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Receptive and expressive language in children with velocardiofacial syndrome

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RECEPTIVE AND EXPRESSIVE LANGUAGE IN CHILDREN WITH VELOCARDIOFACIAL SYNDROME

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ABSTRACT

RECEPTIVE AND EXPRESSIVE LANGUAGE IN CHILDREN WITH VELOCARDIOFACIAL SYNDROME

by Jennifer M. Marden

Velocardiofacial syndrome (VCFS) is a chromosomal disorder which results in craniofacial anomalies. Language and cognitive development are also affected, and this thesis examines the resulting profile of receptive and expressive language skills. Twenty children with VCFS between the ages of six and eighteen were given the Clinical Evaluation of Language Fundamentals – Third Edition (CELF-3) and the Wechsler Intelligence Scales for Children – Third Edition (WISC-III). The VCFS children were on average found to have severely delayed receptive language and moderately delayed expressive language. Previous findings of rote memory strengths and auditory processing weaknesses in VCFS were confirmed. WISC-III results showed moderate cognitive delay, with no significant difference between Verbal and Performance IQ. Considerable individual variation in language and cognitive skills were seen, and no affects of age were apparent.

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Chapter I: Introduction

A. Overview

Velocardiofacial syndrome (VCFS) is a chromosomal disorder which causes craniofacial anomalies and may also affect the speech, language, cognition, and psychological health of individuals with the disorder. While the craniofacial and speech aspects of VCFS are fairly well understood, the profile of receptive and expressive language skills in children with VCFS has not yet been systematically explored. This study examined the language skills of children with VCFS, and developed a profile of the linguistic strengths and weaknesses of the VCFS individual as he or she matures from the age of six to eighteen years old.

B. Brief Review of the Literature

VCFS is a genetic syndrome caused by a small deletion on chromosome 22 (Driscoll, Budarf, & Emanuel, 1992; Morrow et al., 1997; Shprintzen, 1994). The genes in the deleted region appear to control development of the embryonic neural crest (Hall & Hörstadius, 1988; LeDouarin, Ziller, & Couly, 1993). Adult structures which derive from the neural crest include the bones of the face and anterior skull, the palate, endocrine glands, and portions of the heart (Chieffo et al., 1997; Hall & Hörstadius, 1988; LeDouarin et al., 1993). These structures and others may be affected in individuals with VCFS. Some common VCFS findings are velopharyngeal insufficiency, cleft palate, submucous cleft, learning disabilities, mild to moderate cognitive delay, delayed language development,

and psychiatric conditions such as mood disorders and schizophrenia (Golding-Kushner, Weller, & Shprintzen, 1985; Lipson et al., 1991; Ryan et al., 1997; Shprintzen, Goldberg, Golding-Kushner, & Marion, 1992; Shprintzen et al., 1978; Swillen et al., 1997; Thomas & Graham Jr., 1997).

C. Problem of the Study

While research shows that language is clearly affected in VCFS, a profile of VCFS language skills has not been developed. Such a profile would have both scientific and practical applications. VCFS, with its combination of CNS, cognitive, linguistic, and psychological anomalies, presents a unique opportunity to examine the interaction among these factors in the developing child. On a more practical level, knowledge of the skills and deficits which children with VCFS may be expected to exhibit would aid teachers and speech-language pathologists in devising methods to accurately assess and effectively teach these children. Parents, families, and the VCFS children themselves would also be better able to cope with the disorder if they knew what to expect at each developmental stage of the child's life, and understood how to help the child compensate for deficits and capitalize on strengths.

D. Purpose of the Study

This study was intended to examine the relationship between expressive and receptive language skills in children with VCFS, as compared to those of normal children, and to those of children with various other language learning disabilities.

E. Questions of the Study

This study addressed the following questions:

1. Do the language skills of children with VCFS differ significantly from those of normally developing children of the same age?

2. Do the language skills of children with VCFS differ significantly from those of children of the same age who are diagnosed as language disordered?

3. Are there any unusual patterns of development in the language skills of children with VCFS as they develop from six to eighteen years of age?

F. Hypotheses of the Study

In order to answer the above questions, the following hypotheses were tested:

1. The receptive and expressive language skills of VCFS children are significantly delayed when compared to normal children of the same age. Language skill estimates for these children were obtained using data from the Clinical Evaluation of Language Fundamentals (CELF-3; Semel, Wiig, & Secord, 1995a) standardization sample which are published in the CELF-3 Technical Manual (Semel, Wiig, & Secord, 1995c).

2. The expressive language skills of VCFS children are significantly better than their receptive language skills.

3. The language skill profiles of children diagnosed with a language disorder (CELF-3 Total Language Score of 85 or less) differ significantly from the language skill profiles of children with VCFS. Language skill estimates for these

children were obtained using data from the CELF-3 discriminant analysis study which are published in the CELF-3 Technical Manual (Semel et al., 1995c).

4. As children with VCFS become older, their receptive and expressive language skills tend to fall behind as compared to those of normal children.

Chapter II: Review of the Literature

A. Introduction

Velocardiofacial syndrome was first delineated in 1978 (Shprintzen et al., 1978), when Shprintzen and colleagues noted a common cluster of findings among several patients at the Montefiore Medical Center Craniofacial Clinic. Since that time, a wide range of medical, cognitive, and psychosocial anomalies have been associated with VCFS. The phenotype of VCFS is variable in both its findings and its severity, with some individuals quite impaired in functioning, while others show few signs of the disorder (Devriendt et al., 1997b; Dinulos, Pagon, Sybert, & Hudgins, 1996; Ryan et al., 1997; Shprintzen et al., 1978; Stalkin et al., 1996; Yamagishi et al., 1998). Due to such variability it is difficult to establish the exact incidence of VCFS. Rates of 1 in 2,000 to 1 in 5,000 have been reported (Shprintzen, Shanske, Marion, & Goldberg, 1996; Thomas & Graham Jr., 1997).

B. Review of the Literature

Etiology of VCFS

As the above brief review of the literature has shown, the effects of VCFS are extensive. These widespread anomalies are caused by a microdeletion on chromosome 22, which affects the embryo at an early stage of development (Driscoll et al., 1992; Morrow et al., 1997; Shprintzen, 1994). The microdeletion is denoted "22q11.2", which indicates a deletion on the proximal portion of the

long arm of chromosome 22. VCFS is autosomal dominant. The 22q11.2 deletion is de-novo in approximately 70% of cases (Morrow et al., 1997; Swillen et al., 1997), but may be inherited from an affected parent (Ryan et al., 1997; Swillen et al., 1997).

The incidence of VCFS is relatively high, indicating a high rate of sporadic deletions at the same site on chromosome 22. Several studies have supported the view that this region of the human genome may be genetically unstable. Baumer et al. (1998) and Morrow et al. (1997) reported a larger than normal number of meiotic crossovers in the VCFS critical region. Puech et al. (1997) found that the mouse homologues of genes from a section of human chromosome 22 were located on three separate chromosomes in the mouse genome. The mouse homologues of the genes which are located inside the VCFS critical region were all found on a single mouse chromosome, but the order in which they appeared on the mouse chromosome was different from that of human chromosome 22. Puech et al. concluded that "the instability of the 22q11 region is not restricted to humans but may have been present throughout evolution." (1997, p. 14608).

The mechanism by which the 22q11.2 microdeletion causes the features of VCFS is not yet known. The microdeletion leaves a single copy of the genes in the deleted region available to the developing organism. This may lead to a decrease in the production of the proteins for which these genes code (Chieffo et al., 1997; Yamagishi, Garg, Matsuoka, Thomas, & Srivastava, 1999). If the single copy of a gene has a defect, the effect of the defect may be increased since it is unopposed by a second correct copy of the gene (Budarf et al., 1995).

Alternatively, changes in the architecture of chromosome 22 due to the microdeletion might cause problems by altering the location of genes relative to each other (Bedell, Jenkins, & Copeland, 1996; Dallapiccola, Pizzuti, & Novelli, 1996).

