Psychiatric Disorders and Behavioral Problems in Children with Velocardiofacial Syndrome: Usefulness as Phenotypic Indicators of Schizophrenia Risk

Carl Feinstein, Stephan Eliez, Christine Blasey, and Allan L. Reiss

Background: Velocardiofacial syndrome (VCFS), a genetic deletion condition with numerous cognitive sequelae, is associated with a high rate of psychiatric disorders in childhood. More recently, VCFS has been identified as a high-risk factor for developing adult onset schizophrenia. However, it has never been demonstrated that the childhood psychiatric disorders found in children with VCFS differ from those found in children with a similar degree of cognitive impairment. Identification of a specific behavioral (psychiatric) phenotype in childhood VCFS offers the potential for elucidating the symptomatic precursors of adult onset schizophrenia.

Methods: Twenty-eight children with VCFS and 29 age- and cognitively matched control subjects received a standardized assessment of childhood psychiatric disorders and behaviors measured by the Child Behavior Checklist (CBCL). Findings from the two groups were compared.

Results: The rates and types of psychiatric disorder and behavior problems in VCFS and cognitively matched control subjects were very high, but showed no significant differences.

Conclusions: Psychopathology in children with VCFS may not differ from that found in cognitively matched control subjects. Another explanation is that subtle phenotypic differences in behavior found in VCFS can not be observed using standard symptom inventories. The high rate of psychopathology in children with VCFS is not a useful phenotypic indicator of high risk for adult onset schizophrenia. Biol Psychiatry 2002;51:312–318 © 2002 Society of Biological Psychiatry

Key Words: Velocardiofacial syndrome, psychiatric disorders, behavior problems, schizophrenia, neurodevelopmental disorders, behavioral phenotype

Introduction

Velocardiofacial syndrome (VCFS) is one of the most common of the genetically based developmental disorders and is manifested by a complex of several medical abnormalities, a reduction in intelligence, learning disabilities, and psychiatric disorder (Bassett and Chow 1999; Cohen et al 1999; Feinstein and Eliez 2000; Moss et al 1999; Murphy et al 1999; Ryan et al 1997; Shaikh et al 2000; Swillen et al 1999). It is estimated to occur in at least 1 per 2000 to 4500 live births (Tezenas Du Montcel et al 1996). In most affected individuals, a de novo 3 Mb deletion at chromosome 22q11.2 is responsible for the syndrome (Carlson et al 1997; Driscoll et al 1993; Lindsay et al 1995; Scambler et al 1992; Shaikh et al 2000). Recently, investigators utilizing both psychiatric assessments of subjects known to have VCFS and genetic testing of patients with schizophrenia have demonstrated a strong association between VCFS and schizophrenia in adulthood. Shprintzen and coworkers (Shprintzen et al 1992) reported that 20–30% of his cohort of VCFS patients 16 years or older developed schizophrenia or schizoaffective disorder. Murphy and coworkers found 30% of 50 adult patients with VCFS to be psychotic (24% schizophrenia, 2% schizoaffective, 2% psychosis not otherwise specified, and 2% rapid-cycling bipolar disorder) (Murphy et al 1999).

In 1995, Karayiorgou and colleagues identified by genetic testing two patients with VCFS in a random sample of 100 schizophrenic patients (Karayiorgou et al 1995). Gothelf et al (1997) identified three individuals with VCFS by genetic testing of 20 hospitalized schizophrenic patients who had medical anomalies suggestive of VCFS. Bassett and coworkers applied a screening procedure based on five types of medical or developmental anomalies characteristic of VCFS to identify VCFS in a schizophrenic sample. Ten of 15 schizophrenic patients who had at least two of these were found to have VCFS by genetic testing (Bassett and Chow 1999; Bassett et al 1998). These patients had intelligence quotients (IQs) ranging from borderline to mild mental retardation. In
addition to symptoms and signs diagnostic of schizophrenia, most of these patients had a cluster of behavioral features that included impulsivity, frequent aggressive or temper outbursts, mood lability, anxiety, and compulsions. Usiskin and colleagues have recently reported that 6.4% of a cohort of youngsters with childhood-onset schizophrenia had VCFS (Usiskin et al 1999).

