ORIGINAL CONTRIBUTION

Depression and anxiety disorders in children and adolescents with velo-cardio-facial syndrome (VCFS)

Alice Fabbro · Eleonora Rizzi · Maude Schneider ·
Martin Debbane · Stephan Eliez

Abstract Velo-cardio-facial syndrome (VCFS) is characterized by a high prevalence of depression and anxiety disorders in childhood and adolescence. These disorders are a source of great impairment in everyday functioning, as well as important risk factors for the emergence of later psychotic disorders. Impairment in daily and social functioning as well as loss of IQ throughout growth are also are well-established correlates of the VCFS. This study aimed to confirm the high prevalence of depression and anxiety disorders. The second objective was to ascertain the correlation between anxious and depressive symptoms and the decline in adaptive and cognitive functioning. A total of 73 children and adolescents with VCFS (mean age 11.9 years) underwent psychiatric evaluation. Subjects were further divided into four age groups: ages 6–9, 9–12, 12–15 and 15–18 years. Assessments measuring intelligence, anxious and depressive symptoms, and adaptation skills reported by parents were submitted to a subsample of 62 children (mean age 12.2 years); 62.2 % of the sample showed an anxiety disorder, specific phobia being the most represented at all ages. Lifetime depression concerned 27 % of the sample, peaking at age 12–15 years. Anxious and depressive symptoms and low IQ were significantly associated with low adaptive functioning. Anxiety and depression are common disorders in children and adolescents with VCFS and have a great impact on adaptive functioning. Clinicians should pay great attention to diagnosis and treatment.

Keywords VCFS · 22q11.2 deletion syndrome · Depression disorders · Anxiety disorders · Adaptive skills · Psychotic disorders

Abbreviation
DICA Diagnostic Interview for Children and Adolescents

A. Fabbro (✉) · E. Rizzi · M. Schneider · S. Eliez
Department of Psychiatry, Office Médico-Pédagogique Research Unit, University of Geneva School of Medicine, 1 David Dufour, CP 50, 1211 Geneva 8, Switzerland
e-mail: alice.fabbro@unige.ch

M. Schneider · M. Debbane
Faculty of Psychology, University of Geneva,
40 Pont d'Arve, 1205 Geneva, Switzerland

S. Eliez
Department of Genetic Medicine and Development,
University of Geneva School of Medicine, Michel-Servet 1,
1206 Geneva, Switzerland

Introduction

Depression and anxiety disorders in children have recently aroused great interest among researchers in the field of velo-cardio-facial syndrome [1–5]. These pathologies are highly prevalent, can have a dramatic impact on the daily lives of patients and their families and can affect future development. Also known as DiGeorge or Shprintzen syndrome, VCFS is a genetic neurodevelopmental disorder involving a microdeletion on the long arm of chromosome 22 at the q11.22 band. Clinical features include palatal abnormalities, cardiac defects, unique facial characteristics, hypernasal speech, hypotonia and thymus defects. At present, the estimated prevalence of the syndrome ranges from 1/6,000 to 1/2,000 [6]. However, VCFS's great variability in terms of clinical expression (up to 180 clinical traits have been recognized and are not all displayed by affected individuals [7]) reasonably implies that many cases still go undiagnosed.

🖄 Springer

In the past decades, a large number of published studies on VCFS have reported an increased rate of psychiatric disorders, including ADHD, anxiety disorders (such as simple phobia and social phobia, general anxiety disorder, obsessive–compulsive disorder), schizophrenia, major depressive disorder, dysthymia and autism spectrum disorders [8]. The prevalence of psychiatric disorders varies among different studies, according to the mean age of the sample, recruitment sources and cultural bias. A recent study by Green and collaborators reported a psychopathology prevalence of about 73 % among individuals with velo-cardio-facial syndrome [5]. Moreover, most studies on the VCFS show a high rate of ADHD and anxiety disorders in children and adolescents [1, 9], whereas mood disorders and schizophrenia tend to emerge later in adulthood [11–14].

Research on psychotic disorders is overrepresented among the studies on VCFS, which is partly related to the severity of their clinical expression and by the degree of impairment caused to the patients and their families. As a consequence, the strong clinical association between schizophrenia and VCFS has motivated concomitant research in the field of genetic etiology, brain development and the pathogenesis of psychotic disorders in VCFS [11–13, 15].

