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Brief Report / Kısa Araştırma

Tardive Dyskinesia in Long Term Hospitalized Patients with Schizophrenia

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ABSTRACT

Tardive dyskinesia in long term hospitalized patients with schizophrenia

Objective: Tardive dyskinesia (TD) is a group of delayed-onset iatrogenic movement disorders caused by dopamine receptor-blocking agents. TD prevalence is estimated as 20-50% of all patients treated with neuroleptics. This study aimed to investigate the prevalence rate of TD in long-term hospitalized patients with schizophrenia.

Method: We recorded age, gender, duration and type (first/second generation or mixed) of medication both at the time of interview and over preceding years. Dyskinesia was assessed by using the Abnormal Involuntary Movements Scale (AIMS). We also used the Simpson–Angus Scale for tardive parkinsonism. Akathisia was measured using the Barnes Akathisia Rating Scale (BARS).

Results: Mean duration of the longest used antipsychotic was 206.63 months. Probable TD was found in 18 (22.5%) of patients. None of the patients had tardive akathisia. Relation between type of the longest used treatment and prevalence of TD was not statistically significant. Relationship between type of ongoing treatment and prevalence of TD was not determined statistically significant either. There was a statistically significant relationship between the mean age and TD.

Discussion: Despite very long duration of antipsychotic use, 22.5% rate of prevalence is still lower than expected. This can be explained that these patients are under direct and close follow-up of healthcare providers and in hospital conditions, so that risky conditions can be intervened rapidly. Another noteworthy finding of our study is that there is no statistically significant difference betwen first and second generation antipsychotic use and TD prevalence.

Keywords: Antipsychotic, schizophrenia, tardive dyskinesia

ÖZET

Uzun süreli ve yatırılarak izlenen şizofreni hastalarında tardiv diskinezi

Amaç: Tardiv diskinezi (TD) dopamin reseptör blokajı yapan ilaçlar tarafından ortaya çıkan bir grup geç başlangıçlı hareket bozukluğudur. Risk faktörleri arasında en çok suçlananlar yaş, kadın cinsiyet, birinci kuşak antipsikotikler ve uzun süreli ilaç kullanımıdır. Nöroleptik kullananların tümünde TD prevalans değerleri %20-50 olarak belirlenmiştir. TD'nin Türkiye'deki durumu hakkında yeterli çalışma bulunmamaktadır. Bu araştırma, uzun süredir yatmakta olan şizofreni hastalarında TD yaygınlığını araştırmayı amaçlamaktadır.

Yöntem: Yaş, cinsiyet ve hastaların hem araştırma esnasında hem de geçmişte kullandıkları antipsikoitklerin türü (1./2. kuşak, karışık) ve süresi kaydedildi. Hastaları tardiv hareket bozuklukları açısından değerlendirmek amacıyla Anormal İstemsiz Hareketler Ölçeği kullanıldı. Simpson-Angus Ölçeği tardiv parkinsonizmi değerlendirmek amacıyla kullanıldı. Akatizi değerlendirmesi için Barnes Akatizi Ölçeği kullanıldı.

Bulgular: Geçmişte en uzun süre kullanılan antipsikotik açısından ortalama süre 206.63 aydı. Katılımcıların 18'ine (%22.5) TD tanısı kondu. Hastaların hiçbirinde tardiv akatizi saptanmadı. Geçmişte en uzun süre kullanılan antipsikoitiğin tipi ile TD arasındaki ilişki istatistik olarak anlamlı bulunmadı. Aynı şekilde, halen kullanılan antipsikotik türüyle TD arasındaki ilişki de istatistik olarak anlamlı bulunmadı. TD ile yaş ortalamaları arasında istatistik olarak anlamlı bir ilişki saptandı.

Sonuç: Uzun süreli ilaç kullanımı olan bir grupta %22.5 oranı, yine de, beklenenden düşüktür. Hastaların hastane ortamında ve sağlık çalışanları gözetiminde doğrudan ve yakın izlemde olmaları ve risk oluşturabilecek durumlara erken müdahale edilmesi bu durum için bir açıklama olabilir. 1. ve 2. kuşak antipsikotik kullanımıyla ile TD yaygınlığı arasında çalışmamızda istatistik olarak anlamlı fark bulunmaması da bir diğer önemli bulgudur.