While the exact genetic mechanisms by which the features of VCFS are produced is not yet clear, observations based on animal experiments have given researchers clues as to which areas in the developing embryo are affected (Hall & Hörstadius, 1988; LeDouarin et al., 1993). Removal of portions of the neural crest at the level of the first three somites in chick embryos leads to craniofacial, endocrine, and cardiac malformations similar to those found in VCFS. These experiments have shown that the bones of the face and anterior portion of the skull are derived from the neural crest, while the posterior portion of the skull is derived from an embryonic layer called the mesoderm. The sphenoid bone, cochlea, and external auditory meatus are each partially derived from the mesoderm and partially from the neural crest (LeDouarin et al., 1993). The thymus and parathyroid glands are also neural crest derivatives (Chieffo et al., 1997). The developing heart is derived in part from the neural crest (Hall & Hörstadius, 1988). It has been postulated, based on these results, that VCFS is caused by a failure of neural crest cells to migrate to the correct location in the embryo, or to develop into the correct types of cells once they have reached their allotted destination (Hall & Hörstadius, 1988). The process of cell migration and differentiation is a vital but little understood component of embryonic development. The migrating neural crest cell is influenced by the point in time at

which it leaves the neural crest, the location from which it leaves the crest, substances in the extracellular space through which it moves, and substances on the surfaces of other cells with which it comes in contact (Bronner-Fraser, 1993; Hall & Hörstadius, 1988). Slight alterations in any of these factors may cause developmental anomalies such as VCFS to occur.

Several genes which lie in the VCFS critical region have been identified. Two of these genes appear to be involved in controlling embryonic cell migration and differentiation (Lindsay et al., 1996; Pizzuti et al., 1996; Sirotkin et al., 1996) . Other genes were reported to be expressed in the branchial arches, otic vesicle, medial telencephalon, aortic arch, and vertebral column of the developing embryo, all areas affected by VCFS (Chieffo et al., 1997; Yamagishi et al., 1999). The catechol-o-methyltransferase (COMT) gene which lies in the VCFS deleted region is of particular interest, because an allele of this gene has been implicated in a rapid-cycling form of bipolar disorder. If the remaining copy of the COMT gene has this particular allele, the person with VCFS would be predisposed to develop the disorder (Gogos et al., 1998; Lachman et al., 1996; Papolos, 1995). Another gene found in the VCFS critical region is expressed in a midline area of the embryonic pons which produces serotonin in the adult brain (Galili, Epstein, Leconte, Nayak, & Buck, 1998). Galili et al. stated that "These neurons are thought to coordinate complex sensory and motor patterns during varied behavioral states." (1998, p. 89).

VCFS is not the only syndrome associated with the 22q11.2 microdeletion. There are several other syndromes and anomalies with overlapping phenotypes

which appear to be caused by the same 22q11.2 microdeletion that causes VCFS. Differing opinions exist as to whether these are separate disorders, or different manifestations of the same disease mechanism (Shprintzen, 1994; Stevens, Carey, & Shigeoka, 1990; Wilson, Burn, Scambler, & Goodship, 1993). DiGeorge Syndrome (DGS) is the most common of this group of associated syndromes. Characteristics of DGS are thymic and parathyroid hypoplasia, hypocalcemia, congenital heart defects, and immune system disorders (Jones, 1997; Wilson et al., 1993). Also associated with 22q11.2 microdeletions are conotruncal anomaly face syndrome (Kitano et al., 1997), Robin sequence (Shprintzen, 1994), Cayler syndrome (Bawle, Conard, Van Dyke, Czarnecki, & Driscoll, 1998; Rauch et al., 1998), Potter sequence (Devriendt, Moerman, Van Schoubroeck, Vandenberghe, & Fryns, 1997a), and Opitz syndrome (McDonald-McGinn et al., 1995a; McDonald-McGinn et al., 1995b; Robin et al., 1995).

Craniofacial Findings

Overt clefts of the secondary palate (Ryan et al., 1997; Shprintzen et al., 1978; Thomas & Graham Jr., 1997), submucous clefts (Ryan et al., 1997; Shprintzen et al., 1978), hypoplastic velum (Shprintzen et al., 1978), and short velum (Haapanen & Somer, 1993) are frequent craniofacial findings. Clefts of the hard palate and lip, although reported by Kozma (1998), appear to be rare. VCFS is believed to be the most common syndrome associated with clefting. The Montefiore Medical Center Craniofacial Clinic reported that 8% of cleft palates

without cleft lip were found to be caused by VCFS (Goldberg, Motzkin, Marion, Scambler, & Shprintzen, 1993).

A striking feature of VCFS is its characteristic facies (Goldberg et al., 1993; Lipson et al., 1991; Ryan et al., 1997; Shprintzen et al., 1978; Thomas & Graham Jr., 1997). The maxillae are often longer than normal, making the face appear to be unusually long. The face may also have a hypotonic, flaccid expression. The malar area is often flattened, and the mandible may be retruded, causing a class II malocclusion (Shprintzen et al., 1978). The nose tends to have a squared nasal root, bulbous nasal tip, and narrow nostrils and alar base. A bifid nasal tip has also been reported (Kirkpatrick & Pauli, 1998), and the palpebral fissures may be narrow and downward slanting.

Velopharyngeal insufficiency (VPI) occurs quite frequently with VCFS, even when the velum is intact and of normal length, thickness, and mobility (Lipson et al., 1991; Shprintzen et al., 1978; Thomas & Graham Jr., 1997; Zori et al., 1998). This tendency towards VPI is due to platybasia (an abnormally flat, wide skull base) which is found frequently in VCFS (Goldberg et al., 1993; Seines, Ross, & Siegel-Bartelt, 1997). The increased skull base area causes the pharynx to be deeper than is normal, such that a normal velum might not be able to make complete contact with the posterior pharyngeal wall. Compounding this problem, the lateral pharyngeal walls may be hypotonic, and thus may not be able to aid in velopharyngeal closure by moving inward (Shprintzen et al., 1978; Thomas & Graham Jr., 1997). Hypoplastic adenoids may also occur, increasing

the area which the velum must cover in order to achieve complete closure (Goldberg et al., 1993).

This disordered velopharyngeal mechanism was found to cause hypernasal speech and compensatory articulation errors (Shprintzen et al., 1978), and nasal regurgitation during feeding (Lipson et al., 1991). Authorities differ with respect to the efficacy of pharyngoplasty in achieving velopharyngeal closure, with some studies reporting high success rates (Lipson et al., 1991), and others low rates (Haapanen & Somer, 1993). Also, anomalies of the internal carotid arteries are sometimes found which place the arteries at increased risk of damage during pharyngoplasty surgery (Goldberg et al., 1993).

The muscles of the hypopharynx may also be poorly coordinated, leading to dysphagia, gastroesophageal reflux, and nasal regurgitation (Zackai et al., 1996). Anomalies have also been found in the larynx and trachea: laryngomalacia (Ryan et al., 1997; Shprintzen et al., 1996), laryngeal webs (Fokstuen et al., 1997; Ryan et al., 1997; Stoler, Ladoulis, & Holmes, 1998), and subglottal stenosis (Fokstuen et al., 1997) have occasionally been reported.

Other Physical Findings

The effects of VCFS are not confined to the craniofacial area, but can occur throughout the body. Congenital heart defects and anomalies of the internal carotid arteries are common findings (Ryan et al., 1997; Shprintzen et al., 1978; Thomas & Graham Jr., 1997). Midline structures of the endocrine system may be affected: hypoplastic thymus (leading to immune system dysfunctions) and

hypoplastic parathyroid glands (which may cause hypocalcemia and epilieptic seizures) (Ryan et al., 1997; Wilson et al., 1993).

Pneumonia and bronchitis have been found to be common in VCFS children under the age of six (Cunningham, Weiner, & Shprintzen, 1997). Short stature is a common VCFS feature (Ryan et al., 1997; Thomas & Graham Jr., 1997), with some children exhibiting a growth hormone deficiency (Weinzimer et al., 1998). Skeletal anomalies may also be present. Slender, tapered fingers with small nails are frequently seen (Shprintzen et al., 1978; Thomas & Graham Jr., 1997).

Abnormalities of the cervical and thoracic vertebrae have been observed, as well as extra pairs of ribs (Kirkpatrick & Pauli, 1998; Ming et al., 1996; Ryan et al., 1997; Siegel-Bartelt & Armstrong, 1997). Loose joints and joint dislocation have been reported (Shprintzen et al., 1996), and juvenile rheumatoid arthritis was recently found to be an occasional feature of VCFS (Sullivan et al., 1997). Hypotonia, especially during infancy and childhood, is frequently seen (Moss et al., 1995; Shprintzen et al., 1978; Thomas & Graham Jr., 1997). Hypoplastic or missing kidneys have been noted (Ryan et al., 1997; Stewart, Irons, Cowan, & Bianchi, 1997), and chronic constipation occurred in some children and young adults (Shprintzen et al., 1996). Spontaneous oxygen desaturation has also been reported (Shprintzen et al., 1996).