The research on VCFS focusing on psychiatric disorders appearing in early and middle childhood have underlined the high prevalence of anxiety disorders at all ages, particularly concerning specific phobia. While appearing to peak in adulthood, mood disorders are also a major concern during childhood and adolescence. Clinical accounts often reflect that depression and anxiety can be a challenging issue for caregivers and a source of great impairment in everyday functioning, social well-being and academic achievement for patients. Moreover, parent-reported anxious and depressive symptoms are important risk factors for the emergence of psychotic disorders in adulthood [16]. During childhood and adolescence, the occurrence of psychotic symptoms is associated with more severe parent-reported anxious-depressive symptoms [17].

The first purpose of our study was to confirm the high prevalence of anxiety and mood disorders among children and adolescents affected by VCFS, and in particular to assess the differences between childhood and adolescent psychopathology. VCFS, like other genetic disorders, is often associated with high impairment in daily routine and family functioning and social performance [18]. The adverse influence of anxious and depressive symptoms on children's social, academic and family functioning has also been well established [19]. Therefore, the second objective was to ascertain the effects of anxious and depressive symptoms of children and adolescents affected by VCFS on their level of impairment in adaptive, social and family functioning, controlling for age, gender and intellectual functioning. Since impairment in cognitive abilities and evolving psychopathology throughout growth are well-established correlates of the velo-cardio-facial syndrome, a further concern was the predictive value of age and IQ on the loss of daily functioning skills.

Methods

Participants

Seventy-four children and adolescents (36 males, 38 females) with VCFS between the ages of 6 and 18 ($M = 11.9 \pm 3.35$) participated in this study. The presence of the 22q11.2 microdeletion was confirmed by fluorescence in situ hybridization. Sixty-two children in the sample (28 males, 34 females) aged 6–17 years ($M = 12.2 \pm 3.2$) underwent clinical and cognitive assessment. Participants were recruited through several European VCFS patient associations (Switzerland, France, England and Belgium). In order to avoid recruitment biases, subjects referred by psychiatric or pediatric units were not included in the sample. All patients were Caucasian, French or English speaking and were tested in their native language. In the entire sample, 64 % was receiving psychotherapy or had received it in the past; 20 % of the participants were being treated with psychotropic medications at the time of evaluation. The remaining part of the sample was drug naïve. Written informed consent was received from all parents and/or subjects under protocols approved by the Institutional Review Board of the University of Geneva School of Medicine.

Clinical evaluation

Participants' parents were given a semi-structured computerized interview called the DICA-IV [20]. The parental responses to this computerized inventory were automatically tabulated and scored by the DICA-P software generating specific DSM-IV diagnoses and a complete listing by diagnostic criteria of all symptoms reported present or absent by the parents. Diagnosis was then confirmed by a clinical evaluation of the child. All the procedures were performed by the same senior child and adolescent psychiatrist (SE).

Cognitive evaluation

The children and adolescents' general intellectual functioning was assessed by well-trained master-level psychologists using the Wechsler Intelligence Scale for Children and the Wechsler Adult Intelligence Scale

[21, 22]. Participants showed a mean borderline IQ (71.3 ± 11.2).

Adaptive behavior measures

The Vineland Adaptive Behavior Scales, Interview Edition, Survey Edition [23] was used to measure children and adolescents' personal and social skills. Well-trained psychologists interviewed parents in their native language. Results were organized within a three-domain structure. The Communication domain reflects expressive and written communication skills, as well as the ability to listen. The Daily Living Skills domain assesses personal habits and domestic task performance as well as behavior in the community. The Socialization domain evaluates interpersonal relationships, play, leisure time activities and various interaction skills.

Emotional assessment

The severity of depressive symptoms was assessed with the Children's Depression Inventory (CDI) [24], a self-report questionnaire of 27 items adapted for children and adolescents aged 7–17 yeara. Each item consists of three choices, keyed 0/1/2, with higher scores indicating increasing severity. This test quantifies a range of depressive symptoms including disturbed mood, hedonic capacity, vegetative functions, self-evaluation and interpersonal evaluation. Anxious symptoms were assessed with the Children's Manifest Anxiety Scale-Revised (R-CMAS) [25], a self-reported measure of 37 items that evaluates the level and the nature of anxiety, from somatic complaints to social correlates, in children and adolescents aged 6–19 years. The questionnaire is divided into four subscales: Physiological Anxiety (10 items), Worry/Oversensitivity (11 items), Social Concerns/Concentration (7 items), and the Lie Scale (9 items). All patients completed the questionnaires prior to their clinical evaluation.