Anahtar kelimeler: Antipsikotik, şizofreni, tardiv diskinezi

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INTRODUCTION

Tardive movement disorders comprise a group of disorders which are due to prolonged use of antipsychotics, occurring during on medication or shortly after cessation (1). Other than antipsychotics; antiemetics, antidepressants, lithium, antiepileptics, anticholinergics, calcium channel blockers, sympathomimetics and antiparkinsonians can cause tardive movement disorders (2).

Tardive dyskinesia (TD) is an iatrogenic entity which involves especially mouth, tongue and face and also can be observed in extremities and the body. It is characterized by stereotypic, choreiform or athetoid involuntary movements. Movement disorder must be associated at least one antipsychotic drug exposure for at least three months (above 60 years of age, one month) and must continue for at least one month after cessation of oral drug (for depot medications, 8 weeks). In addition, there must not be any other etiological factors that may cause movement disorders (3).

In their review, Kane and Smith (4), included 56 studies conducted between 1959 and 1979, and they reported that TD prevalences were between 0.5-65% and 20% on average. Yassa and Jeste (5) determined TD prevalence as 24% in their review which included 76 studies.

Tardive syndromes have been a rising problem with the use of classical antipsychotics in the treatment of schizophrenia since 1950s, and it is still a problem after use of so-called "atypical" second-generation antipsychotics. The incidence of tardive syndromes and treatment-related researches still an interesting issue. It has been suggested that second-generation antipsychotics are less risky in terms of TD because of their "atypical" effects especially on dopamine receptors (6,7). However, as these new and promising drugs are more commonly used, and as independent studies on this area have emerged, the "innocence" of these drugs constitutes a problem (8-10). The studies which claim that atypical antipsychotics are less risky in terms of TD are criticized, because of high doses of haloperidol use in comparisons, and no use of prophylactic anticholinergics (11,12).

Age is one of the most prominent risk factors for TD. A linear relationship between age and TD incidence was indicated (13). Although results in the literature about the relationship between gender and TD prevalence were different; in recent years a high risk was reported in postmenopausal women (14). Besides, age and gender, additional neurological disease, high dose antipsychotics, mood disorders, negative symptoms, alcohol and drug use and diabetes are other risk factors for TD (15,16).

Another risk factor for TD is prolonged use of antipsychotics. In the literature, an incidence of TD was reported for the first few years as 3-5%, increasing cumulatively, and became constant at 20-25% level (17). The TD prevalences are detected as various ratios for different ethnicities. While some studies reported that Afro-Americans had high risk for TD, Asians were identified to have low risk (18).

Despite the above research, we can say that scientific data about frequency of tardive movement disorders in patients with schizophrenia and related factors in our country are limited. Moreover, due to the expansion of community-based psychiatry models and downsizing or closing of large mental health hospitals, research of tardive movement disorders conducted with patients who are treated in hospital for a long time, is limited even in the world.

Considering patients' compliances to medication ranges between 4% and 72%, and the mean is nearly 50% (19); we believed that a research of movement disorders in patients, who were under supervisions of health professionals and treated regularly for a very long time, would be valuable.

The aim of this study was to determine the tardive movement disorders' prevalence and related factors in Bakirkoy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery; in which, patients with schizophrenia were hospitalized in chronic wards for a long time and treated by health professionals regularly. Despite expectation of long and regular use of antipsychotics could result in high rates of tardive movement disorders; on the contrary, our hypothesis was that TD rates might be lower than expected by controlling some of the well-known risk factors and due to genetic traits of our population.

METHOD

Participants of this study were in-patients of the Bakirkoy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery. All of participants were staying in six different chronic wards. Inclusion criteria were the diagnosis of schizophrenia, reliable medical records, no missing data in the files, antipsychotic treatment for at least three months, and good treatment adherence measured by scales. The study was conducted during 2014.

Of the 283 chronic in-patients, who had diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) were detected (20), 120 patients were eligible for the study, and 80 patients included and completed it. Those who had any medical conditions which compromised measurements were excluded. An informed consent form was provided and this study was approved by the local ethics committee of the hospital.

Assessment

Sociodemographic information were obtained from case records and age, gender, any medical or neurological illness were recorded with medication status. Movement disorders were assessed with the scales below.

Abnormal Involuntary Movements Scale (AIMS): TD was assessed with the Abnormal Involuntary Movements Scale (AIMS) (21). Schooler & Kane criteria were used to asses AIMS and dyskinesia was defined as probably present, if movements were 'mild' in at least two of seven body areas or 'moderate' in at least one.

There are three diagnostic criteria in the Schooler-Kane diagnostic criteria for TD. These are:

1- At least 3 months of cumulative antipsychotic drug exposure,

2- At least moderate in one or more area, or mild in 2 or more areas in the AIMS,

3- Absence of other causes.

