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Running head: Duration of untreated illness in adult ADHD

Diagnostic delay in ADHD: Duration of untreated illness and its socio-demographic and clinical predictors in a sample of adult outpatients

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Abstract

Aim: To investigate the Duration of Untreated Illness (DUI) and its socio-demographic and clinical predictors in a sample of adult ADHD outpatients.

Methods: The DUI of 150 adult outpatients with a confirmed diagnosis of DSM-IV ADHD was calculated. Non-parametric tests were used to evaluate differences in DUI among subgroups and to build a correlation matrix. Subsequently, a multiple linear regression model was performed.

Results: The median DUI was 17 years (interquartile range [IQR]=14). DUI was longer in employed patients, those with a family history of ADHD, those with a history of major depressive disorder and those who had predominantly inattentive ADHD in childhood. The current age, age at administration of the first proper treatment and education level were correlated with DUI. Current age (63.3% of total variance), family history of ADHD and the presence of a predominantly inattentive type in childhood (together, 2.6% of total variance) were all predictors of DUI.

Conclusions: Information programs for caregivers and training for health care professionals should be promoted to foster the early recognition of covert inattentive symptoms and shorten DUI.

Keywords

ADHD, adult, duration of untreated illness, diagnostic delay, underdiagnosis, early treatment

Introduction

Attention Deficit-Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders and is characterised by different combinations of attention deficit, hyperactivity, and/or impulsivity symptoms, which outline three subtypes (DSM-IV-TR, American Psychiatric Association, 2000) or clinical presentations (DSM-5, American Psychiatric Association, 2013) of ADHD, i.e., predominantly inattentive, predominantly hyperactive and combined. However, the clinical manifestation of ADHD is actually heterogeneous, with different levels of severity and prevalences of each core symptom (Faraone et al., 2015; Franke et al., 2018; Kooij et al., 2019).

ADHD has been worldwide recognised as a lifespan disorder that over time interferes with functioning and development (American Psychiatric Association, 2013), leading to serious medical conditions and long-term consequences (Fayyad et al., 2007; Hodgkins et al., 2011; Kooij et al., 2019; Shaw et al., 2012) with severe functional impairment (Agnew-Blais et al., 2016; Faraone, Biederman, & Mick, 2006) and multiple psychiatric comorbidities (Franke et al., 2018; Furczyk & Thome, 2014; Jacob et al., 2007).

Among the long-term outcomes, we could include some harmful behaviours such as self-medication with alcohol, cigarettes, cannabis and stimulants (Franke et al., 2018; Jacob et al., 2007; Wilens et al., 2011); gambling (Waluk, Youssef, & Dowling, 2016); higher speeding ticket rate (Vaa, 2014); delinquency and crime (Lichtenstein et al., 2012; Shaw et al., 2012); and incorrect use of contraceptives resulting in unplanned pregnancies (Hosain, Berenson, Tennen, Bauer, & Wu, 2012; Skoglund et al., 2019) and sexually transmitted diseases (Barkley, Fischer, Smallish, & Fletcher, 2006). Obesity and overeating (Hodgkins et al., 2011; Kaisari, Dourish, & Higgs, 2017; Shaw et al., 2012), as well as multiple

divorces (Wasserstein, 2005), job-hopping and unemployment (Barkley et al., 2006; Biederman et al., 2006) are also frequent in ADHD patients, being an expression of impulsivity.

These long-term outcomes reduce the self-esteem of untreated patients, increasing suicide ideation or the risk of attempts (Balazs & Keresztesy, 2017; Hodgkins et al., 2011; Shaw et al., 2012). Suicide is the third most frequent cause of death among 15-24 year old ADHD patients (Chronis-Tuscano et al., 2010).

A recent epidemiological study confirmed higher mortality rates among ADHD patients, not only because of suicide but also due to other unnatural causes, especially accidents (Dalsgaard, Østergaard, Leckman, Mortensen, & Pedersen, 2015). Other authors detected a higher prevalence of injuries (Amiri, Sadeghi-Bazargani, Nazari, Ranjbar, & Abdi, 2017), vehicle crashes (Vaa, 2014) and bone fractures (Chou, Lin, Sung, & Kao, 2014) among ADHD patients, which seemed to be reverted by pharmacological treatment (Surman, Fried, Rhodewalt, & Boland, 2017).

ADHD patients are more likely to develop mood, sleep, somatic, anxiety and cluster B/C personality disorders (Fayyad et al., 2016; Franke et al., 2018; Katzman, Bilkey, Chokka, Fallu, & Klassen, 2017; Oliva, Mangiapane, Nibbio, Portigliatti Pomeri, & Maina, 2018), thus worsening their clinical burden (Katzman et al., 2017).