Statistical analyses

We first performed descriptive statistics on the prevalence of anxiety and mood disorders in a sample of 74 children and adolescents with VCFS. We further divided our sample into four age groups (6–9 years, 9–12 years, 12–15 years, 15–18 years) to examine the age distribution of these disorders. We computed confidence intervals for prevalence using the Minitab 16 Statistical Software (http:\\www.minitab.com). We then performed Chi-square tests to compare the prevalence between age groups.

Secondly, we compared the RCMAS and the CDI total scores between age groups using MANOVAs and post hoc Tukey HSD pairwise comparisons.

Finally, we performed stepwise linear regressions to identify the best predictors of adaptive functioning in a subsample of 62 individuals ($m_{age} = 12.17$, SD = 3.21). Adolescents aged 16 years or higher were not included in the present analyses since the adult version of the RCMAS ($m_{total\ score} = 56.29$, SD = 10.394) and the CDI ($m_{total\ score} = 54.47$, SD = 9.104) were used for these participants. The Vineland total score was used as dependant variable. Age, gender, full-scale IQ, anxiety total score and depression total score were used as stepwise independent variables. We created two separate models, one using the anxiety total score and the other using the depression total score, in order to avoid multicollinearity.

All the analyses excepting confidence interval calculations were performed using SPSS Statistical Software version 19.

Results

Prevalence of anxiety disorders and depression

The rate of anxiety disorders and depression in the entire sample is presented in Table 1. A current anxiety disorder was found in 62.2 % of the sample (46 subjects). The most common anxiety disorder is specific phobia (46 %) followed by general anxiety disorder (14.9 %), social phobia (10.8 %), obsessive–compulsive disorder (9.5 %) and separation anxiety (8.1 %). Current or past depression was present in 29 % of the subjects.

Though the four age groups showed different prevalence rates for anxiety disorders and depression, Chi-square comparisons revealed that they did not significantly differ, as reported in Table 2. The youngest group of children (aged 6–9 years) showed a high rate of specific phobia (29.4 %) in comparison to the other disorders namely separation anxiety, general anxiety disorder (GAD), obsessive–compulsive disorder (OCD) and depression which are all equally represented at 17.6 %. Only one patient fulfilled the criteria for social phobia. In the group of children aged 9–12 years, specific phobia was still highly represented (45 %). Depression and GAD were diagnosed in 20 % of the sample, while social phobia rose to 15 %. Separation anxiety was diagnosed in only one patient as was OCD. Only one patient was diagnosed with separation anxiety and only one with OCD. The preadolescent group (12–15 years old) showed their highest percentage of psychiatric disorder for depression (42.1 %) and specific phobia (52.6 %). Separation anxiety and OCD appeared in 10.5 % of the sample while social phobia was reduced to 5.3 %. Specific phobia was by far the most represented disorder in the adolescent group (66.7 %), followed by depression (27.8 %) and social phobia

Table 1 Prevalence of psychiatric disorder (Diagnostic DSM-IV) in children with VCFS and adolescents for total sample and divided by age groups

[a] Generalized anxiety disorder
[b] Obsessive compulsive disorder

	Total sample N = 74 N (%)	6–9 years N = 17 N (%)	9–12 years N = 20 N (%)	12–15 years N = 19 N (%)	15–18 years N = 18 N (%)
Separation anxiety	6 (8)	3 (17.6)	1 (5)	2 (10.5)	0
GAD[a]	11 (15)	3 (17.6)	4 (20)	3 (15.8)	1 (5.6)
Specific phobia	36 (49)	5 (29.4)	9 (45)	10 (52.6)	12 (66.7)
Social phobia	8 (11)	1 (5.9)	3 (15)	1 (5.3)	3 (16.7)
OCD[b]	7 (9)	3 (17.6)	1 (5)	2 (10.5)	1 (5.6)

Table 2 Prevalence of depression and anxiety in children and adolescents for total sample and divided by age groups and χ^2 differences between age groups

