Psychiatric Re-Evaluation of Patients with 22q11.2 Deletion Syndrome Presenting with Psychotic Symptoms, with Special Reference to Autism Spectrum Disorder

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Abstract

Background: Patients with 22q11.2 deletion syndrome (22q11.2DS) presenting with psychotic symptoms tend to be diagnosed with schizophrenia. However, it has recently been argued that these individuals may have Autism Spectrum Disorder (ASD). There is much controversy over this diagnosis and whether these symptoms may precede schizophrenia.

Methods: We studied the psychosis phenotypes of 11 patients with 22q11.2DS presenting with psychosis symptoms and of 11 non-syndromic patients with schizophrenia, matched by age and gender, using the Revised Autism Diagnostic Interview (ADI-R) and the Positive and Negative Syndrome Scale (PANSS). We compared these scores between groups using chi-square tests, Mann–Whitney U tests, and multiple regression analysis.

Results: The ADI-R scores indicated that the psychotic patients with 22q11.2DS had childhood and current autistic scores that were significantly more severe than those of the participants with schizophrenia. The PANSS positive symptom, general psychopathology, and total symptom scores did not differ significantly between the two groups. In contrast, the PANSS negative symptom scores were significantly lower in psychotic patients with 22q11.2DS. Current autistic features, apart from social interaction, and the PANSS symptoms were not associated with age, and no gender differences were observed between any of the variables.

Conclusions: The limited size of our case study does not reflect the overall epidemiological picture of psychotic patients with 22q11.2DS; however, all 11 psychotic patients with 22q11.2DS could be diagnosed as having ASD, which could preliminarily lead to a better social life. Children with 22q11.2DS usually require long-term treatment for systemic comorbidities. Earlier referral to a specialty clinic and psychiatric consultation as well as periodic psychiatric re-evaluation over a long-term follow-up period are therefore essential for the clinical management and proper support of the psychotic patients and their families.

Keywords: Velocardiofacial syndrome; Schizophrenia; Autism spectrum disorders; ADI-R; PANSS

Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2DS), also known as velocardiofacial syndrome or DiGeorge syndrome, is a disorder caused by the deletion of a small region in the middle of chromosome 22 at a location designated as q11.2. The deletion affects an estimated one in 4000 live births and is the most common micro-deletion syndrome known in humans [1]. It is either inherited as an autosomal dominant condition or arises de novo by deletion or translocation, without gender or racial differences [2]. This deletion or translocation results in the loss of the T-box1 gene (TBX1), which is considered to be responsible for many of the characteristic features of 22q11.2DS, including heart defects, cleft palate, distinctive facial features, hearing loss, and low calcium levels [3]. Many other genes in the region [e.g. catechol-O-methyltransferase (COMT) gene, proline dehydrogenase (PRODH) gene, among others] also might influence the clinical phenotype of patients with 22q11DS. Multi-system care is therefore necessary for individuals with 22q11.2 deletion syndrome, so that they can be evaluated for their various health needs and carefully monitored. Children with 22q11.2DS receive ongoing support, medical care, and information regarding major comorbidities from a team of health care workers. As a result, psychiatric referrals can often be delayed, due to serious comorbidities.

Many children with 22q11.2DS experience developmental delays, including delayed growth [4], poor speech development [5], and learning disabilities [6]. Later in life, these individuals are at an increased risk of developing mental illnesses such as schizophrenia, depression, anxiety, attention disorders, and bipolar disorder [7]. In particular, the affected children are more likely to develop attention-deficit hyperactivity disorder [8] and autism spectrum disorders (ASDs) that can affect communication and social interactions [9].

Table 1: Sociodemographic and clinical characteristics of the participants.