Because VCFS can be diagnosed reliably early in life, it should be possible to determine if there is a characteristic pattern of childhood behavior problems associated with this genetic disorder that arises prior to the high-risk period for the onset of schizophrenia. Such a behavior profile could possibly represent a phenotypic indicator of later-onset schizophrenia that might be of general use in identifying children at high risk. Perhaps more salient from a humane perspective, it appears that clinical neuroscience has advanced to the unsettling point where the families of children with VCFS know that a significant subgroup of their children will develop schizophrenia, a severely impairing lifelong psychiatric disorder. Yet, we cannot help families with VCFS predict the future for any specific child. We do not know if VCFS is simply a powerful general risk factor for schizophrenia or whether some yet-undetected aspect of the genetic deficit is specifically responsible for a child’s developing schizophrenia from VCFS. Furthermore, our ability to formulate a preventive intervention strategy is greatly hampered by our inability to determine which children will develop the disorder.

Velocardiofacial syndrome has been associated with a high rate of psychiatric disorder in both children and adults (Feinstein and Eliez 2000). Studies of VCFS children have documented problems with social interaction, mood lability, disinhibition, and shyness (Golding-Kushner et al 1985; Swillen et al 1999). Papolos and colleagues reported that children with VCFS commonly suffer from attention-deficit/hyperactivity disorder, separation anxiety disorder, and obsessive-compulsive disorder, and that 64% of their cohort met criteria for bipolar spectrum disorders in adolescence (Papolos et al 1996). Gerdes et al (1999) found that 75% of preschool children with VCFS in their sample were overactive, impulsive, highly emotional, and disorganized. Swillen and colleagues, utilizing behavior checklist data, found significant behavioral difficulties, such as “social problems,” “attention problems,” “thought problems,” “withdrawn behaviors,” and anxiety (Swillen et al 1997, 1999).

Even though we have ample evidence of a high rate of psychiatric disorder and behavior problems in children with VCFS, the relationship between these childhood psychiatric conditions and the later onset of schizophrenia is unknown. The psychiatric problems of children with VCFS could also be explained as simply deriving from their developmental delays and cognitive deficits, rather than having any specific relationship to increased risk for schizophrenia. In fact, it is well documented that the rate of childhood psychiatric disorder is generally elevated in children with developmental disabilities, developmental language disorders, and learning disabilities (Beitchman et al 1986; Beitchman and Young 1997; Cantwell and Baker 1991; Einfeld and Tonge 1996; Feinstein and Reiss 1996), all problems consistently found in children with VCFS. We are not aware of any published reports comparing psychiatric disorders and behavior problems in VCFS children with those found in other groups of developmentally disabled children. This raises the question of whether the psychiatric disorders found in children with VCFS are phenotypic indicators of later-onset schizophrenia, or simply a nonspecific outcome of brain dysfunction due to VCFS.

This article approaches the issues raised above by comparing the psychiatric diagnoses and behavioral profiles found in a sample of children and adolescents with VCFS with those found in a matched control group of youngsters with mental retardation and learning disabilities. The main research question is whether there is a unique profile of childhood psychiatric disorders or behavioral profiles in VCFS that can be distinguished from the behaviors of a group of comparably disabled children without VCFS. The identification of a unique psychiatric profile for VCFS would strengthen the hypothesis that the behavioral problems that children with VCFS experience are a phenotypic indicator of vulnerability to schizophrenia.

Methods and Materials

Subjects

Participants included 28 children and adolescents with velocardiofacial syndrome (18 boys and 10 girls) and a matched comparison group of 29 children and adolescents with developmental delays (17 boys and 12 girls). Prospective recruitment was performed through the Northern California VCFS Association and by advertising on our web site (www.cap.stanford.edu). Only subjects with VCFS who proved to be deleted on chromosome 22q11.2 using a fluorescent in situ hybridization technique were included in the study. Children presenting the VCFS clinical phenotype without deletion were excluded to increase diagnostic certainty.