Early intervention appears crucial in order to prevent such poor outcomes, because they improve or may even disappear with the appropriate pharmacological and non-pharmacological treatment (Dalsgaard et al., 2015; Katzman et al., 2017; Shaw et al., 2012). Therefore, a correct and prompt diagnosis is needed in order to start effective treatment. The time-lag between first ADHD symptoms and their recognition, however, may be long (Shelton et al., 1998). This delay is a relevant item for ADHD (Shaw et al.,

2012), as well as for other psychiatry disorders. In particular, over the past thirty years increasing attention was paid to the duration of untreated psychosis—i.e., the period between the onset of psychotic symptoms and the initiation of pharmacological treatment—and the duration of untreated illness or DUI—i.e., the interval between the onset of a specific psychiatric disorder and the administration of the first appropriate pharmacological treatment (Altamura et al., 2015; Dell’Osso et al., 2016; Murru & Carpiniello, 2018)—to underline the impact of early pharmacological intervention on the distinctive functional and cognitive deterioration of schizophrenia spectrum disorders (Murru & Carpiniello, 2018; Palazzo et al., 2016). More recently, some authors have applied the concept of DUI from schizophrenia to other psychiatric disorders (Altamura, Dell’Osso, et al., 2010), studying the impact of late recognition and treatment on the most important disorder-specific outcomes (U. Albert et al., 2019; Altamura et al., 2015; Fritz et al., 2017).

Although, to our knowledge, there are no prior studies concerning DUI among adult ADHD patients, a few have investigated similar aspects in children with ADHD (Ghanizadeh, 2007; Purper-Ouakil et al., 2007; Yamauchi, Fujiwara, & Okuyama, 2015).

Purper-Ouakil and colleagues (2007) reported that the mean diagnostic delay for ADHD (the period between first consultation for impairing symptoms and the time of definitive diagnosis) in a consecutive sample of children and adolescents referring to a French University-Hospital outpatient service was around 2.8 years and it was not associated with the severity, subtype or family history of ADHD. They also stressed that co-occurrence of internalising or externalising symptoms and of any comorbid psychiatric disorders seemed to increase the diagnostic delay. Ghanizadeh (2007) investigated some characteristics of young ADHD patients and their mothers and found a mean time-lag of 1.5 years from the

parents' first suspicion of ADHD and the first ADHD assessment, mainly explained by parents as due to a lack of knowledge about where and how ADHD could be assessed. More recently, Yamauchi and colleagues (2015) focused their attention on the time-lag between early symptoms and first clinical evaluation in young patients who were then diagnosed with ADHD and on its predictors. This time-lag was not predicted by a family history of ADHD, gender or the severity of impairment; however, some socio-economic conditions involving children and their parents, the lack of information about specific mental health services and the presence of behavioural problems were shown to be predictors of the time lag (mean time-lag of 2.6 years).

The aims of the present study were to estimate the DUI in a sample of adult ADHD outpatients and to evaluate the role of some socio-demographic and clinical features as its predictors.

Methods

Study design and sample

The present study was conducted on a sample of adult patients with a diagnosis of ADHD according to the DSM-IV-TR. All patients accessing the adult ADHD outpatient centre of the 'San Luigi Gonzaga' University Hospital (Orbassano, Turin, Italy), between January 2015 and December 2018, were informed about the procedures and purpose of the study and asked to participate in the research. All participants signed an informed consent form. The study inclusion criteria required participants (1) to be age ≥ 18 years and (2) to have a confirmed diagnosis of ADHD according to DSM-IV-TR criteria.

Assessment

Since patients were usually referred to the adult ADHD outpatient centre by their psychiatrist, child neuropsychiatrist or general practitioner, according to the assessment protocol of the centre, at the first clinical examination they were checked for DSM-IV-TR criteria for other psychiatric disorders by a psychiatrist trained in adult ADHD diagnosis. Patients were then screened for adult ADHD through the administration of the Adult ADHD Investigatory Symptoms Related Scale (ASRS 1.1) and questioned about socio-demographic and clinical features (i.e. age, gender, education level, employment status, actual and lifetime psychiatric and medical comorbidity, family history of psychiatric and medical conditions). Subsequently, the same psychiatrist administered the Diagnostic Interview for ADHD in Adults (DIVA 2.0) to patients with the help of at least one parent, or a person who had known the patient well during childhood, in order to confirm the DSM-IV-TR ADHD diagnosis and to establish the age of onset, the ADHD type during childhood, and even the domains involved in the functional impairment. The severity of ADHD symptoms was, eventually, estimated through the administration of the ADHD Investigator Symptom Rating Scale (AISRS).

