Prevalence and treatment of psychiatric disorders other than psychosis in children and adolescents with 22q11DS: examining associations with social and role functioning

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Abstract

Background: Individuals with chromosome 22q11 deletion syndrome (22q11DS) have high rates of psychotic disorders. Less is known about the psychopathology prior to the peak period of risk for psychotic disorder. There is also a lack of evidence on the treatment of early psychopathology and its impact on psychosocial functioning. The aim of this study was to investigate the prevalence and treatment of psychiatric disorders, and how these factors are associated with psychosocial functioning in children and adolescents with 22q11DS.

Method: 127 individuals with 22q11DS aged 8-17 participated in the study. Participants were assessed for psychiatric diagnoses, social and role functioning, anxiety and depressive symptoms and IQ. Information on current treatments was collected.

Results: 52.8% of the sample presented with at least one psychiatric disorder. Mood and anxiety disorders were the most frequent, followed by behavioral disorder. Individuals with a psychiatric disorder had significantly lower general, role and social functioning. Only 27% of participants with a psychiatric diagnosis were receiving any mental health treatment at the time of assessment.

Conclusions: Findings suggest the high prevalence of psychiatric disorders in youth with 22q11DS, which significantly impacts psychosocial functioning. Despite this, psychiatric disorders tend to remain untreated in young individuals with 22q11DS.

Key-words: 22q11.2 deletion syndrome (22q11DS), velocardiofacial syndrome, DiGeorge syndrome, psychiatric diagnosis, treatment, psychosocial, functioning.

1. Introduction

22q11.2 deletion syndrome (22q11DS), first referred to as DiGeorge syndrome and also known as velocardiofacial syndrome, is genetic syndrome (Scambler et al., 1992) associated with a microdeletion of the chromosome 22 band q11 with an estimated prevalence of between 2.000 and 4.000 live births (Bassett et al, 2011). The physical and neurobehavioral phenotype of the syndrome includes high rates of congenital dysmorphic features (Bassett et al.; 2001, McDonald et al., 2011), structural brain abnormalities (Schmitt et al., 2013) and cognitive dysfunction (Antshel et al., 2010), as well as high rates of psychiatric disorders (Schneider et al., 2014), particularly schizophrenia (Murphy, 2005, Schneider et al., 2014). 22q11DS is characterized by a hemizygous deletion on the 22nd chromosome of 3 million base pairs of DNA, but approximately 8% of individuals with the disorder have smaller nested deletions of 1.5 million base pairs (Armando et al., 2012). Thirty to forty genes are involved, including those impacting neurotransmission (i.e., catechol-O-methyltransferase and proline dehydrogenase) and myelination (i.e., phosphatidylinositol 4-kinase). This makes 22q11DS a particularly interesting syndrome from a psychiatric perspective (Schneider et al., 2013). These physiological features, together with the high psychiatric morbidity in individuals with 22q11DS, provides a window for a better understanding the development of mental illness.

Studies of school-age children with 22q11DS demonstrate high rates of abnormal behaviours and psychiatric morbidity, such as attention deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (OPD), specific and social phobias, generalized anxiety disorder, obsessive-compulsive disorder (OCD) and autism spectrum disorder (Feinstein et al., 2002; Antshel et al., 2006; Gothelf et al., 2006). By late adolescence and early adulthood, approximately half of all individuals with the syndrome report psychotic experiences and up to one-third develop psychotic disorders resembling schizophrenia and schizoaffective disorder (Murphy et al., 1999; Bassett et al., 2003; Gothelf et al., 2007).

A recent study by the 22q11DS International Consortium (Schneider et al., 2014) on a large cohort of 1,402 individuals with 22q11DS showed a high prevalence of psychiatric disorders throughout the life course. In children and adolescents aged 6-17 years (N=802), there was a high prevalence of anxiety (33%-35%) and mood disorders (3.3% in 6-12 year olds; 11.8% in 13-17 year olds), ADHD (37.1% in 6-12 years old; 23.9% in 13-17 year olds). Psychotic disorders were also reported prior to adulthood (1.9% in 6-12 years old; 10.1% in 13-17 years old). Overall, 88% of children and adolescents met the criteria for a psychiatric disorder. Similarly, in a sample of 112 individuals with

22q11DS aged 8-45 years old, Tang et al. (2014) found that 83% of the 59 youth (8-17 years old) in the sample met criteria for a psychiatric disorder.