Central Nervous System Findings

A higher than normal rate of central nervous system abnormalities have been found in individuals with VCFS. Small head circumference has been noted by some authors (Golding-Kushner et al., 1985; Ryan et al., 1997). Cerebellar hypoplasia has been seen in several CT and MRI studies (Devriendt, Van Thienen, Swillen, & Fryns, 1996; Lynch et al., 1995; Mitnick, Bello, & Shprintzen, 1994; Ryan et al., 1997; Vataja & Elomaa, 1998). The brainstem has been found to be smaller than normal in some cases (Lynch et al., 1995), and in one such case, the pons was the most affected area of the brainstem (Galili et al., 1998). Anomalies of the ventricles have also been reported: enlarged ventricles (Devriendt et al., 1996; Ryan et al., 1997), asymmetric ventricles (Haapanen & Somer, 1993), cysts near the frontal horns of the lateral ventricles (Mitnick et al., 1994), and cysts in the septum pellucidum (Haapanen & Somer, 1993; Ryan et al., 1997; Vataja & Elomaa, 1998). The cerebral cortex may also be affected by VCFS. Cerebral and cerebrovascular anomalies were reported in a survey conducted by Ryan et al. (1997), but the descriptions of these anomalies were not available. Bingham et al. (1997) found that the right and left Sylvian fissures of infants with VCFS were enlarged, when compared with those of normal infants. In the same study, the right sylvian fissures of adults with VCFS were of near normal size, but the left sylvian fissures, though smaller than those of the VCFS infants, were still larger than those of normal control adults. The authors postulated that growth of the perisylvian cortex and underlying white matter might be delayed or decreased in individuals with VCFS. Some white matter anomalies have been

reported in VCFS subjects: hypoplastic corpus callosum (Ryan et al., 1997), and focal white matter lesions consistent with demyelination (Altman, Altman, Mitnick, & Shprintzen, 1995; Lynch et al., 1995). Calcification of the basal ganglia was also noted in one patient who exhibited white matter demyelination (Lynch et al., 1995). Epileptic seizures are not uncommon (Haapanen & Somer, 1993); however they are usually caused by hypocalcemia secondary to hypoparathyoidism rather than being the result of structural abnormalities (Ryan et al., 1997). Three cases of VCFS and meningomyelocele have been reported (Nickel et al., 1994), but its incidence in VCFS appears to be rare.

The reports of CNS anomalies are especially interesting in the context of the psychiatric, cognitive, and linguistic findings in VCFS which are described below. However, CT and MRI studies of VCFS are still in their early stages, and sample sizes in these studies have been small, so these results, while intriguing, are not yet conclusive.

Psychiatric Findings

Several studies have found an increased incidence of psychological disorders in the VCFS population. There have been reports of late-onset schizophrenia in adolescents and young adults with VCFS (Chow, Bassett, & Weksberg, 1994; Murphy & Owen, 1997; Ryan et al., 1997; Shprintzen et al., 1992; Siegel-Bartelt, Arnold, Cytrynbaum, Teshima, & Schachar, 1996; Thomas & Graham Jr., 1997; Vataja & Elomaa, 1998). From a reverse perspective, studies have shown a higher than expected incidence of VCFS in the schizophrenic

population (Bassett et al., 1998; Chow et al., 1998; Gothelf et al., 1997; Yan et al., 1998). Mood disorders such as depression (Murphy & Owen, 1997; Ryan et al., 1997; Siegel-Bartelt et al., 1996; Swillen et al., 1997) and a rapid-cycling form of bipolar disorder (Lachman et al., 1997; Lachman et al., 1996; Murphy & Owen, 1997; Papolos et al., 1996) are unusually frequent among those with VCFS, as are anxiety disorders (Swillen et al., 1997).

People with VCFS often present with very bland affect and lack of facial expression, even though they are physiologically capable of producing varied facial expressions (Golding-Kushner et al., 1985). They tend towards behavioral extremes, either being passive and hypoactive, or disinhibited and hyperactive (Golding-Kushner et al., 1985). This disinhibited behavior may cause difficulties with socialization, and oppositional defiant disorder (ODD) has been noted in the VCFS population (Siegel-Bartelt et al., 1996). Attention deficit and hyperactivity disorders are frequent findings (Haapanen & Somer, 1993; McCandless, Scott, & Robin, 1998; Papolos et al., 1996; Ryan et al., 1997; Siegel-Bartelt et al., 1996; Swillen et al., 1997). One case of autism was reported in a child with VCFS (Kozma, 1998), but this appears to be a rare finding.

Cognition and Learning Disabilities

Learning disabilities have been noted to some degree in almost all cases of VCFS (Murphy, Jones, Griffiths, Thompson, & Owen, 1997). Mild to moderate developmental delay was often found, though individuals with normal cognitive development were not uncommon (Kok & Solman, 1995; Lipson et al., 1991;

Moss et al., 1999; Ryan et al., 1997; Thomas & Graham Jr., 1997). Severe developmental delay was found to be rare, but has been reported (Devriendt et al., 1996; Kozma, 1998). In a cross-sectional study of VCFS children aged six to eighteen years (Golding-Kushner et al., 1985), both verbal and performance IQ appeared to decrease in older children, as measured by the Wechsler Intelligence Scales for Children–Revised (WISC-R; Wechsler, 1974). The authors observed that the WISC-R measured increasingly more abstract reasoning skills in older children, and postulated that VCFS children might have difficulty with abstract concepts, while exhibiting normal skills with the more concrete concepts emphasized in WISC-R tests for younger children. Among children eleven to eighteen years old in the same study, the average verbal IQ was nine points higher than the average performance IQ, although the authors noted that the small sample size in that age range made the results statistically insignificant. However, some recent studies have supported this result (Golding-Kushner et al., 1985; Haapanen & Somer, 1993; McCandless et al., 1998; Moss et al., 1995; Moss et al., 1999; Swillen et al., 1997). Swillen et al. (1997) and Moss et al. (1999) theorized that the discrepancy between verbal and performance IQ was due to specific deficits in visual-spatial skills, which depressed scores on WISC–R performance subtests. Other studies found that VCFS subjects had poor problem solving and generalization skills (Kok & Solman, 1995), and difficulties in the areas of mathematics (Golding-Kushner et al., 1985; Kok & Solman, 1995; Moss et al., 1999; Shprintzen et al., 1978), visual-spatial skills (Vataja & Elomaa, 1998), and visual-motor coordination (Haapanen & Somer, 1993; Shprintzen et al.,

1978). Motor developmental milestones were generally found to be delayed (Golding-Kushner et al., 1985; Ryan et al., 1997; Swillen et al., 1997), and poor fine motor skills were also reported (Shprintzen et al., 1978).

The academic skills of children with VCFS have not been extensively studied. Kok and Salmon (Kok & Solman, 1995) noted that children with VCFS tend to have poor phonemic awareness. Moss et al. (1999) found that the average spelling and reading scores obtained by children with VCFS on the Wechsler Individual Achievement Test (WIAT; Wechsler, 1992) were within the normal range, and were significantly higher than their average math reasoning and rote calculation scores. Golding-Kushner et al. (1985) examined the academic skills of VCFS children using the Wide Range Achievement Test (WRAT; Jastak, Bijou, & Jastak, 1978) and the Peabody Individual Achievement Test (PIAT; Dunn & Markowardt, 1970). The results indicated that the childrens' skills in sight reading and spelling exceeded their skills in reading comprehension and arithmetic. The authors summarized their impressions in this way:

> "[Reading comprehension and arithmetic] are skills that can not be learned by rote and require higher levels of abstraction. The children with VCF seem to be unable to extract the process learned for application to novel stimuli. In the sample population, reading comprehension and mathematical abilities were disproportionately below language abilities. This is well illustrated by a report on a high school student with VCF from his teacher: 'His memory is good but he just can't get the concepts.'" (Golding-Kushner et al., 1985, p. 263).

This difficulty with abstract concepts appears to include pragmatics and social skills (Fuerst, Dool, & Rourke, 1995; McCandless et al., 1998). Many children with VCFS must be taught both academic and social skills in a very

structured and direct manner, because it is difficult for them to infer rules, routines, and concepts from the interactions they observe (Landsman, 1996; Marchette, 1997).

Fuerst et al. (1995) theorized that nonverbal learning disability (NLD) was a consistent feature of VCFS. In NLD, verbal IQ exceeds performance IQ by ten or more points. Other characteristics which NLD and VCFS may share are hypotonia, delayed motor developmental milestones, poor visuospatial and visuomotor skills, good rote verbal memory, concrete thinking, and difficulties with abstract concepts, mathematics, general problem solving. Both groups also have higher than normal rates of social skill problems, depression, and attention and hyperactivity disorders (Rourke & Tsatsanis, 1996). However, the receptive and expressive language delays and reading comprehension deficits which are commonly seen in VCFS are not features of NLD (Fuerst et al., 1995).