The DUI was calculated as the difference between the age at first proper treatment administration and the age of onset.

Assessment tools

The ASRS 1.1 (Kessler et al., 2005) is a self-report screening questionnaire for adults, based on the DSM-IV-TR criteria. It was developed by the World Health Organization (WHO) and then validated internationally (Adler et al., 2006). It consists of a six-item checklist and the scoring system refers to the frequency of occurrence of each symptom. The result is considered positive when at least four answers are above the cut-off value.

The DIVA 2.0 (J. J. S. Kooij, 2013) is a validated (Ramos-Quiroga et al., 2019), semi-structured interview to assess adult ADHD patients, according to the DSM – IV criteria. It consists of a two-section interview each composed of nine questions. The first section evaluates inattentive symptoms, whereas the second concerns the hyperactivity/impulsivity domain. It investigates the presence of DSM-IV symptoms (criterion A) in both childhood and adulthood, and requires real-life examples supporting the answers. It also includes explicit questions about the age of onset (i.e. the presence of symptoms before the age of 7 years, criterion B) and the presence of other psychiatric disorders or substance use which could better explain the reported symptoms (criterion E). A third section consists of an in-depth evaluation of the main areas of functioning impacted by ADHD symptoms (criteria C and D). Furthermore, all the collateral information should be reported, in terms of both content and source (i.e. the presence of parents/third parties; school reports).

According to DSM-IV, a diagnosis can be approved in the presence of at least six out of nine symptoms in adulthood and in childhood, in one or both of the two domains (inattention and/or hyperactivity/impulsivity). Moreover, the functioning impairment criterion must be met (i.e. the symptoms must impact at least two of the following: education/work, family and/or relationships; social contacts; free time/hobbies; self-esteem/self-image).

The AISRS is a validated (Spencer et al., 2010), 18-item scale matching the 18 DSM-IV criteria. It is divided into two subscales of nine items each, one investigating inattentive symptoms and the other about hyperactivity/impulsivity. The items are provided with examples to minimise interrater variability. The scoring system ranges from zero (none) to three (severe). The maximum score for each subscale is 27 points, with a maximum total score of 54.

Statistical Analysis

The distribution of DUI and other continuous variables was tested using the Shapiro-Wilk test. As DUI was non-normally distributed ($W = 0.957$, $p\text{-value} < 0.001$), nonparametric tests were used for the comparisons and the correlation matrix. The Mann-Whitney U test was adopted to compare the DUI distribution in subgroups defined by dichotomous variables (i.e., gender, ADHD type in childhood and in adulthood, psychiatric comorbidities, family history of ADHD or of any other psychiatric disorder). Differences in DUI among employment status subgroups were analysed with the Kruskal-Wallis test. The strength of the associations between DUI and other continuous/ordinal variables was studied performing a correlation matrix, reporting Kendall's rank correlation coefficients and their p-values (i.e., current age, age of onset, age at first proper treatment administration, education level, AISRS baseline score). Finally, continuous variables significantly correlated with DUI and the categorical variables defining subgroups with significant differences in DUI were included as independent variables in a multiple linear regression model through a forward method ($p\text{-value} < 0.05$ to enter and $p\text{-value} > 0.01$ to exit the predictor), in order to estimate their single predicting value for DUI.

A p-value of 0.05 was used to designate statistical significance.

The analyses were performed using the IBM SPSS Statistics for MAC OS package (version 22.0, IBM Corporation, Armonk, NY, USA).

Results

Sample Description

All socio-demographic and clinical features are reported in Table 1.

One hundred and fifty patients were eligible for the present study, and less than a third of these were female. Less than a half of the sample had a high school diploma (70, 46.7%) and about a quarter finished middle school (24, 16%), whereas only a smaller had obtained a Bachelor's (14, 9.3%) or a Master's (16, 10.7%) degree. A little less than a third of the sample was unemployed and another third was studying at time of the assessment.

The median age of our population was 25 years (interquartile range [IQR] = 13), whereas the median DUI was 17 years (IQR = 14, Min = 0, Max = 55), with a median age of onset of six years (IQR = 1) and a median age at first proper treatment administration of 24 years (IQR = 14). Notably, the age of first proper treatment administration coincided with the age of first diagnosis in all patients (n = 150, 100%). The majority of the sample (n=107, 71.3%) underwent an ADHD assessment for the first time within the study period, the remainder had been already assessed and diagnosed with ADHD in the past and were on specific medication since then (i.e., methylphenidate, atomoxetine).

