Increased Basal Ganglia Volumes in Velo-Cardio-Facial Syndrome (Deletion 22q11.2)

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Background: This study evaluated differences in caudate volumes in subjects with velo-cardio-facial syndrome due to a 22q11.2 (22qDS) deletion. Because psychosis is observed in 30% of adult subjects with 22qDS, this neurogenetic disorder could represent a putative model for a genetically mediated subtype of schizophrenia.

Methods: Caudate volumes were measured on high-resolution magnetic resonance images in 30 children and adolescents with 22qDS and 30 gender- and age-matched normal comparison subjects.

Results: Caudate head volumes were increased in the 22qDS group independent of neuroleptic medications. Subjects with 22qDS also displayed an abnormal pattern of asymmetry in the anterior caudate, with left side greater than right.

Conclusions: Alterations in the basal ganglia circuitry have been implicated in learning, cognitive, and behavioral problems in children and therefore could be involved in the expression of the neurobehavioral phenotype expressed by subjects with 22qDS. Abnormal caudate volume is a neurodevelopmental feature shared with schizophrenia, further establishing 22qDS as a potential neurodevelopmental model for this disorder.

Key Words: Deletion 22q11.2, 22q11, velo-cardio-facial syndrome brain, caudate, MRI

Introduction

Recent clinical and neuroimaging studies (Feinstein and Eliez 2000) suggest that velo-cardio-facial syndrome and other 22q11.2 deletion–related syndromes (22qDS) could serve as a model for a genetically mediated sub-type of schizophrenia. Twenty to thirty percent of adult subjects diagnosed with 22qDS develop schizophrenia during childhood or early adulthood (Feinstein et al 2000). Children and adolescents with 22qDS show brain alterations that are similar to those observed in schizophrenia (Eliez et al 2000, 2001a, 2001b; Kates et al 2001; van Amelsvoort et al 2001). Typically, subjects with 22qDS have reduced parietal lobes and posterior fossa volumes (Eliez et al 2000, 2001c; Kates et al 2001), as well as possible decreases in temporal lobes (Eliez et al 2001b; Kates et al 2001; van Amelsvoort et al 2001); however, the caudate nucleus, a neuroanatomical structure altered in schizophrenia, has only recently been measured in two studies involving subjects with 22qDS (Sugama et al 2000; van Amelsvoort et al 2001). The first study (Sugama et al 2000) identified abnormal asymmetry of the caudate in a pediatric 22qDS sample (17 subjects with 22qDS and 15 control subjects). The second study (van Amelsvoort et al 2001) reported the absence of caudate volume differences in a small group of 10 adults with 22qDS compared to 13 intelligence quotient (IQ)-matched control subjects.

Studies measuring caudate volumes in early and adult-onset schizophrenic subjects (McCarley et al 1999; Wright et al 2000) have shown abnormal volumes of the caudate; however, results from the schizophrenia literature to date have been contradictory and are often confounded by the use of neuroleptics among study participants. Thus, we hypothesized that caudate volumes would be aberrant in 22qDS, although the directionality of the change (increase or decrease) could not be predicted a priori.

Methods and Materials

The sample consisted of children and adolescents with velo-cardio-facial syndrome (n = 30, mean age = 12.1 ± 3.8 years), confirmed using fluorescent in situ hybridization, and a group of control subjects (n = 30, mean age = 12.2 ± 4.4) who were matched individually for age and gender. Only two subjects with 22qDS were treated with neuroleptic drugs (for mood problems and psychosis, respectively) before magnetic resonance imaging (see Feinstein et al, in press for a clinical description of this sample). Control subjects were recruited by advertising in local newspapers and parent group newsletters, as well as among nonaffected siblings of children affected with identified genetic conditions (fragile X and Turner syndrome). A minimum IQ of 85 (one SD below the population mean) and absence of previous...
neurologic or psychiatric disorders were used as the inclusion criteria for control subjects. Intelligence quotient scores were obtained using the Wechsler scales of intelligence (WISC-III and WAIS-III). The average full-scale IQ was 69.5 ± 16.7 for the 22qDS group and 115.9 ± 11.6 for the control group. Written informed consent was received from children and parents under protocols approved by the Institutional Review Board of Stanford University. Magnetic resonance images were obtained using a GE-Signa 1.5 T scanner (General Electric, Milwaukee, WI). Coronal images were acquired with a three-dimensional volumetric radio frequency spoiled gradient echo with repetition time 1.5 T scanner (General Electric, Milwaukee, WI). Coronal images were acquired with a three-dimensional volumetric radio frequency spoiled gradient echo with repetition time 256, echo time 6 msec, flip angle = 45°, Number of exitation (NEX) = 1, matrix size = 256 × 192, field of view = 24 cm², slice thickness = 1.5 mm, 124 slices. Images were segmented and measured with the software BrainImage 4.29, Stanford University, Stanford, CA using methods described elsewhere (Reiss et al 1998). Caudate nuclei were drawn manually, then divided into head (HC) and body (BC) of the caudate by a coronal plane perpendicular to the AC–PC axis at the level of the anterior commissure. The posterior border of the caudate body was defined as the slice where the opening of the fourth ventricle was visible. (A detailed protocol is available from the authors upon request.) Inter-rater reliability (NBG, YL) for total caudate volume on 10 datasets was 0.98, as determined by the interclass correlation coefficient. Reliability measures for caudate subdivisions were 0.98 for the caudate head and 0.90 for the caudate body. After examining data for normality of distributions, a general linear model, with a significant .05 (two-tailed) threshold for statistical significance, was used to analyze the data. Caudate volumes were adjusted for whole-brain gray matter volumes (analysis of covariance). Repeated measures analysis of variance examining group × hemisphere interactions were used to detect changes in symmetry.