Speech and Language Findings

As might be expected with any syndrome which combines cognitive and motor delays, onset of speech and development of language were also found to be delayed in many studies (Golding-Kushner et al., 1985; Haapanen & Somer, 1993; Lipson et al., 1991; Moss et al., 1999; Ryan et al., 1997; Swillen et al., 1997). Hypernasality and nasal emission were found in all subjects studied by Golding-Kushner et al. (1985) and Lipson et al. (1991). Speech intelligibility was also decreased, and the children with VCFS were at high risk of developing compensatory articulation patterns often associated with VPI.

Delayed language developmental milestones were reported by parents in studies conducted by Swillen et al. (1997), Haapenen and Somer (1993), and Ryan et al. (1997). Golding-Kushner et al. (1985) examined the language skills of VCFS children using academic and vocabulary tests. For children ages three to six years, a mean standard score of 84 was achieved on the Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 1981). This score indicated that on average, the childrens' receptive vocabulary was in the low-normal range. The standard scores ranged from 33 to 119. Examiners noted additional signs of language delay in the children's conversational skills, including reduced responsiveness to questions and excessive reliance on nonverbal communication, even when speech was of adequate intelligibility. Language skills in VCFS children aged six to ten years were for the most part more delayed than those of the younger group of VCFS children. The mean PPVT score for the older children was 75, with a range of 18 to 87, indicating a severe delay in receptive vocabulary. Scores on the Illinois Test of Psycholinguistic Abilities (ITPA; Kirk, McCarthy, & Kirk, 1969) also declined when compared with the younger childrens' scores, especially on subtests which required abstract reasoning. The syntax of the six to ten year old group was found to be immature, with reduced expressive vocabulary predominated by concrete words and concepts. The degree of language delay was not found to correlate with the incidence of otitus media or other hearing loss. Children in the eleven to eighteen year old group had an average PPVT score of 82, showing borderline normal receptive

vocabulary. The small sample size of this last group made interpretation of their results difficult to extrapolate to the larger VCFS population.

In a more recent study, Moss et al. (1999) administered the CELF-R and WISC-III to twenty children with VCFS. The average Receptive Language score was 70.6 and the average Expressive Language score was 66.4. The Expressive Language score was found to be significantly below the average Verbal IQ score of 78.1, indicating an expressive language impairment.

Audiological Findings

The outer, middle, and inner ear may be affected by VCFS. The outer ear may be small, cup-shaped, or have overfolded helices (Thomas & Graham Jr., 1997), and the external auditory meatus may be narrow (Lipson et al., 1991). Both conductive and sensorineural hearing losses have been reported, as well as an increased incidence of otitus media in childhood (Cunningham et al., 1997; Ryan et al., 1997; Shprintzen et al., 1996; Thomas & Graham Jr., 1997). Auditory processing problems have been reported anecdotally, but no formal research findings are currently available on the central auditory processing capabilities of VCFS children (Landsman, 1996; Shprintzen, 1997).

C. Summary

VCFS is a genetic disorder which disrupts development of the embryonic neural crest. This disruption may cause heart defects, craniofacial anomalies, central nervous system abnormalities, cognitive delays, learning disabilities, and

psychiatric disorders. Language development also appears to be adversely affected, though further research is needed to determine the characteristics typical of VCFS language skills over the lifetime of the individual.

Chapter III: Methodology

A. Introduction

This study employed a cross-sectional design, and utilized standardized language and intelligence tests to gather data from VCFS and control subjects.

B. Subjects

Twenty children, ages six to eighteen, with confirmed diagnoses of VCFS and 22q11.2 microdeletion were assessed. Subjects were recruited by Stanford University Medical Center, using the records of children with VCFS who had been treated by the craniofacial center at Lucille Salter Packard Children's Hospital, and from the VCFS Educational Foundation, which is a family support group. After providing a complete description of the study to the subjects and their parents, written informed consent was obtained under protocols approved by the Institutional Review Boards of Stanford University and San Jose State University.

C. Instrumentation

Receptive and expressive language skills were measured using the Clinical Evaluation of Language Fundamentals, Third Edition (CELF-3; Semel et al., 1995a). Cognition was measured using the Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R; Wechsler, 1989) for children aged six – seven years; the Wechsler Intelligence Scales for Children, Third Edition (WISC-III; Wechsler, 1991) for children aged eight to 17 years; and the Wechsler Adult

Intelligence Scale – Revised (WAIS-R; Wechsler, 1981) for eighteen year old subjects.

D. Research Procedures

All testing was conducted at Stanford University Medical Center's Department of Psychiatry and Behavioral Sciences. The author administered and scored the CELF-3, and the WPPSI-R, WISC-III, or WAIS-R was administered and scored by a research psychologist on the staff of the Department of Psychiatry and Behavioral Sciences. Medical and educational records were provided by the parents of the subjects. These records were examined by the author, who compiled a database of language and academic test results.

E. Data Collection Method

Standardized tests were used to gather data from VCFS subjects. Data for normal subjects were obtained from the standardization sample for the CELF-3, as published in the CELF-3 Technical Manual (Semel et al., 1995c). Data for language disordered subjects were obtained from the CELF-3 discriminant analysis study, also published in the CELF-3 Technical Manual.

In order to obtain information regarding the developmental patterns of language skills, medical and educational records of the VCFS subjects were reviewed, and scores of standardized tests of language and academic achievement found in these records were utilized.

F. Statistical Design

A cross-sectional design was used for this study, with VCFS subjects aged six to eighteen years being assessed. The VCFS data were compared to the CELF-3 standardization sample, which was also studied using a cross-sectional design.

Statistical analysis was performed using the StatView statistical analysis package. The following statistical tests were used to evaluate the study hypotheses:

Hypothesis 1: A Student "t" test was performed to test the hypothesis that the mean Receptive Language Score (RLS), Expressive Language Score (ELS), and Total Language Score (TLS) of the VCFS sample were each less than 100 (which is the mean RLS, ELS, and TLS of the CELF-3 standardization sample).

Hypothesis 2: The CELF-3 Examiner's Manual and Technical Manual (Semel, Wiig, & Secord, 1995b; Semel et al., 1995c) provides data on the prevalence of various ELS – RLS differences in the CELF-3 standardization sample, and recommends that any ELS – RLS difference obtained by less than 5 – 10% of the standardization sample can be considered both statistically and clinically significant. The CELF-3 results for each individual subject were assessed for statistical and clinical significance using this method. In addition, a Student "t" test was computed to test the null hypothesis that the mean RLS and ELS for the VCFS population were equal.

Hypothesis 3: The CELF-3 Technical Manual provides the average subtest and composite scores and standard deviations for a sample of 136 children diagnosed as language disordered according to their school districts' criteria. This information was used to calculate Student "t" tests for the null hypothesis that there was no significant difference between the mean subtest and composite scores of the general language disordered population and those of the VCFS population.

Hypothesis 4: ELS, RLS, and TLS data from the CELF-3 administration conducted as part of this study were examined for correlation with the subject's age. Additional administrations of the CELF-3 and CELF-R were found in some subjects' academic or medical records. The sample sizes for scores obtained from subjects' records were too small for statistical significance, but this data was charted to see if any interesting trends appeared to exist.

Chapter IV: Results

A. Introduction

Results of assessments conducted in this study showed that, on average, the children with VCFS had moderate to severe language delays. The results also indicated that the VCFS children had a profile of linguistic strengths and weaknesses which differed significantly from the language profiles of other language disordered children

The data analysis will be presented in several sections. First, data from CELF-3 and WISC-III tests administered at Stanford University as part of this study will be examined. Next, subgroups of the sample will be examined to determine the effects of age, gender, and other factors. Last, data gathered from previous assessments of some of the VCFS subjects will be presented.

B. CELF-3 and WISC-III Assessments

CELF-3 Results

CELF-3 data obtained by direct testing of VCFS subjects is shown in Table 1. The CELF-3 data indicated that, on average, VCFS children in this study had a Receptive Language score (RLS) of 66.85, which was more than two standard deviations below the mean for the CELF-3 standardization sample, and indicated a severe receptive language delay. The average Expressive Language score (ELS) of 71.5 fell at the low end of the moderate expressive language delay range, as defined in the CELF-3 Examiner's Manual (Semel et al., 1995b, p. 106). The

average Total Language score (TLS) of 68.15 also indicated a severe language delay. Forty-five percent of the subjects were diagnosed as having severe delays in both expressive and receptive language, while only 20% of the subjects were judged to be within normal limits both expressively and receptively.