About half the sample had a predominantly inattentive type in childhood and in adulthood. The remainder had a combined type since no patients showed a predominantly hyperactive/impulsive type both in childhood and in adulthood. Adult ADHD was confirmed to have high rates of psychiatric comorbidities as only around one-sixth of the sample did not have any comorbid disorders. A high prevalence of a positive family history of ADHD and of other psychiatric disorders could be also observed in the study sample.

Insert Table1 around here

Comparison of DUI between subgroups defined by dichotomous variables

The DUI was longer in patients with a positive family history for ADHD, those with major depressive disorder and those with a predominantly inattentive type of ADHD in childhood (Table 2). Conversely, patients with a diagnosis of a specific learning disorder(s) had a shorter DUI. A significant difference was observed between the DUI observed in the different employment status groups and, according to the nonparametric post-hoc tests (Mann-Whitney's tests), employed patients had a higher DUI than students and unemployed patients (employed > unemployed, $U = 927.5$, $p = 0.002$; employed > students, $U = 427.5$, $p < 0.001$; unemployed = students, $U = 815.5$, $p = 0.085$).

Insert Table 2 around here

Correlations between DUI and other continuous variables

The correlation matrix with continuous variables confirmed the expected relationship of DUI with the age at first proper treatment administration (Tau B = 0.940, $p < 0.001$) but not with the age of onset (Tau B = 0.111, $p = 0.072$, Table 3). Both current age and education (as ordinals) showed a significant correlation with DUI (Tau B = 0.735, $p < 0.001$ and Tau B = 0.168, $p = 0.006$, respectively) and also with the age at first proper treatment administration (Tau B = 0.783, $p < 0.001$ and Tau B = 0.162, $p = 0.008$). The severity of ADHD symptoms on the AISRS scale had no significant relationship with other continuous variables ($p < 0.05$, Table 3).

Insert Table 3 about here

Evaluation of potential predictors for DUI

The multivariate linear regression, forward method, was built including the current age as a continuous variable and family history of ADHD, education (as an ordinal), employment status, prevalent inattentive ADHD type in childhood, any specific learning disorder and major depressive disorder as factors (Table 4). The age of onset and the age at first proper treatment administration were intentionally excluded as they were involved in the calculation of DUI. The current age was the most important predictor among the variables included in the model and was responsible of 63.3% of the total variance of the DUI (Table 4). As regards the included factors, the family history of ADHD and a predominantly inattentive type in childhood were also significant positive predictors, although together they explained only 2.6% of the variance of the DUI (R^2 change = 0.026, Table 4). All the other variables were excluded from the model because they did not contribute to the variance of DUI (in the last model: Education, $\beta = 0.080$, $p = 0.127$; employment status, $\beta = 0.061$, $p = 0.241$; major depressive disorder, $\beta = 0.043$, $p = 0.405$; any specific learning disorder, $\beta = -0.43$, $p = 0.375$).

Insert Table 4 about here

Discussion

The current age was the main predictor for DUI in our sample of adult ADHD outpatients and it was also strongly associated with the age at first proper treatment administration. Most of the patients were indeed first diagnosed with ADHD at the end of the assessment at the adult ADHD centre (71.3%), though they had suffered at least from attention deficit, and in about half of the cases even from hyperactivity/impulsivity, since childhood without receiving any proper treatment.

Together, these findings suggest that, consistent with previous reports (Ginsberg, Quintero, Anand, Casillas, & Upadhyaya, 2014; Kooij et al., 2019), ADHD is underdiagnosed in adulthood and even in childhood, and this appears to be the main reason for its undertreatment. This may be particularly true for Italy, where the few expertise centres have only recently established a national network for adult ADHD and psychiatrists are still poorly trained in diagnosing this condition.

Moreover, the DUI obtained in the present study sample was much longer than the DUI reported by previous studies concerning other psychiatric disorders: schizophrenia, less than 6 years (N. Albert et al., 2017); bipolar disorder, under 14 years (Altamura, Dell'Osso, et al., 2010); major depressive disorder, less than 11 years (Altamura, Buoli, Albano, & Dell'Osso, 2010); any anxiety disorder, about 13 years (Dell'Osso, Camuri, Benatti, Buoli, & Altamura, 2013).

