FEEDING AND GROWTH IN VCFS, Part 1: THE INTRODUCTION OF GROWTH CHARTS BASED ON A LARGE SAMPLE

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Abstract: Growth curves from birth to adulthood were constructed based on 1682 individuals with VCFS confirmed by molecular genetic tests. The growth curves and long term follow-up of children with VCFS indicate that people with VCFS typically have normal birth weight and reach normal adult height, but growth velocity is different for children with VCFS compared with the general population. As a result, although height and weight at specific ages may be abnormally low at certain points of development, over 90% of children with VCFS reach normal adult heights, often consistent with expected midparental height. Comparing children with VCFS to CDC or WHO growth charts that are based on the general population is therefore inappropriate and can lead to incorrect conclusions about growth and feeding, unnecessary treatments, disruptions in normal family life and social interactions, and medical dependency.

Key Words: Velo-cardio-facial syndrome, VCFS, 22q11.2 deletion, growth curves, growth velocity, congenital heart disease, scoliosis.

INTRODUCTION

Velo-cardio-facial syndrome (VCFS) is the most common microdeletion syndrome in humans with a population prevalence of 1:2000 in the U.S. and other first world nations[1-3]. At present, the majority of cases of VCFS are detected by screening newborns with conotruncal heart anomalies for the detection of the deletion from chromosome 22 at the q11.2 band that causes the syndrome. It has been found that 20% of all established pregnancies with complex conotruncal heart anomalies such as tetralogy of Fallot, interrupted aortic arch, and truncus arteriosus have 22q11.2 deletions[4,5]. VCFS is also the most common syndrome of cleft palate constituting approximately 8% of children with soft palate anomalies[6]. Both congenital heart disease and cleft palate are associated with feeding difficulties. With approximately 70% of babies with VCFS having congenital heart disease, and 70% having palatal anomalies, and therefore many of them having both, it is no surprise that babies with VCFS will be watched very carefully for weight gain. They will be compared to the growth charts that nearly all pediatricians and pediatric

specialists have in their offices, those published by the CDC (Center for Disease Control and Prevention)[7] or those published by WHO (the World Health Organization)[8]. Because of feeding difficulties, slow weight gain, lack of linear growth (height), babies with VCFS are often labeled as having failure to thrive. When so diagnosed, aggressive action is often taken to put weight on the babies and get them to grow more. Such treatments often include surgery or long-term gavage feedings and a major alteration in the quality of life.

Are Short Stature and Failure-to-Thrive Features of VCFS?

Early feeding problems encountered in infants and children who have VCFS are often accompanied by the child falling away from growth charts based on general population norms. It may seem obvious that the coincidence of reduced caloric intake with growth that falls away from population norms is caused by failure to consume sufficient calories to support growth. However, clinicians and scientists must be very careful when it comes to concluding that correlated observations mean that there is a cause and effect relationship between them. Although two events that occur together may have a cause and effect relationship, it cannot be known which event is the cause, and which event is the effect, if any. Sometimes, there is a bidirectional relationship, and sometimes there is no relationship meaning that both events are caused by a third factor. For example, February always follows January, but January does not cause February, nor does February cause January. They are both caused by a third event, their placement on the calendar. Directionality of cause and effect can also be contrary to the obvious. The geocentric vision of the universe in ancient times is a perfect example. When early civilizations looked at the sun circling the sky, they assumed that the sun circled Earth. Drawing conclusions from coincidental events can be dangerous, and this is true for linear growth (height) in VCFS in relation to caloric intake. Is the child not growing because caloric intake is low, or is caloric intake low because the child is not growing at the pace expected for "normal" children. In other words, all of the calories needed to support growth are being consumed. Eating more would overfill their stomachs and make them feel uncomfortable. Scientists and clinicians should never infer cause and effect from correlated events. If the same logic were applied to children with Prader-Willi syndrome (who have voracious appetites and will become severely obese if their diets are not controlled), then they would all be very tall. But children with Prader-Willi (who have a microdeletion from the long arm of chromosome 15) are typically short, often below the 3rd percentile compared to the CDC or WHO charts. If it is suggested by some that increasing calories will make children with VCFS taller, why does it not do the same for children with Prader-Willi syndrome? Or Williams syndrome? Or Down syndrome? In the general

population, if height responded to caloric intake, why do most children get heavy rather than tall when caloric intake is increased?