Table 1.

VCFS CELF-3 Composite Scores

CELF-3 Composite Scores	Mean	Standard Deviation	Minimum	Maximum
Receptive Language Score	66.850	17.682	50.000	100.000
Expressive Language Score	71.500	20.585	50.000	104.000
Total Language Score	68.150	18.596	50.000	102.000
Expressive – Receptive Language Scores	4.650	9.040	-14.000	23.000

Table 2.

VCFS Expressive Language and Receptive Language Diagnoses

		Expressive Language Diagnosis			
	Severity	No delay	Mild delay	Moderate delay	Severe delay
Receptive Language Diagnosis	No delay	20%			
	Mild delay	10%			
	Moderate delay				5%
	Severe delay	5%	10%	5%	45%

The average difference between expressive and receptive language scores was 4.65 points. This difference was statistically significant as shown by results of the Student "t" and Wilcox signed rank tests (Table 3). However, according to the CELF-3 Technical Manual (Semel et al., 1995c), an ELS – RLS difference does not become clinically significant until it is at least 19 points. A 19 point gap is significant because only 10% of the CELF-3 standardization sample obtained a difference of that magnitude. Four VCFS test subjects (20% of the sample) obtained an ELS that was 19 or more points higher than their RLS. While this was twice the rate at which such differences would be expected to occur, χ^2 analysis indicated that it was not statistically significant ($p = 0.25$). However, the VCFS subjects did appear to show consistent strength in ELS scores when compared to the patterns found in the CELF-3 standardization sample. The CELF-3 Technical Manual states that "fewer than 7% of the standardization sample showed no difference [between RLS and ELS]; about half of all examinees earned higher Receptive Language scores and about half earned higher Expressive Language scores" (Semel et al., 1995c, p. 56). In contrast, 10% of the VCFS subjects obtained an RLS larger than their ELS (by an average of 8 points) and 55% had an ELS larger than their RLS (by an average of 10 points.) χ^2 analysis showed that this result was statistically significant ($p < 0.005$).

Table 3.

Student "t" and Non-parametric Tests Comparing VCFS Expressive and Receptive Language Scores

Paired t-test
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value
Expressive, Receptive	4.650	19	2.300	.0329

Wilcoxon Signed Rank Test for Expressive, Receptive

# 0 Differences	7
# Ties	4
Z-Value	-2.446
P-Value	.0144
Tied Z-Value	-2.451
Tied P-Value	.0142

Wilcoxon Rank Info for Expressive, Receptive

	Count	Sum Ranks	Mean Rank
# Ranks < 0	2	10.500	5.250
# Ranks > 0	11	80.500	7.318

CELF-3 Subtest Profile

Table 4 shows the performance of the VCFS subjects on the CELF-3 subtests. It can be seen that the scores were not uniform across all subtests. The Recalling Sentences scores were higher than all other subtests while the Semantic Relationships scores were lower than all other subtests. Table 5 shows Student "t" and Wilcox signed rank tests comparing Recalling Sentences and Semantic Relationships scores. Recalling Sentences is an expressive test while Semantic Relationships is a receptive test, so these scores may help account for the ELS – RLS differences seen in VCFS subjects. In Recalling Sentences, the subject is required to repeat sentences of increasing length and complexity. This subtest stresses rote memory for auditorally presented information, but requires little processing of the information. Semantic Relationships, on the other hand, requires significant processing of auditorally presented information. Statements and questions are read to the subject, who must indicate which two out of four written answers are correct. The average Recalling Sentences score of 6.5 and Semantic Relationships average score of 5.0 were both well below the mean of 10 for the CELF-3 standardization sample, implying that rote auditory memory and auditory processing skills were both below normal when compared to the CELF-3 standardization sample. However, rote memory appeared to be a relative strength for VCFS children. This tendency was also noted by Golding-Kushner et al. (1985).

Table 4.

VCFS CELF-3 Subtest Scores

CELF-3 Subtest	Mean	Standard Deviation	Minimum	Maximum
Concepts and Directions	5.700	3.114	3.000	12.000
Word Classes	5.600	2.162	3.000	9.000
Semantic Relationships	5.000	2.598	3.000	11.000
Formulated Sentences	5.750	2.468	3.000	11.000
Recalling Sentences	6.500	3.749	3.000	14.000
Sentence Assembly	5.824	2.963	3.000	11.000

Table 5.

Student "t" and Non-parametric Tests Comparing VCFS Recalling Sentences and Semantic Relationships Scores

Paired t-test
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value
Semantic, Recall	-1.765	16	-3.922	.0012

Wilcoxon Signed Rank Test for Recall, Semantic

# 0 Differences	7
# Ties	3
Z-Value	-2.803
P-Value	.0051
Tied Z-Value	-2.820
Tied P-Value	.0048

3 cases were omitted due to missing values.

Wilcoxon Rank Info for Recall, Semantic

	Count	Sum Ranks	Mean Rank
# Ranks < 0	0	0.000	•
# Ranks > 0	10	55.000	5.500

3 cases were omitted due to missing values.

Comparison with Language Disordered Sample

In order to determine if there were significant differences between the language profiles of VCFS children and other children with language disorders, the VCFS CELF-3 data were compared with data from a study of language disordered children conducted by the developers of the CELF-3. This study examined 136 children who had been diagnosed as language disordered by their school district, and who were enrolled in language treatment programs at the time of testing. The means and standard deviations for all CELF-3 subtest and composite scores obtained by the language disordered children were published in the CELF-3 Technical Manual. Table 6 shows the results of Student "t" tests comparing the VCFS results with the means of the language disordered sample. Note that all VCFS means were lower than language disordered means, except for Recalling Sentences. Language disordered children received their lowest scores on Recalling Sentences, while this was the VCFS children's highest scoring subtest. The Word Classes and Semantic Relationships subtests were significantly lower for VCFS children when compared to the language disordered sample ($p < .01$). Sentence Assembly was also significantly lower ($p < .05$), and Concepts and Directions and Formulated Sentences approached significance ($p < .06$).

Examining the composite scores, the author found that the language disordered children's RLS was greater than their ELS by an average of 2.5 points, while VCFS children's ELS was higher than their RLS by an average of 4.65 points. This result was not statistically significant, however. The average VCFS

RLS was significantly lower than the RLS of the language disordered children ($p < .01$), while the ELS of both groups did not differ significantly. This implied that the VCFS children had expressive language skills similar to those of other language disordered children, while their receptive language skills lag behind those of the language disordered sample.

Table 6.

Student "t" Tests Comparing CELF-3 Scores from VCFS and Language Disordered Samples

CELF-3 Score	VCFS Mean	Language Disordered Mean	P-Value
Receptive Language Score	66.850	81.1	.0019 **
Expressive Language Score	71.500	78.6	.1394
Total Language Score	68.150	78.6	.0211 *
Expressive Language – Receptive Language	4.650	2.5	.3008
Concepts and Directions	5.700	7.1	.0588
Word Classes	5.600	7.4	.0014 **
Semantic Relationships	5.000	7.1	.0042 **
Formulated Sentences	5.750	6.9	.0509
Recalling Sentences	6.500	6.4	.9063
Sentence Assembly	5.824	7.5	.0330 *

*$p < .05$. **$p < .01$.

Age and Gender Effects

Table 7 shows the correlation matrix between subject age and CELF-3 composite scores. No statistically significant correlations were found. It was not possible to determine the effect of gender, as females made up only 30% of the VCFS sample.

Table 7.

Correlation of Age and CELF-3 Composite Scores in VCFS Sample

Correlation Matrix

	Test Age	Receptive	Expressive	Total Lang.	ELS - RLS
Test Age	1.000	.010	.053	.056	.100
Receptive	.010	1.000	.899	.971	.092
Expressive	.053	.899	1.000	.976	.518
Total Lang.	.056	.971	.976	1.000	.324
ELS - RLS	.100	.092	.518	.324	1.000

20 observations were used in this computation.

WISC-III Results

Table 8 show the results of the WISC-III assessments. These results indicated that, on average, the VCFS children had a Verbal IQ (VIQ) of 72.062, a Performance IQ (PIQ) of 71.0, and a Full Scale IQ (FSIQ) of 69.125, suggesting a moderate degree of cognitive delay. This study did not replicate the findings of previous studies which found VCFS children's VIQ to be significantly greater than their PIQ (Golding-Kushner et al., 1985; Haapanen & Somer, 1993;

McCandless et al., 1998; Moss et al., 1995; Moss et al., 1999; Swillen et al., 1997). The findings of Moss et al. (1999) that VIQ was significantly higher than the CELF-R Total Language and Expressive Language scores were also not replicated.