The group of developmentally delayed control subjects was collected using advertisement to public and private schools with programs for children with learning differences, and through networks and parent support groups of children with learning disabilities. These comparison participants have been group matched to the VCFS sample with comparable distributions in the range of IQ. The primary inclusion criterion for this group was parental report of developmental delay, preferably docu-
Analyses of variance were used to compare CBCL scores diagnostic category and prevalence rate of psychiatric disorders. Wechsler Adult Intelligence Scale, 3rd edition (WAIS III), and Two-way Group comparisons regarding age, IQ, and gender were first Statistics validly in these interviews because of cognitive or linguistic advance that a significant number would be unable to participate subjects or control subjects was performed. It was clear in noted that no direct structured diagnostic interviews of child symptoms reported present or absent by the parents. It should be advanced that a significant number would be unable to participate Validly in these interviews because of cognitive or linguistic disabilities. Following administration of the DICA-P, the psychiatrist interviewed the parents further for evidence of psychosis and mood cycling, using the Screening Question portion of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) Parent Version (Kaufman et al 1997). If any symptom category from the screening interview elicited positive parent responses, the full portion of the K-SADS relative to that possible diagnosis was administered. The psychiatrist then performed a brief unstructured parent interview, supplementing information already obtained from the DICA-P and K-SADS screens, in order to rate the subject or control on the DSM-IV Global Assessment of Function Scale of DSM-IV (American Psychiatric Association 1994). All children and adolescents with VCFS and control subjects received a battery of cognitive tests that included the Wechsler Intelligence Scale for Children, 3rd edition (WISC III) or Wechsler Adult Intelligence Scale, 3rd edition (WAIS III), and the Children’s Evaluation of Language Functioning (CELF-R) (Eleanor et al 1995; Wechsler 1991, 1997). Table 1. Psychiatric Comorbidity in Subjects with Velocardiofacial Syndrome (VCFS) vs. Control Subjects

<table>
<thead>
<tr>
<th>DSM-IV diagnosis or symptom criteria</th>
<th>VCFS (n = 28)</th>
<th>Control subjects (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific phobia</td>
<td>17/28 (60.7%)</td>
<td>15/29 (51.7%)</td>
</tr>
<tr>
<td>Attention-deficit-hyperactivity disorder</td>
<td>13/28 (46.4%)</td>
<td>12/28 (48.8%)</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>12/28 (42.9%)</td>
<td>13/29 (44.8%)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>8/28 (28.6%)</td>
<td>7/29 (24.1%)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>8/28 (28.6%)</td>
<td>4/29 (13.8%)</td>
</tr>
<tr>
<td>Separation anxiety disorder</td>
<td>6/28 (21.4%)</td>
<td>3/29 (10.3%)</td>
</tr>
<tr>
<td>Major depressive disorder–Lifetime*</td>
<td>5/28 (17.9%)</td>
<td>12/29 (41.4%)</td>
</tr>
<tr>
<td>Major depressive disorder–present</td>
<td>4/28 (14.3%)</td>
<td>6/29 (20.7%)</td>
</tr>
<tr>
<td>Major depressive disorder–past</td>
<td>5/28 (17.9%)</td>
<td>8/29 (27.6%)</td>
</tr>
<tr>
<td>Evidence of delusions</td>
<td>4/28 (14.3%)</td>
<td>1/29 (3.4%)</td>
</tr>
<tr>
<td>Evidence of hallucinations</td>
<td>3/29 (10.7%)</td>
<td>4/29 (13.8%)</td>
</tr>
<tr>
<td>Dysthyemic disorder</td>
<td>3/28 (10.7%)</td>
<td>7/29 (24.1%)</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>3/28 (10.7%)</td>
<td>5/29 (17.2%)</td>
</tr>
<tr>
<td>Mania</td>
<td>1/28 (3.6%)</td>
<td>2/29 (6.9%)</td>
</tr>
</tbody>
</table>

*p* \(x^2 = .053\).

between groups. An \(\alpha = .05\) (two-tailed) was chosen as the threshold for significance.