Despite this high prevalence of psychiatric disorders in children and adolescents with 22q11DS, there is still a lack of consistent information concerning the impact of psychiatric morbidity on social and role functioning and how it is associated with cognitive ability. Schneider and colleagues (2014b) showed that IQ was not associated with anxiety and mood disorders in 8-17 years old with 22q11DS. However, they did find that daily living skills and adaptive functioning were significantly associated with the presence of an anxiety disorder. Together, these findings suggest that psychiatric disorders may strongly influence adaptive functioning in 22q11DS, independent from general cognitive ability. These findings are partially confirmed by Fabbro and colleagues (2012) who showed that anxious and depressive symptoms, as well as low IQ, were significantly associated with poor adaptive functioning in a sample of 73 children and adolescents with 22q11DS.

The few studies of treatment for mental illness show that rates of treatment are not commensurate with rates of psychiatric disorder in this population. Tang et al. (2014) found that only 40% of individuals with 22q11DS and a psychiatric disorder were receiving any treatment (psychosocial or pharmacological). Similarly, in a sample of young people with 22q11DS and psychiatric disorder, Fabbro et al. (2012) found that only 20% was currently treated with psychotropic medication.

Overall, the significant interest in 22q11DS as a valuable model for psychiatric illnesses has not been matched with knowledge on risk for psychiatric disorders other than psychosis, their impact and treatment. This is particularly true for children and adolescents with 22q11DS. In the current study, we investigated a sample of young people aged 8-17 years with 22q11DS to determine: (1) the prevalence of current psychiatric disorders other than psychotic disorder; (2) the association between psychiatric disorders, and IQ and psychosocial functioning; and 3) the use of psychiatric treatment.

2. Methods

2.1 Participants

The sample consisted of 127 children and adolescents aged 8-17 years old diagnosed with 22q11DS who were enrolled in a longitudinal study of biomarkers for psychosis in 22q11DS. Participants were consecutively recruited at the Child and Adolescent Neuropsychiatry Unit and the Clinical Genetic Unit of the Clinical and Research Hospital Bambino Gesù of Roma between 2011 and 2014. Participants were all Caucasian and Italian speaking. Diagnosis of 22q11DS was confirmed

by standard cytogenetic studies using fluorescence in situ hybridisation (FISH) and a probe from the commonly deleted 22q11.2 region. The current sample consists of all participants in the aforementioned longitudinal study who did not meet criteria for Attenuated Psychosis Syndrome (APS) or a psychotic disorder. These participants were excluded using the Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) and the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003). Participants were referred from the Genetic Clinical Unit of the Bambino Gesù Hospital from patient associations.

2.2 Procedure

The study is part of an ongoing longitudinal study on 22q11DS, which was approved by the Ethics Committee of the Clinical and Research Hospital Bambino Gesù of Roma. The study was conducted in agreement with the Italian Association of 22q11.2 microdeletion syndrome (AIdel 22) within a wider project aimed at the prevention of psychopathological disorders in individuals with 22q11DS. All parents provided written informed consent and participants provided assent.

2.2 Instruments

Current mental disorders were assessed using the Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) and the alcohol and drug use sections (J and L) of the Composite International Diagnostic Interview (CIDI; World Health Organization, 1993). The interview was administered to participants and their parents in two different sessions. Participants completed the Multidimensional Anxiety Scale for Children (MASC, March et al., 1997) to assess presence and severity of anxiety symptoms and the Children's Depression Inventory (CDI, Lovacs et al., 1998) to measure depressive symptoms. Functioning was rated by the clinician on the Childhood Global Assessment Scale (CGAS; Schaffer et al., 1988) and the Global Functioning: Social (GF:Social; Auther et al., 2006) and the Global Functioning: Role (GF:Role; Niendam et al., 2006) scales. The GF: Social and Role provide separate ratings for social and role functioning on a 10-point scale from superior social/interpersonal functioning or superior role functioning (10) to extreme social isolation or extreme role dysfunction (1). IQ was assessed with the Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 1991).