Understanding Growth in VCFS

How is short stature defined? For most health care professionals, short stature is defined by comparing a person's height and weight to standardized growth charts that are based on data obtained from large sample populations that are comparable to the person's ethnic and racial background, their gender, and their age. Curves that plot growth provide a range of data for a sample population from birth to adult life. They show the mean, or average height and weight, and the percentage of the population that fall between several standard deviations from the mean. The data show percentile rankings for heights and weights for age. "Normal" is often defined as falling between two standard deviations above the mean and two standard deviations below the mean. A "standard deviation" is a statistical computation that measures the amount of variation for a particular statistic (such as height or weight) in relation to the numerical average, or "mean." For example, the "average" or "mean" height for the American adult male population is approximately 69.3 inches (176.02 cm), according to the CDC[7]. One standard deviation from the mean is approximately three inches, two standard deviations about 6 inches. This range usually encompasses about 94% to 96% of the population meaning that approximately 90% to 94% of adult males in the United States are between 5 feet 3 inches (approximately 160 cm) to 6 feet 6 inches (about 198 cm) in height. Growth charts often translate these data into percentiles, such as the tenth, 20th, 30th, etc. Does this imply that heights above and below two standard deviations are abnormal?

Most scientists and physicians think that a measured height and/or weight that falls below the 3rd or 5th percentile is considered to be abnormal and should be labeled as "short stature" or the more emotionally charged term, "failure to thrive." Weight below the 3rd or 5th percentile is especially called failure-to-thrive if it is proportionately lower than height. Short stature and failure-to-thrive have implications to clinicians who are following infants and children that often trigger treatment protocols that can be life altering and unpleasant. It is therefore important that the data obtained on growth in an individual child be interpreted properly to prevent a cycle of treatments that may make the child medically dependent for many years.

The growth charts used by most clinicians in the United States today are those published by the Center for Disease Control and Prevention (the CDC) (Figure 1). They are available on the CDC web site at:
http://www.cdc.gov/growthcharts/

The following statement appears on the web site of The Department of Health and Human Services, Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau (http://depts.washington.edu/growth/cshcn/text/page3a.htm):

> The reference data used to develop the CDC growth charts were drawn from a nationally representative sample. These reference data are not specific for children with special health care needs. Thus, the clinician who uses the CDC growth charts to interpret the growth of a child with special health care needs must understand the potential influence of the specific condition on growth and identify reasons the child's growth might be different than that of other children.

This is an extremely important statement and a concept that relates to all genetic disorders, including VCFS. This statement, however, is consistently ignored. Reviewing records for more than 1800 cases of VCFS I have seen or reviewed over the past 35 years, limiting the sample to cases that had been diagnosed by genomic studies (FISH or microarray) and for whom I had previous medical records from pediatricians, family physicians, or pediatric cardiologists, a total of 1628 cases were available who had multiple height and weight measurements for review. Of these, 743 had been diagnosed with failure to thrive at least once by their primary care physicians or their gastroenterologists based on comparison to the CDC growth charts. Reviewing the records, we found that in most of these cases, the determination was based on a weight comparison only without a consideration of weight to height proportionality. When height and weight percentiles were compared to provide a body mass index, the number of cases that were below the third percentile that would have been appropriately labeled as failure-to-thrive was approximately 26% of the sample. However, physical examination of these children showed that very few of them appeared extraordinarily thin and many of them had subcutaneous fat deposited on their thighs, arms, and face. We did find that in cases with pulmonary atresia or severe inoperable heart anomalies, reports often attributed small stature or low weight to congenital heart disease, but in cases with successful definitive heart repairs or no congenital heart disease, poor growth was not typically attributed to cardiac function. However, many cases were noted to feed poorly, have “reduced caloric intake,” lack of linear growth, and low weight compared to height. In nearly all cases of this type, lack of growth and weight gain was blamed on poor feeding. In many instances, gastrostomies were performed or nasogastric tubes placed to bypass oral feeding prior to their first assessment for VCFS. Following placement of G tubes or gavage (nasogastric or orogastric) tubes, weight occasionally increased, but linear growth did not. Moreover, reports of discomfort in infants fed by G tube or nasogastric tube were very common. Constant