Results

The two groups were well matched for age \(t(55) = .01, p = .99;\) VCFS: range = 6–19 years, \(M = 12.31, \text{SD} = 3.89;\) control subjects: range = 6–18 years, \(M = 12.31, \text{SD} = 3.49\) and for gender \([x^2(1) = .19, p = .79]\).

Results of cognitive testing indicated that the VCFS and control groups were similar in terms of mean full-scale IQ (70.3 and 73.1, respectively; \(F = .26, p = .61\)) and Verbal IQ (73.4 and 74.4, respectively; \(F = .04, p = .85\)). Although the Performance IQ of the subjects was slightly lower than the control subjects (71.8 and 77.3, respectively; \(F = 1.1, p = .31\)), this difference was not statistically significant. The subjects and control subjects were also similar in language functioning, measured by the CELF-R (70.6 and 71.8, respectively; \(F = .77, p = .38\)).

Rates of psychopathology, as defined by DSM-IV diagnoses, are summarized in Table 1. The highest prevalence rates were for specific phobia (60.7% of VCFS subjects and 51.7% of control subjects) and for attention-deficit/hyperactivity disorder (46.4% of VCFS subjects and 44.8% of control subjects). Rates of lifetime diagnosis of major depressive disorder, and the anxiety disorders and other disorders also were very high.

\(x^2\) analyses indicated that rates of DSM-IV disorder were not significantly different when comparing VCFS subjects and control subjects; however, a higher rate of

Statistics

Group comparisons regarding age, IQ, and gender were first performed to ensure that matching procedures were successful. Two-way \(\chi^2\) analyses were used to test the independence of diagnostic category and prevalence rate of psychiatric disorders. Analyses of variance were used to compare CBCL scores...
Table 2. Child Behavior Checklist T Scores for Subjects with Velocardiostomal Syndrome (VCFS) vs. Control Subjects

<table>
<thead>
<tr>
<th>CBCL Scale</th>
<th>VCFS Mean</th>
<th>VCFS SD</th>
<th>Control Mean</th>
<th>Control SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total T</td>
<td>63.22</td>
<td>9.65</td>
<td>66.60</td>
<td>6.665</td>
</tr>
<tr>
<td>Internalizing T</td>
<td>60.11</td>
<td>10.84</td>
<td>60.32</td>
<td>8.44</td>
</tr>
<tr>
<td>Externalizing T</td>
<td>55.44</td>
<td>10.22</td>
<td>62.29</td>
<td>9.08</td>
</tr>
<tr>
<td>Withdrawn T</td>
<td>61.19</td>
<td>13.26</td>
<td>58.27</td>
<td>10.29</td>
</tr>
<tr>
<td>Somatic T</td>
<td>58.19</td>
<td>7.91</td>
<td>58.93</td>
<td>7.06</td>
</tr>
<tr>
<td>Anxiety/depression T</td>
<td>59.67</td>
<td>10.11</td>
<td>60.27</td>
<td>7.13</td>
</tr>
<tr>
<td>Social T</td>
<td>66.8</td>
<td>8.91</td>
<td>67.29</td>
<td>14.89</td>
</tr>
<tr>
<td>Thought T</td>
<td>63.63</td>
<td>10.04</td>
<td>64.89</td>
<td>8.56</td>
</tr>
<tr>
<td>Attention T</td>
<td>67.41</td>
<td>9.70</td>
<td>71.11</td>
<td>7.76</td>
</tr>
<tr>
<td>Delinquent T</td>
<td>55.89</td>
<td>9.76</td>
<td>61.29</td>
<td>9.40</td>
</tr>
<tr>
<td>Aggressive T</td>
<td>57.78</td>
<td>8.59</td>
<td>62.36</td>
<td>9.60</td>
</tr>
</tbody>
</table>

CBCL, child behavior checklist.

*p = .0112,

*p = .0182,

*p = .0081.

lifetime occurrence of major depressive disorder was observed in the control group, and this difference approached statistical significance \( \chi^2(1) = 3.76, p = .052; \) control subjects: 41%, VCFS: 18%. Mean Global Assessment of Functioning Scores were almost identical for control subjects: 41%, VCFS: 18%. The mean CBCL scores for both subjects and control were elevated compared to CBCL norms, but, once again, the VCFS children were not more severely disordered on any dimension of psychopathology measured by this scale.