According to our findings, ADHD patients may deal with their symptoms from childhood (median age of 6) to adulthood (up to the median age of 25) for a median time-lag of 17 years without treatment. Meanwhile, the onset of some psychiatric comorbidities first in childhood and then in adulthood seemed to increase the burden of ADHD, as about 83.3% of patients had at least one additional comorbid psychiatric disorder. This high prevalence of comorbid psychiatric disorders is more consistent with a previous clinical study (Jacob et al., 2007) than that estimated by the most recent cross-national community epidemiological survey (51.7%, (Fayyad et al., 2017)). Such high rates could be partially explained, at least in the present study, by the referral to the ADHD centre from child neuropsychiatrists, psychiatrists and general practitioners who had probably assessed the patients for any other confounding symptoms or disorders. Hence, as previously noted (Fayyad et al., 2007; Ginsberg et al., 2014), ADHD patients are more likely to be treated for comorbid disorders

than for ADHD in psychiatric services. However, no comorbid psychiatric disorder was observed to predict DUI; thus, contrary to expectations, in the present study, the co-occurrence of any other psychiatric condition did not seem to foster nor hinder the diagnosis of ADHD. Although non predictive for DUI, depression was significantly associated with longer diagnostic delays. It could suggest that health care professionals tend to consider ADHD diagnosis only belatedly during the assessment. Thus, ADHD symptoms might be, at first, misinterpreted as depression rather than a separate or even a differential diagnosis. This could be a possible and partial explanation for the lower detection rates and longer DUI found in ADHD compared to other psychiatric disorders. On the other hand, depression might be a consequence of persisting ADHD symptoms.

Furthermore, clinical ADHD type in adulthood did not affect DUI; thus, it could be suggested that the small proportion of patients without comorbidities came to the ADHD centre because of functional impairment and the burden of ADHD symptoms themselves, regardless of the current clinical type.

As far as the other predictors are concerned, although with a weak contribution, a predominantly inattentive clinical type in childhood and a family history of ADHD appeared to further lengthen DUI.

Inattentive symptoms are less overt during childhood and commonly underestimated by parents, relatives and teachers, often being misinterpreted as unwillingness or tiredness (Asherson et al., 2012; Gershon, 2002; Katzman et al., 2017; Milich, Balentine, & Lynam, 2001). Possibly healthcare professionals themselves often fail to recognise these symptoms. Nevertheless, studies focused on the accuracy of self-reports highlighted the tendency of adult ADHD patients to underestimate their past symptoms, especially inattentive symptoms (Barkley, 2002; Zucker, Morris, Ingram, Morris, & Bakeman, 2002).

Both these issues may concur to explain the significant effect of inattentive symptoms and a family history of ADHD on DUI. Since parents with ADHD are so unaware of their dysfunctional core symptoms, they can be extremely tolerant of children's ADHD symptoms, often considering them self-limiting and unworthy of referral to child or adult psychiatric services (Ghanizadeh, 2007; Yamauchi et al., 2015).

According to our findings, the severity of ADHD, measured on the validated scale, did not show any predictive value nor any significant correlation with DUI, supporting prior suggestions by some studies concerning the time-lag between the onset of ADHD symptoms and the referral to specific services for children (Ghanizadeh, 2007; Yamauchi et al., 2015).

The main limitation of the present study is the single-centre design. However, although our study included only one centre in the North-west of Italy, it accurately depicts a real-world context where adult ADHD is commonly recognised and diagnosed for the first time during adulthood, alongside several comorbid disorders.

On the other hand, to our knowledge, this is the first report on the long DUI among adult ADHD patients, which also includes an appraisal of the predicting value of some socio-demographic and clinical variables. According to our findings, more attention should be paid to the covert inattentive symptoms in children, both by clinicians and teachers.

Education and information programs are needed to raise awareness, not only among clinicians and general practitioners, but also among other significant figures (i.e., sport coaches and trainers, care-givers, baby-sitters). A lack of information regarding specific mental health services is indeed commonly reported by parents (Yamauchi et al., 2015; Ghanizadeh 2007). This could reflect the lack of knowledge and training among health care professionals, who should refer patients for specific consultations.

An additional limitation of the present study is the absence of a comprehensive assessment of comorbid psychiatric disorders. Particularly, an in-depth evaluation of treatment history is worthy of further investigation as it could clarify patients' pathway through mental health services and help identify the missed opportunities for a proper diagnosis.

Moreover, further observational studies should be conducted to better investigate DUI predictors, not only in a clinical sample of patients attending child and adult psychiatric services but also in the general population.

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Author contribution

FO and Gd conceived the study and drafted the manuscript. SM, PF and FM collected the data. FO and FM performed the statistical analysis. GM participated in the design and coordination of the study. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Table 1. Socio-demographical and clinical variables (N = 150)

Table 2. Comparisons of DUI among subgroups defined by categorical variables

Table 3. Bivariate correlation matrix of continuous variables

Table 4. Linear regression model for the prediction of DUI

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