	Total sample N = 74 N (%/Int-conf.)	6–9 years N = 17 N (%/Int-conf.)	9–12 years N = 20 N (%/Int-conf.)	12–15 years N = 19 N (%/Int-conf.)	15–18 years N = 18 N (%/Int-conf.)	χ^2 statistic
Depression	20 (27/17-39)	3 (17.6/4-43)	4 (20/6-44)	8 (42.1/20-66)	5 (27.8/10-53)	3.455, $df = 3$, $p = 0.327$
Anxiety	56 (76/64-85)	8 (47.1) 23-72	12 (60/36-81)	14 (73.3/49-91)	12 (66.7/41-87)	2.916, $df = 3$, $p = 0.405$

Table 3 Stepwise regression models to identify the best predictors of adaptive functioning (N = 62)

Dependent variable / Significant independent variables	Model ΔR^{2a}	ΔF^a	Coefficients b	SD b	β	t	p
Vineland total score							
QIT	0.246	19.538	0.350	0.102	0.363	3.414	0.001
CDI total	0.092	8.176	−0.379	0.120	−0.320	−3.148	0.003
Age	0.079	7.832	−0.990	0.354	−0.294	−2.799	0.007
Vineland total score							
QIT	0.246	19.538	0.366	0.105	0.379	3.485	0.001
RCMAS total	0.081	7.109	−0.273	0.109	−0.263	−2.501	0.015
Age	0.056	5.296	−0.841	0.365	−0.250	−2.301	0.025

[a] ΔR^2 and ΔF change in R^2 and F coefficient from step1

(16.7 %). The percentages of GAD and OCD dropped to 5.6 %. No adolescent currently had separation anxiety disorder.

Concerning the specific phobia disorder, several children reported more than one type of phobia. A large part of the phobic subjects (25 participants) reported fear of the dark. Among the other specific phobias, 17 were scared of animals (e.g., dogs and insects), 12 of natural causes (e.g., thunderstorms and wind) and 5 feared heights and avoided noise and different situations such as taking a plane or an elevator. The fear of being left alone was experienced by four participants.

Association with adaptive functioning

A first stepwise linear regression indicated that full-scale IQ ($b = 0.363$, $p < 0.05$), CDI total score ($b = -0.320$, $p < 0.05$) and age ($b = -0.294$, $p < 0.05$) significantly predicted adaptive functioning (see Table 3). The final model with all the predictors explained 41.6 % of variance.

A second stepwise linear regression indicated that full-scale IQ ($b = 0.379$, $p < 0.05$), RCMAS total score ($b = -0.263$, $p < 0.05$) and age ($b = -0.250$, $p < 0.05$) significantly predicted adaptive functioning (see Table 3). The final model with all the predictors explained 38.3 % of variance. These results are consistent with our second hypothesis.

Discussion

Anxiety disorders and depression are very common in individuals with VCFS. In this study, 27 % of children and adolescents suffered from major depression currently or in the past. This rate is considerably higher than the 5 % estimated prevalence in school age population without VCFS [26]. Interestingly, the rate of depression in our sample is higher than the results reported in some previous studies in youth with VCFS [1, 3]. Sample sizes or differences in age ranges could account for some of these

differences. The variability of the assessments (questionnaires vs. parents and child interviews vs. child alone) and a possible diagnostic overlapping between anxiety and depressive disorders are also likely to account for the observed differences. However, other studies have found similar results to ours [27].

We observed an increase in depressive episodes at the beginning of adolescence (age 12–15), as previously reported in a longitudinal study from Anthshel et al. [28]. Given the fact that in the general population depressive disorders mainly appear in late adolescence and early adulthood, this finding could be considered a specific feature of VCFS. Specific factors could play a role in this particular trajectory.

Indeed, clinical observations show that by the age of 12–15 years, preadolescents with VCFS begin to struggle with the psychosocial ramifications of their disorder. Typically at this age, the quest for autonomy from parental figures and the need to independently develop peer relationships amplify the contrast between ordinary and affected individuals. Due to their lack of autonomy, low communication skills and angry temperament, pre-adolescents with VCFS are often unable to meet the social and intellectual standards of their peers. Social isolation and poor grades often result in low self-esteem and highly increase susceptibility to depression.

In a similar way, the beginning of adulthood corresponds to a difficult time emphasizing the syndrome's consequences. At the end of high school, individuals with VCFS often face limited professional and relational opportunities due to their physical and cognitive handicaps. This period of time corresponds to a critical time for depression, as recently identified by Green [5]. Interestingly, the prevalence of lifetime depression in our sample appears to decline in the group aged 15–18 years. However as the "lifetime depression" label considers past and current depressive episodes, this diminution is due to the cross-sectional design of this study.