Variable	22q11.2DS (n=11)	Schizophrenia (n=11)	χ²-test
Patients Scoring above cutoffs on the ADI-R & PANSS domains	Positive (n=11)	Positive (n=11)	
ADI-R childhood communication (>=10)	11	0	**p<0.01
ADI-R childhood social interaction (>=8)	11	0	**p<0.01
ADI-R childhood repetitive interests & behaviors (>=3)	11	0	**p<0.01
Variable	22q11.2DS (n=11)	Schizophrenia (n=11)	M-W-U-test
Age	30.36 ±7.89	30.27 ±7.06	NS
Male	7	7	NS
Female	4	4	NS
ADI-R & PANSS domain scores	**Median (Range)**	**Median (Range)**	
ADI-R childhood communication	20 (15-25)	1 (0-2)	**p<0.01
ADI-R childhood social interaction	15 (10-24)	1 (0-2)	**p<0.01
ADI-R childhood repetitive interests & behaviors	5 (3-7)	0 (0-1)	**p<0.01
ADI-R current communication	10 (7-13)	0 (0-1)	**p<0.01
ADI-R current social interaction	6 (3-11)	1 (0-2)	**p<0.01
ADI-R current repetitive interests & behaviors	3 (1-4)	0 (0-1)	**p<0.01
PANSS positive symptoms	20 (18-22)	18 (15-22)	NS
PANSS negative symptoms	17 (16-19)	19 (18-21)	**p<0.01
PANSS general psychopathology symptoms	30 (28-33)	30 (28-32)	NS
PANSS total symptoms	67 (62-70)	68 (61-70)	NS

The chi-square test was used to compare the frequency of positive scores on the ADI-R between the two groups. Mann–Whitney U tests were used to compare the two clinical groups on the basis of sociodemographic data, childhood and current autistic features (ADI-R), and current psychiatric symptoms (PANSS).
Abbreviations: ADI-R: Revised Autism Diagnostic Interview; PANSS: Positive and Negative Syndrome Scale; M–W: Mann–Whitney; NS: Not Significant.

There is a particularly high rate of psychotic disorders (29%) among individuals with 22q11.2DS, with most of these individuals (22%) meeting the diagnostic criteria for schizophrenia [10,11]. Overall, the prevalence of schizophrenia is reported to be 9%-38% among patients with 22q11.2DS, a rate that is greater than that in the general population [12-17]. The largest study on psychiatric morbidity in 22q11.2DS assessed 1402 patients with the condition (age range in years: 6-68) and found 22q11.2DS to be an important risk factor for psychosis [18]. In that study, ASDs were prevalent in all age groups (13%-27%) but they were shown to peak during adolescence. The prevalence of schizophrenia spectrum disorders was also high, ranging from 23.5% in young adults (18-25 years) to 41% in patients aged >25 years. The study authors, however, noted some limitations in diagnostic reliability [18] but might disagree that the diagnosis of schizophrenia spectrum disorder is not always reliable in 22q11.2DS.

Vorstman and colleagues (2006) [19] reported a high prevalence of ASDs in individuals with 22q11.2DS. However, this report was criticized by Eliez (2007) [20], who argued that the greater incidence rates of specific language delays (i.e., verbal reasoning skills, which are typically stronger than nonverbal intellectual profiles) and social deficits (ranging from "active but odd" to "overly withdrawn") could make the diagnosis of ASD less justified. ASD and schizophrenia were considered distinct nosologic entities; however, emerging evidence has contributed to the blurring of symptomatic and genetic boundaries between these conditions. The phenotypical overlap between ASD and schizophrenia may indicate that both conditions can emerge from related neurodevelopment vulnerabilities or shared pathogenic mechanisms based on genotypic overlap [21]. Childhood-onset schizophrenia is preceded by an ASD diagnosis in 30%-50% of cases [22].

Clinically, any individual with ASD, with or without 22q11.2DS, requires careful assessment vis-à-vis their specific personal needs and strengths, to guide treatment [19]. We therefore investigated whether ASD could be identified in patients with 22q11.2DS who present with psychotic symptoms using age- and gender-matched controls without 22q11.2DS and who had already been diagnosed as having schizophrenia.

Methods

Participants

More than 225 patients have been genetically diagnosed as having 22q11.2DS and treated at various departments in Tokyo Women's Medical University Hospital [23]. Diagnoses of 22q11.2DS were confirmed by the presence of a 22q11.2 hemizygous partial chromosome deletion using the fluorescence in situ hybridization method. From 2011 to 2013, approximately 40 of these patients with 22q11.2DS, (median age 17 years), were referred to the Department of Psychiatry for various neuropsychiatric problems, usually after their systemic comorbidities were well treated and had achieved stable status. Of these patients, those who had been treated over several years for psychotic symptoms were asked to participate in this study. The sample included seven men and four women with 22q11.2DS and psychotic symptoms (aged 17-40 years; mean age, 30.36 ± 7.89 years), with their parents approving participation. Patients (seven

Table 2: Multiple regression analyses with the current ADI-R and PANSS domains as dependent variables.