2.3 Statistical analysis

Descriptive statistics were used to present the prevalence of psychiatric disorders in the sample. The sample was then divided into two groups based on the presence or absence of a psychiatric disorder (22q11DS + psychiatric disorder vs 22q11DS - psychiatric disorder). The assumption that psychopathological variables (MASC, CDI, CGAS, GF:Role and GF:Social scores) and IQ were normally distributed in the population was confirmed using the Kolmogorov–Smirnov test ($p > 0.05$). The two groups were compared on age, gender, IQ and global, social and role functioning, using chi-square analysis for categorical variables and ANOVA for continuous variables. Finally, we divided the 22q11DS + psychiatric diagnosis in three groups (based on Kelleher et al., 2014): mood disorders (major depressive disorder, bipolar affective disorder); anxiety disorders (generalized anxiety disorders, separation anxiety disorder, social phobia, panic disorder, specific phobia, obsessive-compulsive disorder, post-traumatic disorder); and behavioural disorders (oppositional defiant disorder, attention/deficit hyperactivity disorder, conduct disorder). The three groups were then compared in terms of functioning using ANOVA. The Bonferroni's test was used for post hoc comparisons. Statistical analysis was conducted using SPSS version 21.

3. Results

3.1 Clinical and demographic characteristics.

As shown in Table 1, there was a high prevalence of psychiatric disorders in this sample. Sixty seven participants (52.8%) presented with at least one psychiatric disorder. Only 60 participants (47.2%) didn't meet criteria for a diagnosis of psychiatric disorder. Anxiety disorders were most prevalent (30%; $n = 38$), followed by mood disorders (22%, $n = 29$). Nineteen participants (15%) met criteria for a behavioural disorder (see Table 2).

-----TABLE 1-----

3.2 Comparison between groups on level of functioning.

The 22q11DS + psychiatric diagnosis showed significantly lower CGAS scores compared to the 22q11DS - psychiatric diagnosis group ($p < 0.0001$), and significantly lower GF:Role ($p < 0.0001$)

and GF:social ($p = 0.001$) scores. There were no significant group differences in terms of age ($p = 0.398$), gender ($p = 0.177$) and IQ ($p = 0.177$) (see Table 1).

When comparing scores on the CGAS, GF:Social and GF:Role across the three diagnostic categories within the 22q11DS + psychiatric diagnosis group, individuals with anxiety disorders showed significantly lower CGAS and social functioning ($p = 0.0001$) than those with depressive or behavioural disorders (see Table 2). These differences were maintained when analyses were adjusted for IQ and age.

-----TABLE 2-----

3.3 Mental health treatments

Current treatments for psychiatric disorder are presented in Table 3. Of the 67 children and adolescents in the 22q11DS + psychiatric diagnosis group, only 18 (26.9%) were receiving any mental health treatments at the time of assessment. Conversely, 71% of participants with a depressive disorder, 75% of participants with an anxiety disorder and 74% of participants with a behavioural disorder were not under any form of psychiatric treatment. Psychosocial treatment was the most frequently reported intervention, regardless of diagnosis, followed by antidepressants.

-----TABLE 3-----

4. Discussion

In the current study we examined the prevalence and treatment of psychiatric disorders (other than psychotic disorders), and the association with IQ and psychosocial functioning, in a sample of 127 consecutively admitted patients aged 8-17 years with 22q11DS. We found a prevalence of psychiatric disorder of 52.8%, with anxiety disorder being the most common diagnosis, followed by mood and then behavioural disorders. Children and adolescents with 22q11DS and anxiety disorder had significantly lower global and social functioning than those with 22q11DS and depressive or behavioural disorders. Despite the high prevalence of psychiatric disorders, only 26.9% of the sample were receiving any form of treatment for their mental illness.

4.1 The prevalence of psychiatric disorders

We found that 52.8% of the sample met criteria for at least one psychiatric disorder. This is lower than previous reports of 83% (Tang et al., 2014) and 88% (Schneider et al., 2014) in samples of individuals with 22q11DS. One reason for the lower rate in this study is our exclusion of participants with psychotic disorders and those meeting the APS criteria, who are likely to also meet the criteria for non-psychotic disorders. Indeed, Tang et al. (2014) found the prevalence of psychotic disorders and APS was approximately 37%. Schneider and colleagues (2014) found that 11% of their sample had a psychotic disorder. A second reason the prevalence of psychiatric disorder is lower than that cited in other studies is that this sample was formed of all children and adolescents with 22q11DS seen for routine screening, rather than those referred specifically for psychiatric diagnosis.

