidone doses (mean dose = 1.20 (±1.01) mg/day) were close to "high dose risperidone treatment" and among children with ASD, in order to control behavioral problems, risperidone doses might need to be increased. Studies examining the effects of aripiprazole in ASD sample reported that aripiprazole was effective in reducing irritability on all doses (5 – 10 – 15 mg/day) (19, 20). Nevertheless, we found that symptoms of individuals who were using aripiprazole treatment were under control on 4.93 (±4.52) mg/day mean dose and this may indicate that relatively lower doses might be sufficient and increasing aripiprazole doses might not be necessary in the follow-ups. Research on the effectiveness of olanzapine (7.5 – 12.5 mg/day) and haloperidol (0.25 – 4 mg/day) in autistic children state that; haloperidol was effective in reducing behavioral problems whereas olanzapine was not and negative side effect profiles (extrapyramidal side effects, weight gain) limit the clinical usage of these drugs (21, 22). Furthermore there are no randomized double-blind placebo-controlled drug trials conducted for determining the efficacy of quetiapine, ziprasidone or newer agents (such as paliperidone, iloperidone, acenapine or lurasidone) in ASD sample (6). In line with these, we found that haloperidole (3.8%), quetiapine (2.9%), olanzapine (2.9%) or clozapine (1%) choices among other antipsychotics for the treatment of behavioral problems seen in ASD were rare.

MPH treatment (7,5 – 50 mg/day) is effective for the treatment of ADHD comorbidity in ASD patients; but likelihood of experiencing side effects which reported to be higher in children with autism compared to their normally developing peers (23, 24). In our sample, we found that clinicians generally kept the dose of MPH rather low (mean dosages are 28.42 [±14.97] mg/day for extended-release [osmotic-controlled release oral delivery system] MPH and 7.86 [±2.67] mg/day for normal MPH) and this might be due to the efforts on preventing the possible side effects which seems to be more frequent among these patients. Atomoxetine (ATX) which is another agent used in the treatment of ADHD has also been found to be effective in ASD on mean dose of 1.2 mg/kg/day which is similar to the mean ATX dose (1.42 mg/kg/day) that we determined in our sample (25, 26, 27).

Selective serotonin re-uptake inhibitors (SSRI) are used in order to reduce repetitive/stereotypical behaviors and movements or anxiety symptoms seen in autism (6). Studies with large sample sizes examining the effectiveness of citalopram and fluoxetine reported that, efficacy of these medications on repetitive/stereotypical behaviors did not differ from placebo and they had negative side effect profiles including energy increase, impulsivity and insomnia (28, 29). There are no randomized double-blind placebo-controlled drug trials done among ASD patients for other SSRI drugs such as sertraline, paroxetine or escitalopram. Moreover in their review, Williams et al. (2013) underline that, "there is not enough evidence proving the efficacy of SSRI drugs for children with autism" (30). Respectively, we also observed that SSRI drugs are rarely used (6.5% among all children who use at least one psychotropic medication) in the clinical management of ASD.

Mood stabilizers are often used to reduce behavioral symptoms and sodium valproate has been found to be effective in children with ASD (31, 32). However, one study showed that sodium valproate had no significant effect on aggression among ASD patients (33). Our results indicate that, even though most commonly selected mood stabilizer for the treatment of problematic behaviors of children with ASD is sodium valproate; mood stabilizers are not frequently preferred in these patients. Another delicate issue to mention about is the sleep disorders of autistic children and unfortunately, our accumulated knowledge about melatonin use in order to treat sleep disturbances seen in ASD is quite limited. One study compared the efficacy of cognitive-behavioral therapy (CBT) and melatonin in the treatment of

insomnia symptoms of children with ASD, and they found that melatonin plus CBT group was the most effective followed by melatonin alone and then the CBT alone group compared with the placebo group (34). While 9 cases in our study had sleep disturbances only 3 of them (%33.33) were using melatonin; so we think that further research and scientific evidence are highly needed in this field.

The major strength of this research is the comprehensive nature of how we examined the of wide range of characteristics of ASD patients such as the diagnosis age, psychiatric symptoms, medications and medication doses; and to our knowledge, this is also the first study to compare different ASD types regarding these parameters. However, it still has some limitations. The major limitation is the retrospective nature in which patients were evaluated through their medical records, so we were not able to confirm the psychiatric comorbidities via (semi)structured psychiatric interviews. This approach reflects the major symptom clusters which can be present in ASD, rather than specific psychiatric diagnoses; so it is difficult to establish a direct relationship between psychiatric comorbidities and treatment modalities/medication doses. Furthermore, even though our study has fairly large sample size (n=200); it is still quite small compared to other studies done in this field with larger sample sizes. In addition, retrospective examination of last two years' referrals of ASD patients might provide us with a cross-sectional definition; but our results cannot be used to infer causality due to the cross-sectional design.

CONCLUSION

In conclusion, we investigated the treatment accessibility and used treatment modalities among children with ASD who live in rural areas/non-central districts. Results indicate that, treatment approaches utilized in rural hospitals are in line with the universal trends. However, considerably higher MDA in the study sample compared to other studies in the literature show that, in order to ensure early diagnosis and better prognosis for the children with ASD who live in rural areas/non-central districts new interventions should be promoted and proper steps should be taken by the local and/or general authorities.

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Author Contributions: MB: Project design, Review of the literature, Data collection and statistical analyzes **MB:** Writing and Revisions

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