Source	Dependent Variable	Simple Corr	P	Significance	Partial Corr	P	Significance
Age	ADI-R current social interaction	-0.1254	0.57808	NS	-0.4891	0.02864	*
	ADI-R current communication	-0.07	0.757	NS	-0.1465	0.53778	NS
	ADI-R current repetative interests & behaviors	0.0194	0.93175	NS	-0.0217	0.92777	NS
	All 3 ADI -R current domains	-0.09	0.6905	NS	-0.3139	0.1777	NS
	PANSS positive symptoms	0.0336	0.88198	NS	0.0593	0.80388	NS
	PANSS negative symptoms	-0.1046	0.64312	NS	-0.1656	0.48521	NS
	PANSS general psychopathology symptoms	0.1258	0.57688	NS	0.1251	0.59922	NS
	PANSS total symptoms	0.0161	0.94326	NS	0.0225	0.92495	NS
Diagnostic Group	ADI-R childhood social interaction	0.9748	0	**	0.9799	0	**
	ADI-R childhood communication	0.9301	0	**	0.931	0	**
	ADI-R childhood repetitive interests & behaviors	0.9442	0	**	0.9457	0	**
	All 3 ADI -R childhood domains	0.9762	0	**	0.9785	0	**
	ADI-R current social interaction	0.9584	0	**	0.9685	0	**
	ADI-R current communication	0.8379	0	**	0.841	0	**
	ADI-R current repetative interests & behaviors	0.8078	0.00001	**	0.8225	0.00001	**
	All 3 ADI -R current domains	0.9398	0	**	0.947	0	**
	PANSS positive symptoms	0.3198	0.14682	NS	0.3245	0.16276	NS
	PANSS negative symptoms	0.7278	0.00012	**	0.7348	0.00022	**
	PANSS general psychopathology symptoms	0.0688	0.76081	NS	0.0686	0.77388	NS
	PANSS total symptoms	0.2122	0.34309	NS	0.2125	0.36843	NS
Gender	ADI-R childhood social interaction	0.0245	0.9138	NS	0.1884	0.42624	NS
	ADI-R childhood communication	-0.0023	0.9919	NS	0.0096	0.9679	NS
	ADI-R childhood repetitive interests & behaviors	0.0535	0.81296	NS	0.1545	0.51546	NS
	All 3 ADI -R childhood domains	0.0184	0.93521	NS	0.1315	0.58053	NS
	ADI-R current social interaction	0.0389	0.86343	NS	0.2284	0.33287	NS
	ADI-R current communication	0.0269	0.90545	NS	0.0699	0.76974	NS
	ADI-R current repetative interests & behaviors	0.1879	0.40242	NS	0.3186	0.17103	NS
	All 3 ADI -R current domains	0.0611	0.78703	NS	0.2295	0.33043	NS
	PANSS positive symptoms	0.1662	0.45978	NS	0.1819	0.44264	NS
	PANSS negative symptoms	0.0835	0.71177	NS	0.1451	0.54165	NS
	PANSS general psychopathology symptoms	-0.013	0.95418	NS	0.0046	0.98469	NS
	PANSS total symptoms	0.0308	0.8916	NS	0.0344	0.8855	NS

Multiple regression analyses were used to estimate the relationships between current Revised Autism Diagnostic Interview (ADI-R) and Positive and Negative Syndrome Scale (PANSS) domains as dependent variables and age, diagnostic group, and gender as independent variables.

men and four women aged 18–39 years, with a mean age: 30.27 ± 7.06 years) with an established diagnosis of schizophrenia and without other systemic or psychiatric comorbidities were matched by age and gender and recruited as controls. The control patients were confirmed as having a schizophrenia diagnosis using the Japanese edition of Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association Text Revision (DSM-IV-TR), fourth ed. Igakushoin, Tokyo [24]. All participants and their parents provided written informed consent. This case-control study was approved by the Research Ethics Committee of Tokyo Women's Medical University.