Table 8.

WISC-III Composite Scores from VCFS Sample

WISC-III Composite Scores	Mean	Standard Deviation	Minimum	Maximum
Verbal IQ	72.062	16.118	46.000	94.000
Performance IQ	71.000	14.774	47.000	93.000
Full Scale IQ	69.125	15.866	42.000	88.000
Verbal IQ – Performance IQ	1.062	8.218	-12.000	18.000

An examination of the WISC-III subtest results showed another distinctive pattern of VCFS strengths and weaknesses (see Table 9). VCFS subjects scored significantly higher on the Digit Span subtest than the Arithmetic subtest (see Table 10). The Digit Span test requires the subject to repeat increasingly longer series of digits, and thus stresses rote memory, as does the Recalling Sentences subtest of the CELF-3. The most difficult subtest for VCFS subjects was

Arithmetic, confirming previous findings of mathematical skill deficits associated with VCFS (Golding-Kushner et al., 1985; Kok & Solman, 1995; Moss et al., 1999; Shprintzen et al., 1978). No statistically significant correlations between WISC-III performance and age were found.

Table 9.

WISC-III Subtest Scores from VCFS Sample

WISC-III Subtest	Mean	Standard Deviation	Minimum	Maximum
Picture Completion	5.353	3.622	1.000	11.000
Information	4.882	2.472	1.000	9.000
Coding	5.765	3.308	1.000	12.000
Similarities	5.647	3.258	1.000	10.000
Picture Arrangement	5.176	3.644	1.000	13.000
Arithmetic	4.471	2.764	1.000	9.000
Block Design	5.294	3.368	1.000	11.000
Vocabulary	5.000	3.240	1.000	11.000
Object Assembly	4.625	2.473	1.000	9.000
Comprehension	5.294	3.236	1.000	10.000
Symbols	4.600	2.640	1.000	9.000
Digit Span	7.125	3.304	1.000	12.000

Table 10.

Student "t" Test Comparing WISC-III Digit Span and Arithmetic Subtests from VCFS Sample

Paired t-test, Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value
Dig.Span, Arithmetic	2.625	15	3.656	.0023

C. Higher Scoring VCFS Subgroup

A significant subgroup (35%) of the VCFS subjects obtained RLS, ELS, and TLS scores of 50, the minimum score possible on the CELF-3. For these children, the CELF-3 was not a sensitive enough test instrument to determine their strengths as well as their weaknesses. Additional statistical analysis was therefore conducted using only those subjects who scored greater than 50 on the ELS and RLS scales. The average age of the entire VCFS group was 11.95, and the average age of the higher scoring subgroup was 11.615, a difference of only four months. The male/female ratios of the main group and subgroup were the same.

Table 11 shows the CELF-3 composite scores for this subgroup, and Table 12 shows the statistical significance tests for the ELS – RLS difference. On average, the higher scoring subgroup's ELS of 82.846 and RLS of 75.923 gave them a diagnosis of moderate receptive and expressive language delay. The general language profile was similar to that of the entire group of VCFS subjects, with some findings becoming more statistically significant. The average ELS – RLS difference was 6.923, and was statistically significant ($p < 0.05$), but was still not clinically significant. Thirty-one percent of the subgroup had an ELS at least 19 points higher than their RLS. This was three times the rate of such ELS - RLS differences found in the CELF-3 standardization sample. χ^2 analysis showed this result to be statistically significant ($p < 0.025$). The subtest scores are shown in Table 13. The Recalling Sentences scores were again the highest, and the

Semantic Relationships were the lowest. Table 14 compares the higher scoring VCFS subgroup with the language disordered CELF-3 sample. Scores of the two groups were no longer significantly different, but the same pattern of higher VCFS scores for Recalling Sentences persisted, and VCFS Recalling Sentences scores approached being significantly higher than those of the language disordered sample ($p = 0.0543$).

Table 11.

CELF-3 Composite Scores from Higher Scoring VCFS Subgroup

CELF-3 Composite Scores	Mean	Standard Deviation	Minimum	Maximum
Receptive Language Score	75.923	15.500	53.000	100.000
Expressive Language Score	82.846	16.487	53.000	104.000
Total Language Score	77.923	15.872	50.000	102.000
Expressive – Receptive Language Scores	6.923	10.618	-14.000	23.000

Table 12.

Student "t" and Non-parametric Tests Comparing Expressive and Receptive Language Scores from Higher Scoring VCFS Subgroup

Paired t-test
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value
Expressive, Receptive	6.923	12	2.351	.0367

Wilcoxon Signed Rank Test for Expressive, Receptive

# 0 Differences	1
# Ties	3
Z-Value	-2.314
P-Value	.0207
Tied Z-Value	-2.320
Tied P-Value	.0204

Wilcoxon Rank Info for Expressive, Receptive

	Count	Sum Ranks	Mean Rank
# Ranks < 0	2	9.500	4.750
# Ranks > 0	10	68.500	6.850

Table 13.

CELF-3 Subtest Scores from Higher Scoring VCFS Subgroup

CELF-3 Subtest	Mean	Standard Deviation	Minimum	Maximum
Concepts and Directions	7.077	3.068	3.000	12.000
Word Classes	6.846	1.573	3.000	9.000
Semantic Relationships	6.091	2.663	3.000	11.000
Formulated Sentences	6.769	2.314	3.000	11.000
Recalling Sentences	8.385	3.355	3.000	14.000
Sentence Assembly	7.364	2.580	3.000	11.000

Table 14.

Student "t" Tests Comparing CELF-3 scores from Higher Scoring VCFS Subgroup and Language Disordered Sample

CELF-3 Score	VCFS Mean	Language Disordered Mean	P-value
Receptive Language Score	75.923	81.1	.2517
Expressive Language Score	82.846	78.6	.3714
Total Language Score	77.923	78.6	.8803
Expressive Language – Receptive Language	6.923	2.5	.1590
Concepts and Directions	7.077	7.1	.9788
Word Classes	6.846	7.4	.2283
Semantic Relationships	6.091	7.1	.2374
Formulated Sentences	6.769	6.9	.8420
Recalling Sentences	8.385	6.400	.0543
Sentence Assembly	7.364	7.5	.8643

Subgroup WISC-III results are shown in Table 15 and Table 16. They were similar to the results obtained by the entire group. In particular, Digit Span remained the subtest with the highest average score. No age or gender effects were detected in either the CELF-3 or the WISC-III scores for this subgroup.

Table 15.

WISC-III Composite Scores from Higher Scoring VCFS Subgroup

WISC-III Composite Scores	Mean	Standard Deviation	Minimum	Maximum
Verbal IQ	79.083	11.341	56.000	94.000
Performance IQ	78.083	8.775	64.000	93.000
Full Scale IQ	76.583	9.737	58.000	88.000
Verbal IQ – Performance IQ	1.000	9.361	-12.000	18.000

Table 16.

WISC-III Subtest Scores from Higher Scoring VCFS Subgroup

WISC-III Subtest	Mean	Standard Deviation	Minimum	Maximum
Picture Completion	6.462	3.357	2.000	11.000
Information	5.846	1.908	2.000	9.000
Coding	6.923	2.813	2.000	12.000
Similarities	6.923	2.532	3.000	10.000
Picture Arrangement	6.154	3.579	2.000	13.000
Arithmetic	5.538	2.222	2.000	9.000
Block Design	6.538	2.817	2.000	11.000
Vocabulary	6.077	2.900	1.000	11.000
Object Assembly	5.667	1.826	3.000	9.000
Comprehension	6.154	2.882	1.000	10.000
Symbols	5.417	2.275	1.000	9.000
Digit Span	8.333	2.708	3.000	12.000

D. Chart Review Results

The parents of several VCFS subjects made their children's academic and medical records available for this study. The author examined these records for results of previous language assessments which might provide information about the developmental patterns of individuals with VCFS. Four subjects had one or more sets of CELF's results in their records. These results are shown in the graphs below. This data demonstrates the large degree of individual variation which was found in children with VCFS.