According to Schooler-Kane criteria TD is classified as probable, masked, transient, withdrawal and persistent. For probable TD, a case must meet all three criteria (22). There is not any Turkish validity and reliability study of AIMS.

Barnes Akathisia Rating Scale (BARS): Akathisia was measured using the BARS and was said to be present if the score was 2 ('mild') or more on the global scale (23).

Simpson-Angus Scale (SAS): Parkinsonism was assessed using the SAS and was said to be present if the Schooler & Kane criteria were met (24). The aim of using Schooler-Kane criteria for tardive parkinsonism was to make a more sensitive evaluation. Turkish validity and reliability study of SAS has not been performed yet.

Setting

Age, gender, smoking status, education, and any additional medical or psychiatric illness were recorded. The types of antipsychotics which patients were using during the study were recorded as "ongoing treatment". Subsequently, patients' medical records were reviewed retrospectively. The type of antipsychotic which patients used for the longest time in the past was recorded as "the longest used treatment". When recording any given type, only the types of antipsychotics were taken into consideration. If there were two or more antipsychotics belonging to same generation, they were recorded just as the type of which they are in. If a patient was using or have used for the longest time from both generations at the same time, then such case was recorded as "mixed".

Patients' medical records were reviewed retrospectively all through their chronic hospitalization, and these were the only time that was taken into account for antipsychotic use, because we wanted to include antipsychotic use which only carried out by medical staff. By doing this, we could overcome the compliance problems. We determined treatment duration by calculating the whole treatment duration in hospital for each patient. This duration sometimes

extended to nearly forty years. We calculated the total time separately for the first and second generation antipsychotics and then recorded as "treatment used for the longest duration".

Medical records were also assessed for participants whether they were using any first generation antipsychotics, and anticholinergic medications both currently and previously.

Scales were performed by psychiatrists who were blind to patients' medical situations. Evaluators were trained for the assessment of the three scales above. Not to be a burden on patients, a patient was evaluated by a single evaluator. To make similar decisions, evaluators' training and discussions on similar cases were supplied by supervisors.

Statistical Analysis

Descriptive statistics were made and after t-tests, Chi-square test and Mann-Whitney U were used to measure significance. Correlation analyses were performed for the continuous data. $p<0.05$ was determined as the level of statistical significance.

RESULTS

Of the 80 participants 35 (43.8%) were females, 45 (56.3%) were males. The mean age was 59±11.3 years. Mean duration of education was 4.76±3.2 years, and 52 (65%) participants were smokers.

Of patients, 20 (25%) were under the treatment by the first generation, 43 (53.8%) were receiving second generation antipsychotics, and 15 (18.8%) were using both. Of patients, 2 (2.5%) were using no medication. Patients' medication history and status are summarized in Table 1.

Mean duration for the longest used antipsychotics was 206.63±124 months. During their treatment period, 77 (96.3%) patients were receiving or had received any first generation antipsychotics for a period of time, and 77 (96.3%) patients were receiving or had received any anticholinergic medication for sometime.

According to AIMS, 18 (22.5%) patients were determined to have TD. Relationship between type of the longest used treatment and prevalence of TD was not statistically significant (p=0.443). Relationship between type of the ongoing treatment and prevalence of TD was not determined statistically significant either (p=0.632). The mean duration of medication used the longest was not statistically different between groups with TD and without TD (p=0.345).

There were no significant relationships between TD and current medical illness (p=0.753) or smoking status (p=0.342). Statistically significant relationship was determined between the mean age and TD (p=0.001).

Neither no significant difference was determined between TD and gender (p=0.631), nor between gender and mean SAS points (p=0.632) was determined.

In the correlation analyses, there were no statistically significant difference between the duration of the longest used antipsychotics and SAS points

Table1: Patients' medication status and history

	First generation		Second generation		Both		None	
	n	%	n	%	n	%	n	%
Ongoing antipsychotic (n=80)	20	25.0	43	53.8	15	18.8	2	2.5
Longest used antipsychotic (n=80)	67	83.8	11	13.8	2	2.5	-	-

Table 2: Tardive movement disorders and gender

	Male (n=45)		Female (n=35)		Total (n=80)	
	n	%	n	%	n	%
Tardive dyskinesia	11	24.4	7	20.0	18	22.5
Tardive parkinsonism	18	40.0	10	28.6	28	35.0
Tardive movement disorders (total)	22	49.9	14	40.0	36	45.0

(p=0.163; r=0.157). Similar relationship was determined between treatment duration and AIMS points (p=0.762; r=0.034). Relationship between age and AIMS was significantly correlated (p=0.002, r=0.342). Relationship between age and SAS was also significantly correlated (p<0.001, r=0.414).