anxiety over feeding and making sure that infants received the recommended number of calories was very consistent among parents of these children. In an effort to provide sufficient calories, the babies were often overfed and overfilled (hyperalimentation), leading to spitting up or significant emesis (often mistakenly referred to as "reflux"). In some cases, persistent emesis was followed by Nissen fundal plication surgery. This operation can lead to secondary digestive tract problems, persistent wretching, and discomfort from chronic gas pains. Therefore, the escalating medical management of what is perceived as growth failure related to insufficient caloric intake can cause major interruptions in family life, anxiety, and medical dependency. Moreover, feeding aversions become commonplace in such infants because the feeding process is either painful or unpleasant.

Short Stature Reported in VCFS

In the earliest reports of VCFS, "relative short statue" was discussed as a clinical finding. Most of the children reported in the original journal article that described VCFS (Shprintzen et al., 1978) had height and weight in the normal range, but all were below the 25th percentile for both measures based on general population. Two children in the sample were below the 3rd percentile for height and weight. In subsequent studies, the frequency of reported short stature increased (Young et al., 1980; Motzkin et al., 1993), ranging up to 50% of cases studied. The data reported in these early studies were cross-sectional, meaning one-moment-in-time measures, and very few adults with VCFS were encountered so that it was not possible to determine how many eventually reached adult height within the normal range.

It is now more than 36 years since the initial description of VCFS (Shprintzen et al., 1978) and 15 years since our report of short stature in children with VCFS (Motzkin et al., 1993). We have been able to follow most of our patients from these early studies into adulthood and have determined that none of those cases we followed early in life were of very short stature as adults. Nearly all, in fact, all were within a reasonable range of expected midparental height, a calculation that predicts how tall a boy or girl will be in adult life based on the heights of their parents. We also had the opportunity to determine that only one of our patients had been treated with growth hormone to enhance height. Although a statistical analysis of significance cannot be calculated from a single case compared to population norms, it is evident that very few of our patients with VCFS have been treated with growth hormone for short stature. It is apparent from this retrospective review that relatively small size at three or seven years of age has not translated to abnormally short stature in adult life. In addition, it must be considered that none of our earlier studies, nor those of other investigators, took into account other clinical features that would reduce adult height, such as persisting perfusion problems from

pulmonary atresia or other cardiovascular anomalies, or scoliosis that can reduce adult height by three, four, or five percent.

Growth Velocity Versus Total Growth

Why would cross-sectional data obtained for childhood growth velocity not translate to short stature in adulthood? The answer is that it is not total growth per se that is abnormal, but growth velocity. Our 1993 study (Motzkin et al., 1993) is a good example of this phenomenon. This study documented the phenotype in 18 cases of VCFS, two of whom were adults over the age of 40, one young adult, and the balance being school age children and adolescents. We reported that 50% of our cases were of short stature when compared to established norms for the general population. In reviewing the individual cases, all three adults were within the normal range for height and weight, and the majority of our cases with short stature were the younger patients in the sample. Reviewing those cases, all now adults, it has been found they are all within the normal range for height and weight.