Anxiety disorders were reported in 62.2 % of the sample. These results are particularly significant considering that diagnosis rates for anxiety disorders in non-syndromic children, which vary widely between different studies, range from a minimum figure of 2.6 % to a maximum of 41.2 % [29]. In our study, the rates tended to increase with age, affecting up to two-thirds of the adolescents in the age group 15–18 years. As stated previously, specific phobia is the most common anxiety disorder at all ages in our study. These findings were consistent with previous studies [1, 3]. Interestingly, OCD occurred rather infrequently compared to the results found in other studies on VCFS [10]. General anxiety disorder and separation anxiety affected, respectively, 15 and 8 % of the sample and seemed to decline with age.

The type of anxiety disorders expressed at the earlier ages reflects the practical and social consequences of the syndrome. Indeed, SA and GAD can be considered, at least initially, as reactions to the feelings of inadequacy and physical vulnerability inherent to VCFS. As children age, the rates of anxiety diseases increase as well as their severity, resulting in a high prevalence of specifically described psychopathologies, such as specific phobia and social phobia.

A recent study from Essex and collaborators focused on early behavioral inhibition as a risk factor for the development of chronic high school age inhibition [30], adding more evidence to the association established between childhood inhibition and later social anxiety disorders. Since severe childhood inhibition is a characteristic often displayed by VCFS children, the pathway leading to an increased rate of adolescent anxiety disorders may not differ from that of the general population. Further research on this hypothesis may contribute to a better understanding of the pathogenesis of anxiety disorders in VCFS population as well as in the general population.

In our sample, low Vineland total scores were strongly associated with higher CDI or R-CMAS total scores, lower IQ and older age. These results show that the loss of everyday adaptive skills and social functioning, as described by parents, can be associated with an increase in the severity of the depressive and anxiety symptoms reported by the patients. Comparably, the association between childhood depression and both low activities in daily life and poor social adaptation has also been demonstrated in children not affected by known genetic syndromes [19].

Additionally, this study points out age as a powerful predictor of poor performance on the Vineland scale. The decline of cognitive functioning throughout growth, especially verbal IQ, is a well-established correlate of the syndrome [5, 16], recently linked to brain structural changes [31, 32].

The results of our study suggest an association between age-correlated cognitive loss, increased anxious–depressive symptoms and age-correlated loss of daily and social skills. Further studies could investigate brain structural changes as possible common pathways of emotional, cognitive and adaptive disruption occurring with age.

Limits

Our study had some limitations. First of all, the difficulty of this research field in recruiting a large sample gave a limited power to our statistical analyses. Particularly, the differences in psychopathology rates between the age groups were not statistically significant. For the same reason, age had to be considered as a discontinuous rather than a continuous variable. Another limitation of the present article is the absence of a normative group. Therefore, we had to rely on independent studies in order to perform comparisons with the general population [33].

Clinical implications

Both our clinical experience and current literature reveal that caregivers as well as clinicians do not give adequate attention to depression and anxiety disorders among syndromic populations, especially among those characterized by mental retardation [34]. Several reasons could account for this lack of attention. Firstly, even if it is partially explained by hypotonia, individuals with VCFS have a limited ability to express their feelings through facial expression and body posture. Secondly, social withdrawal, one of the most typical features of the syndrome [35, 36], highly affects their ability to communicate emotions, to the extent that the children are often isolated and their feelings neglected. Moreover, clinicians often accept sadness and fear as a natural consequence of the severity of VCFS rather than treatable comorbidity. The underestimation of these difficulties may result in late interventions.

As discussed previously, the concurrent social and academic issues that genetically vulnerable syndromic preadolescents face appear to lead to increased depression and anxiety disorders. In this critical period of life, individuals with VCFS and older individuals should be considered at higher risk and should receive special clinical attention, as underestimating their anxious and depressive symptoms could lead to a greater impairment in their social and daily functioning.

Moreover, as already reported, anxious and depressive symptoms are associated with psychotic symptoms [17, 37] and with an increased risk for the emergence of psychotic disorders in adulthood [16]. Regular screening and prompt treatment of anxiety or depression are therefore likely to decrease the rate of psychotic symptoms and subsequent development of schizophrenia.