Discussion

Our results confirm previous reports of high rates of attention, anxiety, and mood disorders in children and adolescents with VCFS; however, we found no statistically significant evidence that psychopathology in youngsters with VCFS is qualitatively or quantitatively different from that present in a matched control group of developmentally disabled children. In fact, delinquent or aggressive behaviors were significantly lower in the children with VCFS compared to the control subjects, and the rate of major depressive disorder was even higher in the control subjects than in the VCFS group.

Ascertainment bias and small sample size should be considered as possible experimental design factors that could have obscured differences in psychopathology between the two groups. How representative was our VCFS sample? There is, in fact, no gold standard extant to answer this question, because a systematic population-based survey of VCFS has never been attempted. It must additionally be remembered that no VCFS sample, including our own, can be said to be homogeneous even for factors related to the 22q11.2 chromosomal micro-deletion. There are common polymorphisms in the non-deleted alleles (such as COMT, or GSCL) (Funke et al. 1997; Gottlieb et al. 1997, 1998; Lachman et al. 1996, 1997) and possible parent-of-origin effects deriving from imprinting that may well result in genetically based phenotypic differences between individuals in the VCFS sample (Eliez et al. 2000; Feinstein and Eliez 2000). Given the relatively small size of our sample, it is possible that polymorphisms and imprinting effects involving the non-deleted alleles in our sample were accidentally not representative of the total population of VCFS. The IQ and language test data from our VCFS sample, however, is quite consonant with that recently reported from a large
sample by Moss et al, as well as the other reported VCFS group findings described above (Moss et al 1999). Our findings regarding psychopathology also are consistent with other reports.

The same questions could be applied to the control group. Although well matched cognitively and linguistically with the VCFS group, the possibility of unknown ascertainment bias cannot be dismissed. Arguing against this is the fact that patterns of psychopathology found in our control sample appear similar to findings of high rates of psychiatric disorder identified from surveys of similar disability groups (Beitchman et al 1986; Beitchman and Young 1997; Cantwell and Baker 1991; Einfeld and Tonge 1996; Feinstein and Reiss 1996). The one unexpected finding from the control group was the exceptionally high rate of lifetime major depression. Interestingly, this higher rate for lifetime episodes was not reflected in higher CBCL scores on the anxiety-depression subscale or by significantly higher rates of current major depression in the control subjects. The relatively small size of the two samples is another factor that might have obscured significant differences. For example, the evidence for psychotic symptoms was twice as high for the VCFS subjects as for the control subjects (4 vs. 2). It is possible that, if the sample were much larger, this difference would reach statistical significance.

One obvious possible explanation of the generally similar and high rates of psychiatric disorder found in both groups is that both sets of children suffer from developmental central nervous system dysfunction that affects multiple behavioral domains. According to this perspective, even if the childhood brain pathology associated with VCFS were distinctive from the heterogeneous patterns of brain abnormalities found in the control group, the overlap in psychiatric symptoms may have overshadowed more subtle differences in behavior. It could also be that both the categorical diagnostic approach of the DSM system (employing the DICA-P interview) and the dimensional approach of the CBCL are not sufficiently refined to capture more subtle behavioral differences, which could conceivably distinguish the VCFS subjects from the control subjects.

Another possible explanation for the similarities between the VCFS group and the control subjects is that VCFS results in multiple neurodevelopmental abnormalities, only a subset of which underlie later schizophrenia. The remaining abnormalities account for the other cognitive and behavioral problems associated with VCFS; however, there remain important limitations in most of the neuroimaging studies done to date in VCFS, the main one being lack of cognitively matched control subjects. The brain changes that lead to schizophrenia in VCFS may not have progressed to expression in those of the VCFS subjects who later will go on to develop schizophrenia. By this line of reasoning, the psychiatric findings of our VCFS group may reflect other aspects of the brain pathology of VCFS than those responsible for schizophrenia.