There was statistically significant positive correlation between SAS and AIMS scores (p<0.001; r=0.614).

Only 2 patients had tardive akathisia according to BARS. According to SAS, 28 (35%) of patients had tardive parkinsonism. We determined 36 (45%) of the patients had at least one type of movement disorders (Table 2).

DISCUSSION

This study was conducted in our center where patients with schizophrenia had been hospitalized for long years, and treatments had been given regularly, problems during treatment had been intervened quickly by the medical staff. Tardive movement disorders were diagnosed in 45% of this patient population. TD prevalence was 22.5%.

It was reported in previous studies that compliance with antipsychotics was low in schizophrenia (25). Although patients in this study getting their treatments regularly, and the mean anti-psychotic treatment duration was 20 years, TD prevalence (22.5%) was lower than expected in our sample.

As known in the literature, long duration and high doses of antipsychotic use were high risk factors for TD (26). However, in our study we could not find a significant relationship between treatment duration and TD. This result, might be due to early recognition of controllable risk factors of TD in patients who lived in hospitals. Also, early prevention of other well-known risk factors of TD, such as vitamin deficiency, malnutrition or additional somatic disease, can cause the improvement in results (15).

In their review which covering four countries, Yassa and Jeste reported that TD was lower in Asia and they further emphasized genetic traits could change the risk of TD (5). Also it was pointed out that development of TD connected to ethnicity was related to gene polimorphisms on neurotransmitter metabolisms (27). Therefore, it can be said that our relatively low prevalence may be represent Turkey's genetic conditions.

In our study there were no difference between first and second generation antipsychotic use in terms of TD. This result might be contradictory as 97% of participants have used any first generation antipsychotics for a period in their lives and the study was carried out by scaning retrospectively nearly 40 years. Nevertheless, this result was consistent with some recent studies which conducted by independent researchers. According to CATIE study data, Miller reported that there were no significant difference between the first and second generations of antipsychotics in terms of TD risk in 2008, (28).

Similar to our study, from a population that consisted a large proportion of previously used first generation antipsychotics, Woods (29) reported classical and atypical antipsychotics, contrary to popular belief, were not different in terms of TD risk.

Regarding the relationship between gender and tardive syndromes, despite different results; it was reported in several studies that post-menopausal women were more susceptible to tardive disorders probably due to reduced protective effects of estrogen (14,30). Yassa and Jeste (5), in their review, when they grouped TD prevalences according to age, they found increased risk at the age 51 and older in women. In our study we determined no relationship between TD and gender, but it might be caused by lack of protective effect of estrogen in a study population which consisted mostly of postmenapausal women.

Consistenly with the literature, age was the most important risk factor in our study. This parameter was determined by the most prominent risk factor for TD. It was indicated that there was a linear relationship between age and severity and risk of TD (13).

In a population with a mean age of 59 years, we searched retrospectively a period of nearly 40 years for the type and duration of antipsychotic medication use from medical records. This was a substantial period of

time. Nevertheless, many of our patients were experiencing the disease before hospital admissions, were hospitalized, and used variety of psychiatric medications. This situation can be defined as a limitation of our study. Other limitations can be listed as the absence of seperate comparisons of antipsychotics, classification of antipsychotics according to their potencies, and lastly not including doses of the drugs.

Although it can be argued that how much these results reflect patients with schizophrenia in Turkey because of the long term hospitalized patient group; we think, because of containing a group that regular medicine use is provided, these results can provide useful information to the literature.

In terms of complexity of the pathogenesis, difficulties in treatment and carried load, tardive movement disorders are still one of the most important problems and further studies are needed to evaluate the prevalence for TD in Turkey.

Contribution Categories	Name of Author
Development of study idea	E.K.
Methodological design of the study	A.N., A.C., H.S.B., K.F.Y., M.A.D., E.K.
Data acquisition and process	A.N., A.C., H.S.B., A.C.
Data analysis and interpretation	A.N., A.C., H.S.B., A.C., K.F.Y., M.A.D., E.K.
Literature review	A.N., A.C., H.S.B., A.C.
Manuscript writing	A.N., A.C.
Manuscript review and revisation	A.N., A.C., H.S.B., A.C., K.F.Y., M.A.D., E.K.

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