In addition, given their impact on adaptive skills and future autonomy, depression and anxiety disorders should be seriously considered when dealing with a child or an adolescent with VCFS. As there is no evidence to suggest that patients with VCFS respond differently to usual treatments, compared to children and adolescents without this syndrome, as soon as a diagnosis of depression or anxiety is made, vigorous pharmacological and psychotherapeutic treatment should be considered.

Besides all the clinical considerations, the strong association between anxiety and depressive symptoms and adaptive skills suggest that on the long run a suitable treatment can improve social competencies and provide a higher degree of autonomy in adulthood.

References

1. Antshel KM, Fremont W, Roizen NJ, Shprintzen R, Higgins AM, Dhamoon A, Kates WR (2006) ADHD, major depressive disorder, and simple phobias are prevalent psychiatric conditions in youth with velocardiofacial syndrome. J Am Acad Child Adolesc Psychiatry 45:596–603
2. Feinstein C, Eliez S, Blasey C, Reiss AL (2002) Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: usefulness as phenotypic indicators of schizophrenia risk. Biol Psychiatry 51:312–318
3. Jolin EM, Weller RA, Weller EB (2012) Occurrence of affective disorders compared to other psychiatric disorders in children and adolescents with 22q11.2 deletion syndrome. J Affect Disord 136:222–228
4. Jolin EM, Weller RA, Jessani NR, Zackai EH, McDonald-McGinn DM, Weller EB (2009) Affective disorders and other psychiatric diagnoses in children and adolescents with 22q11.2 deletion syndrome. J Affect Disord 119:177–180
5. Green T, Gothelf D, Glaser B, Debbane M, Frisch A, Kotler M, Weizman A, Eliez S (2009) Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11.2 deletion) syndrome. J Am Acad Child Adolesc Psychiatry 48: 1060–1068
6. Oskarsdottir S, Vujic M, Fasth A (2004) Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in western Sweden. Arch Dis Child 89:148–151
7. Shprintzen RJ, Higgins AM, Antshel K, Fremont W, Roizen N, Kates W (2005) Velo-cardio-facial syndrome. Curr Opin Pediatr 17:725–730
8. Shprintzen RJ (2000) Velo-cardio-facial syndrome: a distinctive behavioral phenotype. Ment Retard Dev Disabil Res Rev 6: 142–147
9. Niklasson L, Rasmussen P, Oskarsdottir S, Gillberg C (2009) Autism, ADHD, mental retardation and behavior problems in 100 individuals with 22q11 deletion syndrome. Res Dev Disabil 30:763–773
10. Gothelf D, Presburger G, Zohar AH, Burg M, Nahmani A, Frydman M, Shohat M, Inbar D, Aviram-Goldring A, Yeshaya J, Steinberg T, Finkelstein Y, Frisch A, Weizman A, Apter A (2004) Obsessive–compulsive disorder in patients with velocardiofacial (22q11 deletion) syndrome. Am J Med Genet B Neuropsychiatr Genet 126B:99–105
11. Bassett AS, Scherer SW, Brzustowicz LM (2010) Copy number variations in schizophrenia: critical review and new perspectives on concepts of genetics and disease. Am J Psychiatry 167: 899–914
12. Eliez S, Blasey CM, Schmitt EJ, White CD, Hu D, Reiss AL (2001) Velocardiofacial syndrome: are structural changes in the temporal and mesial temporal regions related to schizophrenia? Am J Psychiatry 158:447–453
13. Eliez S, Debbane M (2008) Why are children and adolescent with 22q11.2 deletion syndrome at high risk of developing schizophrenia? Eur Psychiatr Rev 1:51–55

14. Vorstman JA, Morcus ME, Duijff SN, Klaassen PW, Heineman-de Boer JA, Beemer FA, Swaab H, Kahn RS, van Engeland H (2006) The 22q11.2 deletion in children: high rate of autistic disorders and early onset of psychotic symptoms. J Am Acad Child Adolesc Psychiatry 45:1104–1113

15. Vorstman JA, Chow EW, Ophoff RA, van Engeland H, Beemer FA, Kahn RS, Sinke RJ, Bassett AS (2009) Association of the PIK4CA schizophrenia-susceptibility gene in adults with the 22q11.2 deletion syndrome. Am J Med Genet B Neuropsychiatr Genet 150B:430–433