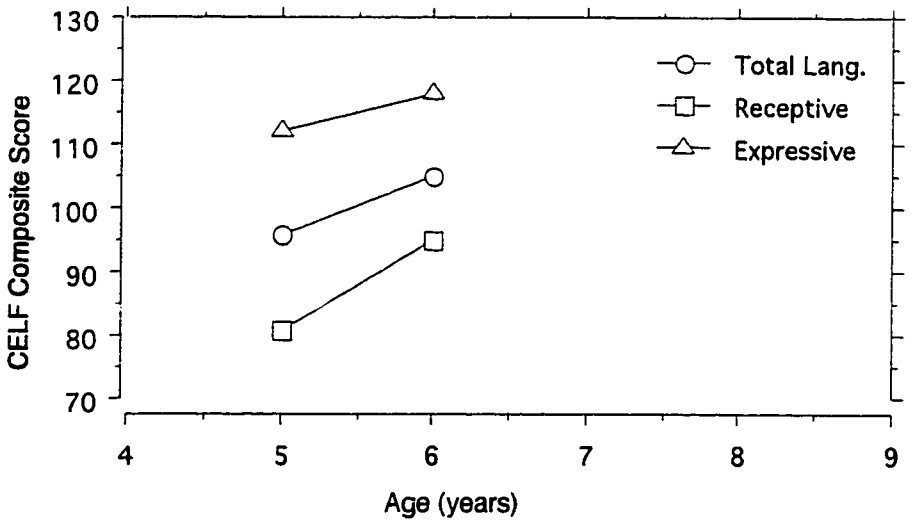

Figure 1. KH's CELF-Preschool Composite Scores

Subject KH received the CELF-Preschool at the ages of five and six. At age five, KH obtained an RLS of 81 and an ELS of 112, and an ELS – RLS difference of 31. A difference of this size was seen in only 1% of the CELF-3

standardization sample. At age six, KH obtained an RLS of 95 and an ELS of 118, and an ELS – RLS difference of 23, a difference obtained by 5% of the CELF-3 standardization sample. KH's expressive and receptive language scores were within normal limits at both ages five and six.

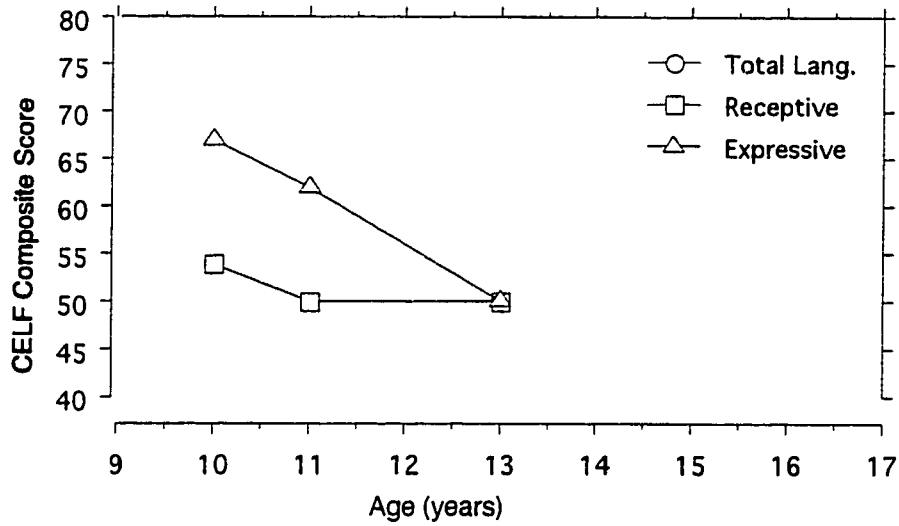

Figure 2. ME's CELF Composite Scores

Subject ME obtained an RLS of 54 and an ELS of 67 at the age of ten, an RLS of 50 and ELS of 62 at age 11, and an ELS and RLS of 50 at age 13. ME's receptive and expressive language skills were classified as severely delayed for all three years.

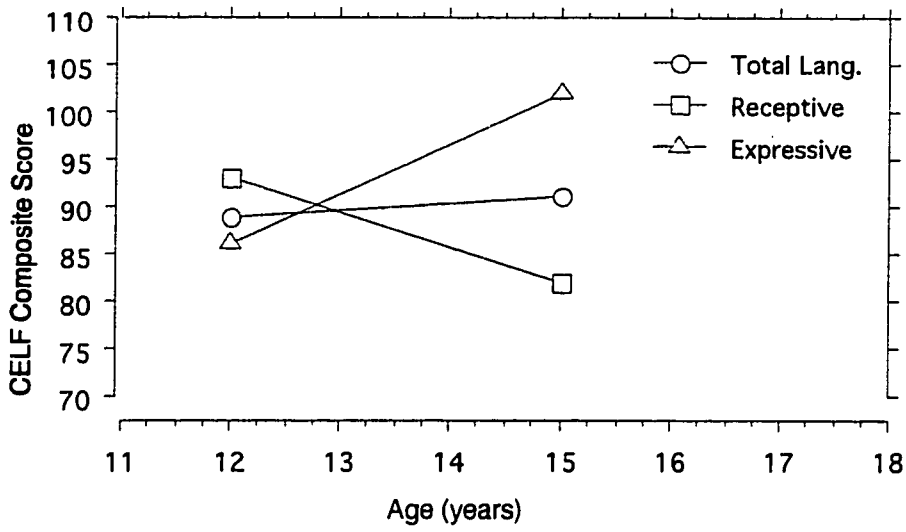

Figure 3. AB's CELF Composite Scores

Subject AB's CELF-R scores at age 12 were an RLS of 93 and an ELS of 86, for an ELS – RLS difference of –7. At age 15, AB received an RLS of 82 (a decrease of 7 points) and an ELS of 102 (an increase of 16 points), for a clinically significant ELS – RLS difference of 20 points. AB's receptive and expressive language would have been characterized as within normal limits at age 12, but at age 13 she could be diagnosed as having a mild receptive language delay and normal expressive language skills.

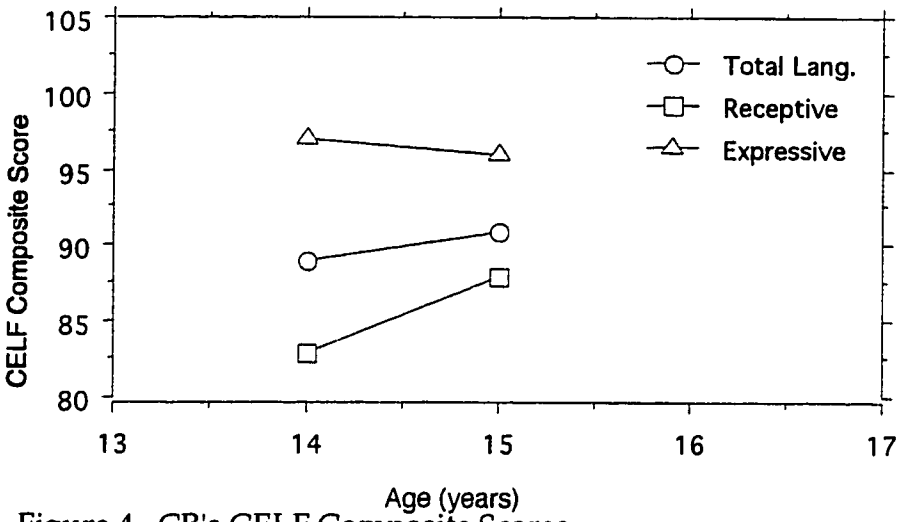

Figure 4. CB's CELF Composite Scores

At age 14, subject CB received an RLS of 83 and an ELS of 97 and an ELS – RLS of 14 points. At age 15, CB received an RLS of 88, an ELS of 96, and an ELS – RLS of 8 points. CB's receptive and expressive language skills were within normal limits, and showed stability over the year between assessments.

E. Hypotheses

Based on the results reviewed above, the hypotheses of this study were evaluated for acceptance or rejection.

Hypothesis 1: The receptive and expressive language skills of VCFS children are significantly delayed when compared to normal children of the same age.

This hypothesis was accepted, as the data in Table 17 shows that the VCFS children performed significantly below the CELF-3 standardization sample on all measures ($p = 0.0005$ for Recalling Sentences, $p < 0.0001$ for all other scores).

Table 17.

Student "t" Tests Comparing CELF-3 Standardization Sample and VCFS Sample

CELF-3 Score	VCFS Mean	CELF-3 Standardization Sample Mean	P-Value
Receptive Language Score	66.850	100	< .0001
Expressive Language Score	71.500	100	< .0001
Total Language Score	68.150	100	< .0001
Concepts and Directions	5.700	10	< .0001
Word Classes	5.600	10	< .0001
Semantic Relationships	5.000	10	< .0001
Formulated Sentences	5.750	10	< .0001
Recalling Sentences	6.500	10	.0005
Sentence Assembly	5.824	10	< .0001

Hypothesis 2: The expressive language skills of VCFS children are significantly better than their receptive language skills.