Measures

The participants and their parents were interviewed, and medical records were scrutinized for past medical histories and sociodemographic data. The patients were physically examined to assess their baseline condition. The ADI-R is a semi-structured interview administered to a patient's parents to assess the presence of ASD. In this study, a well-trained and certified ADI examiner questioned the parents about the participant's current and early childhood levels of functioning with respect to autistic features. The Positive and Negative Syndrome Scale (PANSS) was used to measure the severity of schizophrenia symptoms. This medical scale is used for measuring the severity of positive symptoms, where there is an excess or distortion of normal functions (e.g., hallucinations and delusions), and negative symptoms, where there is a diminution or loss of normal functions. Participants were evaluated using the ADI-R and the

PANSS while they were clinically stable and without having changed medication during the previous 6 months (the stabilization phase).

Data analysis

Mann–Whitney U tests were used to compare the two clinical groups with regard to sociodemographic data, childhood autistic features, current autistic features, and current positive and negative schizophrenia symptoms. The frequency of positive ADI-R scores was tested between the two groups using the chi-square test. Multiple regression analyses were used to estimate the relationship between current ADI-R and PANSS domains (the dependent variables) and age, diagnosis, and gender (the independent variables). The variables analyzed included childhood autistic features, current autistic features, and current positive and negative schizophrenia symptoms. Specifically, the analysis included all three ADI-R childhood domains (qualitative abnormalities in reciprocal social interaction; qualitative abnormalities in communication; and restricted, repetitive, and stereotyped patterns of behavior), all three ADI-R current domains, a combination of all six ADI-R domains, and all four PANSS domains (positive symptoms, negative symptoms, general psychopathology symptoms, and total symptoms).

Results

All of the participants studied were Japanese, including eleven 22q11.2DS patients with psychotic symptoms and eleven age- and gender-matched schizophrenia patients without 22q11.2DS. Their clinical and sociodemographic characteristics are presented in (Table 1). These ADI-R childhood autistic features of the 22q11.2DS group were greater than the cutoff value for the diagnosis of ASD, whereas those of the schizophrenia group were below the cutoff. All 11 22q11.2DS patients with psychotic symptoms were diagnosed with ASD. The ADI-R childhood autism scores of the 22q11.2DS participants were significantly more severe than those of the participants with schizophrenia, including scores for childhood social interaction (20:1, [the ratio of the median scores, 22q11.2DS group: schizophrenia group]), communication (15:1), and repetitive interests and behaviors (5:0) (all p < 0.001). The 22q11.2DS group also had more severe current ADI-R autism scores, including social interaction (10:0), communication (6:1), and repetitive interests and behaviors (3:0) (all p < 0.001). Multiple regression analysis confirmed that these childhood and current ADI-R features of the 22q11.2DS group were greater than those of the schizophrenia group (Table 2). The median PANSS positive symptom scores, general psychopathology scores, and total symptom scores did not differ between the groups (20:18, 30:30, and 67:68, respectively). The median PANSS negative symptom scores, however, were significantly lower in the 22q11.2DS group (17:19, p < 0.01) (Tables 1 & 2). Multiple regression analysis confirmed these PANSS features (Table 2). As a result, these patients received the behavioral and communication help appropriate for individuals with an ASD diagnosis. Preliminary narrative data suggest that they have gone on to lead uneventful, stable lives, with dose-reduced medication, better relationships with family members and/or coworkers, and improving social confidence.

Multiple regression analysis showed that none of the variables, including the ADI-R current domains (except for the ADI-R current social interaction domain) and PANSS domains, were associated with age. Older patients tended to have a lower score on the ADI-R

current social interaction domain (p < 0.05). Gender differences were not observed for any of the variables (Table 2).

Discussion

This is the first study of psychotic symptoms in Japanese 22q11.2DS patients using the ADI-R in structured interviews [25,26] with the parents of patients with 22q11.2DS who had been treated for psychotic symptoms over several years. The ADI-R childhood autistic features of the 22q11.2DS group were greater than the cutoff value for the diagnosis of ASD, whereas those of the schizophrenia group were below the cutoff. All patients with 22q11.2DS who had psychotic symptoms met the diagnostic criteria for ASDs, based on the ADI-R symptom scores related to current social interaction, current communication, and current repetitive interests and behavior; therefore, the schizophrenia controls could be discriminated. Older patients tended to have a lower score on the ADI-R current social interaction domain, suggesting that socialization skill could develop with age. The ADI-R can support diagnostic decisions and provides an empirically validated basis for education and treatment planning. Additionally, the ADI-R has been proven to be particularly effective in measuring ASD severity while considering language ability and age [27]. The ADI-R is a thorough evaluation tool that takes a few hours to complete, leading to criticism that it is time-consuming in clinical practice [28]. In this study, all patients with 22q11.2DS who had psychotic symptoms met the diagnostic criteria for ASDs, based on the ADI-R cutoffs for symptoms related to childhood social interaction, childhood communication, and childhood repetitive interests and behavior. However, some important disagreements among researchers remain over the specific meanings of 'ASD symptoms,' 'above the threshold on ADI-R scores,' and 'ASD diagnosis.' Nevertheless, ADI-R is currently considered to be one of the gold standards (with ADOS) for the assessment of ASDs [18,29].