16. Gothelf D, Feinstein C, Thompson T, Gu E, Penniman L, Van Stone E, Kwon H, Eliez S, Reiss AL (2007) Risk factors for the emergence of psychotic disorders in adolescents with 22q11.2 deletion syndrome. Am J Psychiatry 164:663–669

17. Debbane M, Glaser B, David MK, Feinstein C, Eliez S (2006) Psychotic symptoms in children and adolescents with 22q11.2 deletion syndrome: neuropsychological and behavioral implications. Schizophr Res 84:187–193

18. Msall ME, Tremont MR (1999) Measuring functional status in children with genetic impairments. Am J Med Genet 89:62–74

19. Devine D, Kempton T, Forehand R (1994) Adolescent depressed mood and young adult functioning: a longitudinal study. J Abnorm Child Psychol 22:629–640

20. Reich W (2000) Diagnostic interview for children and adolescents (DICA). J Am Acad Child Adolesc Psychiatry 39:59–66

21. Wechsler D (1991) Wechsler Intelligence Scale for children, 3rd edn. The Psychological corporation, San Antonio

22. Wechsler D (1997) Wechsler Adult Intelligence Scale, 3rd edn. The Psychological corporation, San Antonio

23. Sparrow SS, Balla DA, Cicchetti DV (1984) Vineland Adaptive Behaviour Scales. American Guidance Service, Circle Pines

24. Kovacs M (1992) Children's depression inventory, CDI, Manual. Multi-Health Systems Inc.,Toronto

25. Reynolds CR, Richmond, BO (1999) Echelle revisee d'anxiete manifeste pour enfant (R-CMAS). ECPA, Paris

26. Shaffer D, Fisher P, Dulcan MK, Davies M, Piacentini J, Schwab-Stone ME, Lahey BB, Bourdon K, Jensen PS, Bird HR, Canino G, Regier DA (1996) The NIMH Diagnostic Interview Schedule for Children version 2.3 (DISC-2.3): description, acceptability, prevalence rates, and performance in the MECA Study. Methods for the Epidemiology of Child and Adolescent Mental Disorders Study. J Am Acad Child Adolesc Psychiatry 35:865–877

27. Papolos DF, Faedda GL, Veit S, Goldberg R, Morrow B, Kucherlapati R, Shprintzen RJ (1996) Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? Am J Psychiatry 153:1541–1547

28. Antshel KM, Shprintzen R, Fremont W, Higgins AM, Faraone SV, Kates WR (2010) Cognitive and psychiatric predictors to psychosis in velocardiofacial syndrome: a 3-year follow-up study. J Am Acad Child Adolesc Psychiatry 49:333–344

29. Cartwright-Hatton S, McNicol K, Doubleday E (2006) Anxiety in a neglected population: prevalence of anxiety disorders in pre-adolescent children. Clin Psychol Rev 26:817–833

30. Essex MJ, Klein MH, Slattery MJ, Goldsmith HH, Kalin NH (2010) Early risk factors and developmental pathways to chronic high inhibition and social anxiety disorder in adolescence. Am J Psychiatry 167:40–46

31. Kates WR, Antshel KM, Faraone SV, Fremont WP, Higgins AM, Shprintzen RJ, Botti JA, Kelchner L, McCarthy C (2011) Neuroanatomic predictors to prodromal psychosis in velocardiofacial syndrome (22q11.2 deletion syndrome): a longitudinal study. Biol Psychiatry 69:945–952

32. Schaer M, Glaser B, Cuadra MB, Debbane M, Thiran JP, Eliez S (2009) Congenital heart disease affects local gyrification in 22q11.2 deletion syndrome. Dev Med Child Neurol 51:746–753

33. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A (2003) Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry 60:837–844

34. Borthwick-Duffy SA (1994) Epidemiology and prevalence of psychopathology in people with mental retardation. J Consult Clin Psychol 62:17–27

35. Murphy KC (2005) Annotation: velo-cardio-facial syndrome. J Child Psychol Psychiatry 46:563–571

36. Swillen A, Devriendt K, Legius E, Eyskens B, Dumoulin M, Gewillig M, Fryns JP (1997) Intelligence and psychosocial adjustment in velocardiofacial syndrome: a study of 37 children and adolescents with VCFS. J Med Genet 34:453–458

37. Beaton EA, Simon TJ (2011) How might stress contribute to increased risk for schizophrenia in children with chromosome 22q11.2 deletion syndrome? J Neurodev Disord 3:68–75