Growth Velocity in VCFS

Early observations of children with VCFS reporting that short stature was a common finding in the syndrome represent misinterpretations of growth velocity. This can be concluded because we have observed that adults with VCFS are not abnormally small and birth weight is also typically in the normal range for children with VCFS. Therefore, if stature is in the normal range at the beginning of life, and also within normal limits in adult life, the short stature observed in childhood must be transient, therefore reflecting a difference in the velocity of growth (the "curve").

Growth velocity is a measure of the rate of growth over time. Growth velocity is plotted as a curve with increasing age. The charts provided by the CDC are growth velocity charts for the general population. When children are born within the normal range of length and weight, but then drop away from the normal growth curve, most clinicians would conclude that they have postnatal growth deficiency. If a child is born below the 3rd percentile for height and weight and continues to grow along that same track, most clinicians would conclude that the child has prenatal growth deficiency. Many clinicians believe that postnatal growth deficiency can be caused by poor nutrition and deficient caloric intake. Although this may be an explanation in some cases (albeit rare), it is far more common for growth problems in children to be a part of genetic multiple anomaly syndromes. It is estimated that 1 in every 33 babies, or approximately 3% of all births, have congenital anomalies. The majority of these anomalies are caused by genetic mutations or chromosome rearrangements. Because our genetic code mediates so many aspects of growth and development, it is to be expected that a very high percentage of genetic and chromosomal syndromes result in growth differences. Although it is obvious that

linear growth deficiency would be expected in skeletal dysplasias such as achondroplasia and spondyloepiphyseal dysplasia, constitutional short stature also occurs in syndromes not typically considered to be syndromes of abnormal skeletal development. Lack of normal growth velocity occurs in many syndromes familiar to clinicians. Down syndrome, Williams syndrome, de Lange syndrome, Turner syndrome, Noonan syndrome, Smith-Lemli-Opitz syndrome, Dubowitz syndrome, Aarskog syndrome, Prader-Willi syndrome, and Rubinstein-Taybi syndrome, just to name a few. Clinicians would not presume to compare children with any of these syndromes to population norms in order to base calculations of caloric needs or alternative feeding procedures because it is understood that their growth will not follow the CDC curves. Few if any clinicians would presume to feed children with Williams syndrome more food in the hopes of making them grow taller. Children with Prader-Willi syndrome eat too much, but rather than grow taller, they become more obese. In other words, most syndromes have distinctive patterns of growth and predictable adult growth outcomes. Similarly, syndromes that have tall stature as a finding (Sotos syndrome, Weaver syndrome, Simpson-Golabi-Behmel syndrome and others) cannot have their short stature resolved by reducing caloric intake. The expectation that increasing caloric intake will result in improved growth in VCFS is not logical, but believed by many. However, most of these syndromes have been well known to clinicians for many years and their natural histories are understood to include abnormalities of growth. VCFS has a much shorter history of study, and many clinicians are still not familiar with it. This lack of familiarity with the syndrome and failure to recognize its natural history is enhanced by the fact that VCFS does not have many significantly dysmorphic features associated with its phenotype. Children with VCFS have characteristic facial appearances, but not unusual or dysmorphic facial appearance. Children with VCFS are cute and adorable looking children. They resemble each other because they share a common syndrome, but they do not look abnormal, disproportionate, or malformed except in very rare cases. It can therefore be expected that they would be compared with growth charts constructed for “normal” children because children with VCFS are more likely to be lumped together with other children who are normal in appearance.

Early in the study of people with other multiple anomaly syndromes, such as Down syndrome or Williams syndrome, it became apparent to clinicians and researchers that they grew differently than the general population. Moreover, children with these syndromes were typically of short stature as adults. For example, the average height of adult males with Down syndrome is less than five feet (152 cm), far below the 3rd percentile when compared to the CDC growth charts. Therefore, comparing people with Down syndrome to norms established for the general population is not done. Why then, would one assume that people with VCFS

who are missing 40 genes from one copy of chromosome 22 would grow like people who have those 40 genes in normal copy number?