How do our findings regarding childhood psychiatric disorder in VCFS relate to the pressing need to identify childhood phenotypic indicators of adult-onset schizophrenia? Pertinent to this discussion is the recently reported analysis of findings from the New York High-Risk Longitudinal Study for Schizophrenia (Erlenmeyer-Kimling et al 2000), and that of the Jerusalem Infant Development Study (Hans et al 1999). The availability of diagnostic outcome data from adults enrolled in the study from earliest childhood enabled the authors to propose an analytic strategy for validating childhood behavior problems as phenotypic indicators for later-onset schizophrenia in their genetic high-risk sample (offspring of schizophrenic parents). According to this strategy, candidate "mediating variables" (problems in behavior or cognition) are obtained through childhood assessments in a genetic high-risk sample to determine whether they are: 1) statistically more common than in control subjects; and 2) more highly associated with schizophrenic outcome in the high-risk group than in control subjects. Finally the direct association between high-risk group status and schizophrenia outcome must be significantly greater for the high-risk group than for the control subjects. If all three conditions are met, this constitutes strong support for a causal pathway between genetic risk, childhood mediating variables, and the development of schizophrenia. The mediating variables may then be considered valid (both sensitive and specific) phenotypic indicators.

Evaluating our findings for children with VCFS in the context of the strategy outlined above, it is evident that condition \#1 (a statistically stronger relationship between high-risk status and childhood mediating variables than that found between control group status and the same variables) is not met. Our findings therefore indicate that the specificity of childhood DSM-IV diagnoses and CBCL profiles in VCFS as phenotypic indicators for later-onset schizophrenia appears to be poor. The sensitivity of the child psychiatric findings in the VCFS subjects (or the control group) as childhood phenotypic indicators for later onset schizophrenia findings cannot be determined without adult outcome data from our sample.

Longitudinal adult outcome data for both the VCFS and the control group could answer two important questions that cannot be addressed in the cross-sectional study reported here. First is the question of whether a particular profile of childhood psychopathology in VCFS is associated with schizophrenia in adulthood. Second is whether the presence of a particular profile of childhood psycho-
pathology in the context of developmental disability is also possibly an indication of increased risk for adult-onset schizophrenia. Finally, if both premises turned out to be true, the implicated childhood psychopathology would be a sensitive, but nonspecific indicator of later schizophrenic outcome.

It is also possible that the measurement of childhood psychopathology obtained, either by utilizing DSM-IV categorical diagnoses or by the CBCL, will prove unproductive as a research strategy for identifying childhood phenotypic indicators of vulnerability to schizophrenia. In this regard, it is noteworthy that the New York Longitudinal Study found that neurocognitive findings and laboratory measures of attention (as distinguished from the parental reports of behavior problems utilized in our study) could be used to construct an “attention deviance” phenotypic indicator of high specificity. Unfortunately, even if it could be established that laboratory measurements of attention abnormalities were superior to reports of behavior for the purposes of our VCFS research, most forms of childhood behavior problems do not lend themselves to testing by laboratory procedures.

Finally, the possibility must be considered that children with VCFS are independently at high risk for both childhood behavior disorders and later-onset schizophrenia; however, the childhood behavior disorders in VCFS are not pertinent phenotypic indicators of schizophrenia. Other biologic data might prove more useful as a predictor of schizophrenia.

For example, Eliez and colleagues have recently demonstrated that high resolution brain magnetic resonance imaging can distinguish differences in brain structure between VCFS youngsters and normal, age-matched control subjects and also between subgroups of the youngsters with VCFS, based on the parental origin of the 22q11.2 micro-deletion (Eliez et al 2000). Such biologically based techniques could conceivably prove useful in the prediction of later vulnerability to schizophrenia in children with VCFS, although the generalizability of this finding to other group of children at high risk for schizophrenia remains speculative.

Most of the children with VCFS (as well as the control subjects) in our study have not entered the major risk period for adult onset psychosis. The prospective longitudinal follow-up of both VCFS subjects and matched control subjects into adulthood offers the greatest possibility of determining which, if any, of the behavioral indices will prove to be sensitive or specific indicators in childhood of high risk for schizophrenia in adulthood. In general, it now appears that longitudinal data will prove critical in delineating the risk for severe psychiatric disorder in adults.

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References