In contrast, the PANSS total symptom profiles were similar across the 22q11.2DS and schizophrenia groups, with all the patients presenting with psychotic symptoms; therefore, using the PANSS it was difficult to discriminate between these two groups. However, there were some notable differences in the PANSS negative symptoms (a diminution or loss of normal function). The 22q11.2DS patients with psychotic symptoms in our study appear to be leading a better life after starting treatment and receiving support for newly diagnosed ASD. Autism-like behaviors, including self-directed behavior, poor social skills, and limited facial expressions, have been reported in individuals with 22q11.2DS [30].

Consistent with the results of this study, Roubertie and colleagues (2001) [31] described a patient who met the diagnostic criteria for both 22q11.2DS and ASD. In another study, Fine and colleagues (2005) [32] reported that 14 out of 98 children with confirmed 22q11.2DS qualified for a diagnosis of ASD based on the ADI-R. In an assessment of 60 patients with 22q11.2DS, aged 9-18 years, Vorstman and colleagues (2006) [19] used standard psychiatric protocols, including structured and semi-structured interviews with the parents, videotaped psychiatric interviews, and intelligence assessments. They found the rate of ASDs was as high as 50% (30 of 60) by the DSM-IV criteria, and one-third of the subjects were above the diagnostic threshold in all three ADI-R domains (autism). Furthermore, 12% were above the threshold in two ADI-R Domains (ASD), and 27%

presented with psychotic symptoms (16 of 60) (Vorstman et al., 2006) [19]. In another study, eight of 41 children with 22q11.2DS aged 6.5–25.8 years met the formal DSM-IV criteria for autism based on the ADI-R, and nine others met the criteria for ASD, resulting in an overall ASD rate of 41% [33]. Only 45% of the families participated in the ADI-R interview in that study. Angkustsiri and colleagues (2014) have shown that 5 of 29 children with 22q11.2DS (17%) were above the diagnostic cutoff for ASD when using the ADOS alone [28]; however, ASD may not be as common as previously reported. The use of ADI-R alone may overestimate the prevalence of ASD; the ADI-R and ADOS together may therefore provide a more reliable diagnosis of ASD in the 22q11.2DS population.

22q11.2DS was indicated to be characterized by social deficits and attention disturbances but without prominent conduct disorder; this result is consistent with the core neuropsychiatric phenotype (subtle cogn. Behavioral phenotypes and autistic spectrum behaviors in patients with 22q11.2DS tend to be variable, and therefore, traditional treatment programs designed for children with 22q11.2DS and autism may need to be modified [20]. Furthermore, in patients with 22q11.2DS, the presence of autism may be predictive of more severe psychiatric disorders [19]; thus, there is an ongoing debate as to whether the symptoms classified as reflecting ASDs may be better characterized as prodromal symptoms of schizophrenia, suggesting that early identification of autism during childhood is critical [34].

Indeed, ASD and schizophrenia associated with 22q11.2DS should be regarded as two unrelated and distinct phenotypic manifestations [9]. Individuals with ASD experience early impairments in social areas, similar to those observed in patients who develop schizophrenia, in which they typically experience a decrease in social competences and functioning that begins in adolescence [35]. These results are consistent with research that has shown that ASD and autistic symptoms during childhood are not correlated with schizophrenia in adulthood in patients with 22q11.2DS [9]. Despite the rarity of this condition, we can conclude that those with 22q11.2DS presenting with psychotic symptoms may have ASD; therefore, early intervention to those patients under a diagnosis of ASD is essential.