It is also true that other factors can influence growth. These include severe cardiac perfusion abnormalities, abnormalities of the pituitary gland, severe pulmonary problems, and severe sleep disturbance. All of these problems can occur in VCFS, although none occur in a large percentage of cases.

Severe cardiac perfusion abnormalities

Approximately 70% of newborns with VCFS have malformations of the heart and its major vessels (Shprintzen and Golding-Kushner, 2008). The majority of individuals with congenital heart disease have surgically correctable anomalies. Pulmonary atresia associated with their structural heart malformation has been reported to occur in approximately 25% of cases (Marino et al, 2001), although our own sample has a lower frequency of 16%. Children with VCFS who have cardiothoracic surgery for congenital heart anomalies without pulmonary atresia have outcomes similar to those found in children who do not have VCFS, but when pulmonary atresia is present, the survival rate for children with VCFS is not as good as it is for children who do not have VCFS (Anaclerio et al., 2004). Children with pulmonary atresia have poorer surgical outcomes and a higher mortality rate than those with major anomalies without pulmonary atresia. Moreover, they have restricted growth, especially during infancy and early childhood, although they eventually show significant catch-up growth (Ono et al., 2007). Because congenital heart disease is so common in VCFS, the growth curve may be affected by secondary factors that would reduce growth. It is therefore important to compare children with VCFS who do not have congenital heart disease with those who do. It would also be useful to further distinguish between those cases that have pulmonary atresia from those that do not.

Severe Pulmonary Problems

Children with functional or structural problems of the lungs will also have growth deficiency and poor weight gain. Children with VCFS often have structural abnormalities of the lungs and their associated structures, especially the trachea and bronchi that can be compressed by aberrant major blood vessels in the chest. Vascular rings, aberrant subclavian arteries, and aortic arches that start on the right and descend towards the left can compress the lower airway and also the esophagus. Tracheomalacia and bronchomalacia are common findings in VCFS, although often not detected if bronchoscopies and esophagoscopies are not performed. Occasional hypoplasia of the lung can also be seen, although it is not common. Congenital diaphragmatic hernias are also seen in VCFS and these can significantly impair lung function. Children with VCFS also have frequent reactive

airway disease as part of their overall immune picture. Pulmonary problems prevent adequate perfusion that can restrict peripheral growth, and increased respiratory effort burns calories that normally would be held in reserve for weight gain. Pulmonary issues can also contribute to obstructive sleep apnea that is understood to have potential limiting effects on growth (Goldstein et al., 1985 and 1987).

Severe Sleep Disturbance

It has long been hypothesized that sleep disturbance caused by obstructive sleep apnea can cause growth problems by limiting the secretion of sleep entrained growth hormone (Goldstein et al., 1985 and 1987). Reversal of sleep disturbance has been noted to increase growth and weight gain (Goldstein et al., 1987; Ersoy et al., 2005). Children with VCFS often have significant sleep disturbance and may have obstructive sleep apnea or sleep disordered breathing. This may, in addition to the other issues that affect growth, contribute to lower than normal weight gain and linear growth. Children will be poorly rested, have decreased vitality, and metabolic changes caused by persistent fatigue.

Therefore, it is possible that to some extent, secondary factor rather than primary gene effect may play a role in growth velocity or eventual peak linear growth. The question remains if short stature is truly a finding in VCFS and if that short stature is a primary clinical feature of VCFS. One way to address the question is to construct a growth chart for VCFS based on data derived directly from a population that is limited to people with VCFS, and to have a large enough sample of people at all ages from birth to adult life to have some confidence in the accuracy of the data.