Anxiety disorders were the most prevalent diagnosis in our sample (30%). This is in line with the findings of the recent multisite study from the International Consortium on Brain and Behaviour in 22q11.2 Deletion Syndrome (Schneider et al., 2014) on a total sample of 1,402 individuals with 22q11DS. They showed that 34% of youth had an anxiety disorder. The high prevalence of anxiety disorders in youth with 22q11DS is particularly important because anxiety has previously been found to be one of the strongest predictors of transition to psychosis in people with 22q11DS (Gothelf et al., 2007).

4.2 Psychiatric diagnosis, IQ and level of functioning

In our sample, participants with at least one psychiatric diagnosis showed significantly lower levels of general, role and social functioning compared to the group without psychiatric diagnosis. IQ was not associated with having a psychiatric diagnosis. When considering the association between different psychiatric diagnoses and psychosocial functioning, participants with anxiety disorder showed a lower level of general and social functioning compared to participants with a depressive or behavioural disorder. The association between anxiety disorders and functioning in 22q11DS has previously been shown by Fabbro et al. (2012). They found that lower adaptive functioning (measured on the Vineland) was most strongly predicted by anxiety symptoms and IQ. We add to this evidence by investigating social and role functioning separately, as they may differ in the context of mental illness (Cornblatt et al., 2012). In our sample, the presence of an anxiety disorder was associated with lower social functioning compared to the presence of depressive and behavioural disorders, but not role functioning. It is of interest that a recent study demonstrated that

impaired social functioning (but not role functioning) was one of the strongest predictor of functional outcome in individuals at clinical high risk for psychosis (Carrion et al., 2013). Social functioning has also been shown to be associated with transition to psychosis in the clinical high-risk group (e.g. Cornblatt et al., 2012) and individuals with 22q11DS (Gothelf et al., 2007). Given these findings, the presence of anxiety disorder in young people with 22q11DS may indicate increased risk for later psychotic disorder and long-term impaired functioning. This group of individuals with 22q11DS and anxiety, particularly those with impaired social functioning, may benefit from early intervention and close monitoring to delay or ameliorate these poor outcomes.

4.3 Individuals with 22q11DS are undertreated for their psychiatric disorders

Despite the high prevalence of psychiatric disorders in our sample, a large majority of children and adolescents with 22q11DS were not treated for their psychiatric illnesses. Indeed, only 27% of participants with 22q11DS + psychiatric diagnosis received any psychiatric treatment at the time of assessment. Psychosocial treatments were the most common (19.5%). Only 7.5% of individuals were using psychotropic medication. Seventy one per cent of participants with a depressive disorder, 75% of participants with an anxiety disorder and 74% of participants with a behavioural disorder were not under *any* treatment. These results are consistent with those of Fabbro et al. (2012) who found that only 20% of children and adolescents with 22q11DS received psychotropic medication, despite 60% having a diagnosed psychiatric disorder. Other recent research has confirmed the tendency for young people with 22q11DS to be undertreated for psychiatric illness (Tang et al., 2014).

This trend of under-treatment of psychiatric disorders in 22q11DS is not supported by any evidence of inefficacy or unsafety of psychotropic medications in this population. On the contrary, recent findings (Dori et al., 2015) showed that antipsychotics and antidepressants may be effective and relatively safe in individuals with 22q11.2DS. According to Vicari et al. (2012), this pattern of under-treatment is replicated in other genetic syndromes because of the stigma of mental illness on top of a pre-existing genetic disorder. The trend appears to be even more dramatic in the case of 22q11DS, particularly given the high prevalence of psychiatric disorder in this syndrome. Early intervention is particularly important for individuals with 22q11DS because this syndrome is the greatest known risk factor for psychotic illness. From the clinical high-risk model, we know that anxiety and depressive symptoms (and a deterioration in functioning) are commonly observed in the prodromal phase of psychotic illness (Yung and McGorry, 1996). The absence of or delay in

beginning therapeutic interventions may impact the subsequent development of psychotic onset and the course of illness post diagnosis.