This hypothesis was also accepted, as the data in Table 3 shows that the ELS scores of VCFS children were on average higher than RLS scores. Unusually large ELS – RLS differences occurred at a higher rate in the VCFS population than in the CELF-3 standardization sample, and VCFS subjects were significantly more likely to have ELS scores that were higher than their RLS scores, when compared to the CELF-3 standardization sample. However, a distinction must be made between statistical and clinical significance. An ELS – RLS difference reaches clinical significance only when the difference is at least 19 points, a difference seen in only 10% of the CELF-3 standardization sample. While 55% of the VCFS subjects had an ELS greater than their RLS (as compared to ~ 46% of the CELF-3 standardization sample), only 20% of the VCFS subjects had a clinically significant point difference. This is twice the rate of such differences in the CELF-3 standardization sample, but there were many VCFS subjects whose ELS – RLS difference fell into a more normal range. The number of clinically significant point differences only became statistically significant when the subgroup of VCFS subjects who achieved 50 or greater ELS and RLS scores was considered.

Hypothesis 3: The language skill profiles of children diagnosed with a language disorder differ significantly from the language skill profiles of children with VCFS.

This hypothesis was accepted. Data in Table 6 showed that while VCFS children scored highest on the Recalling Sentences subtest, indicating rote

memory was a relative strength for the VCFS children, the language disordered children scored lowest on Recalling Sentences, indicating rote memory was a relative weakness for this group.

Hypothesis 4: As children with VCFS become older, their expressive and receptive language skills tend to fall behind as compared to those of normal children.

This hypothesis was rejected, because age effects were not found in the VCFS group as a whole, nor in the higher scoring VCFS subgroup. In addition, the small amount of data gathered from records provided by subjects' parents did not show a consistent pattern of improvement or decline of skills with age.

Chapter V: Conclusions and Implications

A. Limitations of the Study

While this study generated clinically and statistically significant findings with regard to the language skills of VCFS children, some factors exist which limit the strength and generalizability of these findings.

Testing Conditions

Testing of each subject took place on a single day, and consisted of the language assessment, as well as the WISC-III, neuropsychological testing, blood tests, and a functional MRI session. These test batteries resulted in a long, tiring, and stressful day for the subjects. Subjects were drawn from as far north as Santa Rosa and as far east as Sacramento, so considerable travel time, and in some cases, an overnight stay, were required in order to take part in the study. Stanford University provided subjects $125 for their participation, which would be insufficient to cover travel expenses and lost wages for most participants. These factors may have affected the results in two ways. Because participation involved a considerable investment of time and energy, it is possible that only the more severely affected VCFS subjects and their families were motivated to participate, causing an ascertainment bias in the VCFS sample. In addition, participants' test results may have been artificially depressed by the stresses of a long day of assessments.

Testing Sample Factors

This VCFS sample of 20 subjects was small, and covered ages six to eighteen years (a 13 year range). This meant that only one or two subjects of each age were assessed, and some ages in the range were not represented in this sample. While VCFS occurs with equal frequency in males and females (Thomas & Graham Jr., 1997), the sample was 30% female and 70% male. Information on the ethnic and socioeconomic backgrounds of the VCFS subjects were not available, so biases may exist in the sample when compared with the general VCFS population. In addition, no age and IQ matched control subjects were available, necessitating the use of the CELF-3 standardization and language disordered samples as controls. An attempt was made by Stanford University to obtain age and IQ matched controls subjects, but this proved unsuccessful. However, the potential control subjects that were given the CELF-3 by the author did not show the same pattern of higher ELS than RLS and higher Recalling Sentences scores which was seen in the VCFS subjects. This does provide limited validation of the results, in that it shows these results were not solely due to testing conditions. However, since the controls were not appropriately matched, their data cannot be used to draw substantive conclusions about the VCFS population.

Testing Instrument Factors

While standardized tests provide considerable advantages in terms of reliability and consistency, they cannot be said to create a natural linguistic interaction. This limits the extent to which the results of the CELF-3 can be

generalized to other contexts. The CELF-3 was most likely not the appropriate test instrument for the 35% of VCFS subjects who obtained ELS, RLS, and TLS scores of 50. Many of these subjects received raw scores of zero on one or more subtests, and one six year old subject received no raw points on any expressive subtest, and still received an ELS of 53. While the CELF-3 is a reliable instrument for assessment of mild and moderate language delays, for young children and those with very severe language delays, it may have reduced validity.

B. Auditory Processing and VCFS

Children with VCFS appear to have a unique profile of linguistic weaknesses as well as relative strengths. Since VCFS may affect the development of the brain, it is interesting to speculate on which cognitive processes or neuroanatomical differences may underlie the VCFS language profile. As was noted earlier, researchers have found various CNS anomalies in VCFS subjects, including cerebellar hypoplasia (Devriendt et al., 1996; Lynch et al., 1995; Mitnick et al., 1994; Ryan et al., 1997; Vataja & Elomaa, 1998), brain stem hypoplasia (Galili et al., 1998; Lynch et al., 1995), and enlargement of the left Sylvian fissure (Bingham et al., 1997). As part of the current study, structural MRI's were obtained from all VCFS subjects and were compared with those of normal age and gender matched peers. Preliminary results showed an 11% reduction in total brain volume, with most of the reduction occurring in the gray matter of the left parietal lobe (Eliez & Reiss, 1999). The left parietal lobe contains the angular and supramarginal gyri, which are known to be involved with language processing (Love & Webb, 1996; Webster, 1995). Several PET and

functional MRI studies have shown that the left parietal lobe is also involved in verbal working memory (Fletcher et al., 1995; Jonides et al., 1998; Tulving et al., 1994), retrieval of semantic and episodic memory (Wiggs, Weisberg, & Martin, 1999), retrieval of previously learned visuomotor sequences (Sakai et al., 1998), and consolidation of memory into long term storage (Izquierdo & Medina, 1997). The association of memory functions with the parietal lobe is especially interesting when the particular VCFS strengths and weaknesses shown by the CELF-3 and WISC-III results are examined. Rote memory, while lower than in normals, was relatively conserved in VCFS, as shown by VCFS subjects' Recalling Sentences and Digit Span subtests. On the other hand, VCFS subjects performed most poorly on the Semantic Relationship subtest of the CELF-3. This subtest also requires the examinee to remember auditorally presented information, but for Semantic Relationships the examinee must process the information and use it to infer which two out of four possible answers are correct. Thus while the Recalling Sentences and Semantic Relationships subtests both stress the short term auditory-verbal working memory system, Semantic Relationships also requires considerable processing of the information as it is held in memory, and for some items, may require retrieval of additional information from long term memory in order to arrive at the correct inference. Perhaps memory retrieval and processing information held in working memory are particularly affected by loss of gray matter in the left parietal lobe.

C. Implications for Education and Treatment of VCFS Children

The findings in this study support the educational approach outlined by Landsman (1996). Landsman noted the difficulty VCFS children have with processing auditory information, and advocated a direct instructional method in which information is presented both auditorally and visually. Landsman also reported that drill and extensive practice were necessary for VCFS students to learn new skills. This is of interest in view of the left parietal lobe's involvement in consolidation of long term memories and their retrieval from long term storage (Izquierdo & Medina, 1997; Sakai et al., 1998; Wiggs et al., 1999). If VCFS students do have reduced left parietal lobes and corresponding deficits in their memory systems, then it is possible that increased practice is needed in order to process information and encode it for long term storage, and to retrieve the information once it is stored.

D. Suggestions for Further Research

In order to more fully delineate the pattern of VCFS strengths and deficits relating to parietal lobe function, the areas of memory and auditory processing of linguistic information should be explored in greater detail. Various central auditory processing tests such as the SCAN (Keith, 1986; Keith, 1994) or Sound Perception in Noise (Kalikow, Stevens, & Elliott, 1977) may be considered. A full audiological evaluation with an emphasis on speech audiometry would also be appropriate. An in-depth test of various areas of memory functioning, such as the Wechsler Memory Scales (Wechsler, 1987) would provide information on memory strengths and weaknesses. Finally, to examine processing and retrieval

of linguistic information, instruments such as the CELF-3 supplemental subtest Listening to Paragraphs and the Test of Word Finding (Germane, 1989) would be useful in further refining our picture of language functioning in individuals with VCFS.

In addition to conducting more standardized testing, the language of VCFS children in more natural contexts should also be examined. As part of the present study, narrative language samples were obtained from each VCFS subject. Due to the absence of appropriate control subjects, it was not possible to analyze this data. However, if language samples could be obtained from age and IQ matched control subjects using the same narrative tasks, it would be possible to determine whether the VCFS language differences found in standardized testing would exist in a less artificial linguistic context.

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