METHODS

CONSTRUCTING A GROWTH CURVE

In order to construct a growth curve for VCFS, the number of data points were maximized by combining data collected on a total of 1,682 individuals with VCFS. This data set is expanded by approximately 55% over the data we published in 2008 (Shprintzen and Golding-Kushner, 2008) that was based on 1,085 subjects. In most cases, we had data documented from multiple physical examinations spanning at least four years to data from birth to adulthood, although with some gaps in some cases. The data obtained included a total of 10,814 measurements of height, and 11,399 measurements of weight. Birth weights were available for all cases from parental recollection and/or medical records (over 85% of cases). We found parental recollection of birth weights to be very accurate when both were available. Data were available for 254 adults, or 15.1% of the cases. Of these,

longitudinal data from childhood to adulthood was available for more than 2/3 of the cases. Males and females were nearly equally represented in the total sample with 823 males and 859 females.

All data points (height and weight) were recorded to the nearest month of age and segregated according to sex. To avoid a bias introduced by prematurity and low birth measurements of infants born prior to 38 weeks of gestation (by report) were excluded until five years of age. Only 9% of the total sample was born before 38 weeks. None of the subjects in the study had a gestation longer than an estimated 42 weeks.

For reasons discussed earlier, it was important to know if congenital heart disease might play a role in eventual growth outcomes, so we then separated those cases with congenital heart disease from those without. The presence or absence of heart disease was determined by review of medical records (including cardiac imaging procedures). Of the total sample, 1144 (68%) had histories of congenital heart disease. Among those with heart anomalies, we culled out those cases with pulmonary stenosis or atresia hypothesizing that they would be most prone to growth problems because of poor peripheral perfusion. Approximately 16% of the heart disease sample (186 cases) had pulmonary atresia or stenosis (approximately 11% of the total sample).

For each month of age, mean weight and height were calculated as was standard deviations from the mean values. Assuming a normal distribution for people with VCFS (in other words, a bell-shaped curve), the mean represents the 50th percentile for the sample, one standard deviation from the mean in both directions (above and below) encompasses 68.2% of the sample and two standard deviations from the mean in both directions encompasses 95.8% of the sample. The data listed is shown to 20 years of age.

The growth curves for the total data including all cases are shown as an appendix to this article. They include separate charts for height and weight for both males and females from birth to 36 months of age, and separate charts for males and females from 2 to 20 years of age consistent with the charts distributed by the CDC. Also included is a superimposition of these data on the CDC charts as a basis of comparison for the growth velocity in VCFS.

Comparisons

Multiple comparisons were made at each age level on the growth charts for subgroups of the sample that are reported below. Males and females were compared separately. Comparisons were made for cases with heart disease and those without. Comparisons were also made for cases with feeding problems and those without, as well as for children with alternative feeding procedures (gavage tubes or

gastrostomy or jejunostomy). Comparisons were made using a Student's t test for each age grouping beginning at three months of age.

Growth Curves for VCFS: What Do They Mean?

The growth charts show that people with VCFS have birth weights that are within normal limits although slightly lower than the average for the general population. At age 20, all but approximately 4% of males and 6% of females fell within the normal range based on the CDC population norms. Included in that 4% of males and 6% of females was a subset of cases that were very close to expected midparental height. In some of cases, ethnic and racial differences may have played a role. Although many growth charts try to use only a single ethnic sample, Eliminating those cases where the height was below the 3rd percentile for general population norms, but within expected outcomes for midparental height brought the number of short stature cases (compared to the CDC norms) to approximately 3% for males and 5% for females, compared to approximately 2.5% below the 5th percentile for the CDC charts. Between birth and adult life, mean stature and weight for children with VCFS was well below that of the general population during infancy and childhood, typically catching up to general population norms in late adolescence. There were several plateaus during which time there was relatively little growth followed by spurts of growth that brought the VCFS sample closer to the curve of the general population. The weight curve was lower compared to the CDC norms than height until early adolescence and the onset of puberty when weight becomes proportionate to height for both boys and girls in relation to the CDC norms. This implies that weight proportion is different for VCFS.