TBX1 haploinsufficiency could also contribute to behavioral problems [36]. However, the role of TBX1 in the behavioral and psychiatric phenotype remains controversial. Some authors argue that because TBX1 is not normally expressed in the brain, it is unlikely to account for the cognitive and psychiatric aspects of the 22q11.2DS deletion syndrome [37]. Furthermore, there is the potential for the loss of the catechol-O-methyltransferase (COMT) gene, found in the same region of chromosome 22, which is typically deleted (the clinical presentations are undistinguishable between the 3 Mb and 1.5 Mb deletions), to further increase the risk of behavioral problems and mental illness [38]. Given the potential implication of dopamine in the pathogenesis of schizophrenia, the genetic polymorphism of COMT, which is involved in dopamine degradation, has received considerable interest with regard to 22q11.2DS [39,40] and schizophrenia [41]. Another gene commonly deleted in 22q11DS is the proline dehydrogenase (PRODH) gene and a functional PRODH variant is associated with schizophrenia that may have a neurochemical impact, altering brain function [40]. Nevertheless,

patients with 22q11.2DS and schizophrenia have previously been identified as possessing gene-centric copy number variants (CNVs) that may lead to a potential second hit [42]. In support of this two-hit hypothesis, there is evidence that a deletion of the 2q23.1 gene Methyl-CpG binding domain protein 5 (MBD5) in patients with 22q11.2DS and psychotic symptoms may result in intellectual disability, epilepsy, and autistic features [42]. CNVs have been identified as major risk factors for several neuropsychiatric disorders, and CNV-related neuropsychiatric phenotypes in 22q11.2DS could share the same genetic etiology. However, ASD and schizophrenia should be regarded as two unrelated and distinct phenotypic manifestations, consistent with true neuropsychiatric pleiotropy [9,43]. Gender differences have been reported for several psychiatric variables. For example, previous research demonstrated that male patients rated more severely on negative and disorganized prodromal symptoms than female patients and scored more severely on childhood repetitive interests and behaviors, current social interaction, and current repetitive interests and behaviors [44]; this is the first study showing that Japanese 22q11.2DS patients presenting with psychotic symptoms had ASD using the ADI-R. This pattern, however, was not shown in our present study. No racial differences have been reported for prodromal and autistic symptoms in 22q11.2DS [44]. Finally, although socialization and communication skills have been shown to be significantly predicted by age [18], we were only able to show an association with socialization.

This present study had a number of limitations. First, the sample was too small to draw any meaningful conclusions. The incidence of 22q11.2DS is one per 4000–5000 of the general population, and schizophrenia is estimated to be prevalent in 20-38% of people with 22q11.2DS, whereas autism is estimated to be prevalent in 10-20%. Therefore, 22q11.2DS patients with psychotic symptoms are as rare as 1 in 25,000 persons. The low incidence of 22q11.2DS limits the ability to study the use of both the ADI-R and the ADOS as a joint reference tool for diagnosing ASD. Second, we should have included patients with ASD symptoms without 22q11.2DS and patients with 22q11.2DS without ASD symptoms to clarify whether ASD is associated with the disease or precedes the onset of schizophrenia. The low incidence of 22q11.2DS also hampers attempts to compare ASD symptoms between 22q11.2DS and idiopathic ASD or between 22q11.2DS with and without schizophrenia. The latter comparison, in particular, could provide useful information regarding prodromal symptoms.

Conclusion

In conclusion, given our small sample size, it is difficult to claim a high prevalence of ASD in all patients with 22q11.2DS. Despite the rarity of this pathology, we were able to enroll 11 cases. Therefore, we can conclude that those with 22q11.2DS presenting with psychotic symptoms may also have ASD; that there are no gender differences in the psychotic symptoms; and that the ADI-R social interaction domain score is associated with age. 22q11.2DS is associated with a risk for ASD. Clinically, 22q11.2DS can be suspected in the presence of characteristic facial features [45]. Additionally, children with 22q11.2DS experience symptoms with multi-system involvement, which require long-term managements and treatments for related problems. As a result, early psychiatric diagnosis, monitoring, and

intervention to reduce the burden of psychopathology is often delayed. The availability of specialty 22q11.2DS clinics is limited, and optimal care requires a multidisciplinary team approach. Finding from our study may prompt early psychiatric consultation of 22q11.2DS cases even with serious comorbidities. Further research in this realm that includes young children is warranted.

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