## Results

Overall brain gray matter was decreased in 22qDS [F(1,58) = 4.1, p < .05]. A comparison of adjusted caudate volumes revealed significant increases in the 22qDS group compared to control subjects (see Table 1). The differences in total caudate volumes were bilateral and driven by differences in the volume of the caudate head. Exploration of symmetry/asymmetry revealed that the total caudate was asymmetric [L > R; F(1,58) = 4.3, p < .05] in the 22qDS group as opposed to caudate symmetry observed in the control group. Similar to volumetric differences, this change in asymmetry was driven by the head of the caudate [F(1,57) = 4.7, p < .05] and not the body [F = 0.4, p = .5103]. The significance of the results did not change when analyzed without the two 22qDS subjects treated with neuroleptic drugs.

### Discussion

The alteration of the caudate head volume is consistent with our hypothesis but inconsistent with prior findings. Previous investigations did not find structural increases of the caudate when comparing subjects with 22qDS to control subjects (Sugama et al 2000; van Amelsvoort et al 2001). Several reasons could explain the discrepancy. First, the previous studies had smaller sample sizes and used comparison populations that were not composed solely of typically developing subjects or IQ-matched control subjects but rather included subjects with psychiatric (schizophrenia or mood disorders) or physical problems (e.g., growth hormone deficiency). Second, different analytical methods were used in each study, rendering the results incomparable. For example, for each subject, Sugama et al (2000) used a single axial slice area measurement of the head of the caudate “at the same level” of the brain, whereas van Amelsvoort et al (2001) did not separate the caudate into head and body, possibly missing and diluting a difference driven only by the head of the caudate.

The volumetric increase of the caudate found in the current study, with head increasing more than body, suggests that a rostro-caudal gradient in brain aberration.
could be an intrinsic feature of 22qDS. This is consistent with a previous observation in children with velo-cardiofacial syndrome (Eliez et al 2000; Kates et al 2001) of an anterior-to-posterior gradient of lobar volumes (relative enlargement of frontal regions and decrease of parietal lobes).

Structural alterations of the caudate have also been reported in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) as well as in subjects with schizophrenia. Therefore, the abnormal increase of the head of the caudate, potentially associated with functional deficit of the striatum, could be contributing to the increased risk for subjects with 22qDS to develop ADHD and schizophrenia. In addition to behavioral problems and psychosis, alterations in caudate volume or morphology may be associated with functional changes of the cortico-striatotegmental–thalamocortical circuit (Alexander et al 1990), resulting in cognitive deficits (Graybiel 2000; Middleton et al 2000). The output of the basal ganglia circuit is via the thalamus to motor associative regions, dorsolateral–prefrontal cortex implicated in language and complex reasoning, and limbic cortex involved in learning and long-term memory encoding (Middleton et al 2000).

In the future, functional imaging research using targeted paradigms will be needed to understand how increased caudate volumes in 22qDS may relate to abnormal patterns of brain activation, resulting in specific neurocognitive and behavioral features. Future studies on 22qDS should give special attention to the selection of comparison groups. In previous studies as well as the current study, the absence of two control groups, typically functioning healthy control subjects and IQ-matched control subjects, limits the interpretability of the relationship between morphologic alterations and the neurobehavioral phenotype characteristic of the disorder.

References