4.4 Strengths and limitations

To our knowledge this is the first study to investigate the association between psychiatric disorders and functioning in individuals with 22q11DS using several different measures of functioning. A strength of the study is that the sample was recruited at the hospital known to be the Italian point of reference for the assessment and treatment of 22q11DS. All the participants were referred to our Unit for a psychiatric screening evaluation, rather than for the suspicion of a psychiatric disorder. This makes the sample highly representative of the 22q11DS population, reducing the risk of the selection biases which are frequent in other studies on the psychiatric status of individuals with 22q11DS. A second strength is that no patients seen by the Unit refused to participate in the study. A third strength of the study is that the total sample was assessed at the same site by two experienced clinicians (M.A., a child and adolescent psychiatrist and M.P., a clinical psychologist). This reduces the risk of assessment bias that is more frequent in multisite studies (Shrout et al., 1998). A limitation of the current study is the cross-sectional design that precluded analysis of causality and the timing of the onset of psychiatric disorders in relation to deteriorated functioning. A second limitation is the lack of information on the effectiveness of mental health treatments used by the participants. This information would be clinically relevant.

4.5 Conclusions

In conclusion, our findings provide further evidence of the high prevalence of psychiatric disorders other than psychotic disorders in youth with 22q11DS. We also provide evidence that anxiety disorders are most strongly associated with an impaired social functioning, both of which are predictive of an increased risk of psychosis onset. Despite these findings, psychiatric disorders in youth with 22q11DS are not sufficiently treated and particular attention should be addressed to this issue.

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Table 1. Characteristics of 22q11DS + psychiatric disorder and 22q11DS - psychiatric disorder groups.

Variable	22q11DS + psychiatric disorder (n=67)	22q11DS - psychiatric disorder (n=60)	Statistics
Male, N (%)	35 (52.2)	30 (50)	$\chi^2 = 1.98; p = 0.194$
Age, M (SD)	14.3 (4.6)	13.6 (4.7)	$F = 0.718; p = 0.398$
IQ, M (SD)	84.5 (11.7)	87 (8.6)	$F = 1.846; p = 0.177$
CGAS, M (SD)	56 (5.7)	60 (6.7)	$F = 13.209; p < 0.0001$
GF: Social, M (SD)	4 (0.7)	4.6 (1.2)	$F = 12.143; p = 0.001$
GF: Role, M (SD)	4.1 (0.8)	4.7 (0.4)	$F = 27.562; p < 0.0001$

Table 2. Current psychiatric disorders and association with level of functioning.

Variable	Depressive disorders (N=29; 22.0%)	Anxiety disorders (N=38; 30.0%)	Behavioural disorders (N=19; 15.0%)	Statistics	Post-hoc (Bonferroni)
IQ, M(SD)	82.5 (12.13)	83 (10.84)	85.9 (11.79)	$F = .513$; $p = 0.601$	
CGAS, M(SD)	56 (6.59)	52 (5.95)	56 (5.9)	$F = 12.112$; $p = 0.001$	Anx < Depr; $p < 0.05$ Anx < Beh; $p < 0.05$
GF: Role, M (SD)	4.5 (0.78)	4.7 (0.62)	4.26 (0.73)	$F = 2.32$; $p = 0.107$	
GF: Social, M (SD)	4.1 (0.78)	3.2 (0.98)	4.6 (0.89)	$F = 13.034$; $p = 0.001$	Anx < Depr; $p < 0.05$ Anx < Beh; $p < 0.05$

Table 3. Current treatments modalities by diagnostic group in children and adolescents with 22q11DS + psychiatric disorder.

Current treatment	Depressive disorders (N = 24; 36.4%)	Anxiety disorders (N = 23; 34.8%)	Behavioural disorders (N = 19; 28.8%)
Any treatment, N (%)	7 (29)	6 (25)	5 (26)
Psychosocial treatment, N (%)	5 (21)	3 (12.5)	5 (26)
Antidepressant/anxiolytics, N (%)	1 (4)	2 (8.3)	0 (0)
Stimulants/alpha 2 agonists, N (%)	0 (0)	0 (0)	0 (0)
Antipsychotics, N (%)	1 (4)	1 (4.2)	0 (0)