We did not "smooth" these curves. The CDC growth curves underwent a statistical procedure known as "smoothing" to literally provide a smooth curve without jagged edges at any one month or year. Our data were not smoothed allowing "growth spurts" and periods of absent or flat growth to be appreciated.

Body Mass Index

Body mass index (BMI) is a measure that compares weight to height in terms of proportionality. The CDC has curves for these values that accompany the growth charts. It is evident looking at the weight values in VCFS than weight is proportionately lower for VCFS than for the general population. In other words, children with VCFS are underweight for their height if one compares them to the general population. However, such values need to be interpreted with caution. One of the common, essentially ubiquitous findings in VCFS is hypotonia. Hypotonia, usually diagnosed based on peripheral muscle strength and coordination, occurs in nearly all children with VCFS. It has already been documented that people with VCFS have reduced muscle mass in the pharynx and palate[9]. It has been observed

that muscle mass is generally reduced in VCFS and because muscle is a dense and heavy tissue, this will reduce weight thereby lowering the BMI[3]. Therefore, comparing children with VCFS to standard BMI curves will lead to false positives for "failure to thrive."

The Effects of Heart Anomalies

Because approximately 70% of children with VCFS have some type of congenital heart disease, it is possible that some of the abnormalities in growth or growth velocity is associated with perfusion abnormalities. In order to determine if heart anomalies contribute to growth patterns in VCFS, mean height and weight were compared for all cases with heart anomalies and those without intracardiac abnormalities. We then further subdivided those with heart disease into those with and without pulmonary atresia or severe pulmonary stenosis. We could not control for age at the time of cardiothoracic surgery, but in cases of severe anomalies, such as interrupted aortic arch, and truncus arteriosus, most newborns had surgery performed in the neonatal period. Surgical correction of ventricular or atrial septal defects was variable depending on severity.

The separation of the growth data for those with and without congenital heart disease compared these two subpopulations for both growth velocity and eventual growth outcomes. With the exception of those individuals who had pulmonary atresia or stenosis, the growth velocities and expected heights of people with VCFS who had no heart anomalies showed no statistically significantly difference for people with VCFS who did have minor or surgically repaired heart anomalies. In cases of severe heart anomalies that were inoperable in early infancy, growth tended to lag behind VCFS norms until repair was affected. This same phenomenon is true in the children with heart anomalies who do not have VCFS or other multiple anomaly syndromes. After surgery, there was a surge in growth with significant catch-up to other children with VCFS who had no heart anomalies. The majority of cases of tetralogy of Fallot, interrupted aortic arch and truncus arteriosus had definitive heart surgery in the neonatal period so that there was not a long period of time with significantly abnormal perfusion. In cases with severe pulmonary atresia, some children did not survive beyond several months or years of life, and those cases remained small compared to other children with VCFS who did not have pulmonary atresia. Such cases were not included in the final growth charts because the data was restricted to the first few weeks or months of life.

Affect of Feeding Problems

We also wanted to know if early feeding difficulties resulted in growth problems, whether short or long term, and if those cases treated with alternative

feeding methods such as gastrostomies or gavage feedings grew at an accelerated pace compared to other VCFS children who had feeding problems, but who were only fed by mouth. Feeding problems were reported in 74% of the sample. Of those, 32% were fed by gavage (nasogastric tubes) or gastrostomy (and its variations, jejunostomy). Almost all of these procedures were implemented for approximately one year, and those with gastrostomies had them for a mean period of three years, ranging from 6 months to seven years. A comparison of height of the children with alternative feeding procedures to the rest of the sample showed no statistically significant difference in linear growth velocity or eventual outcome. We also looked at the cases with reported "failure-to-thrive" and feeding difficulties and compared them to the entire VCFS sample and also found no differences in growth velocity.

We then assessed the expected heights for the adults. We found that 92% of the males in the sample were within ±3 cm of their calculated expected heights. The distribution of those above expected height was essentially the same as those below and the presence or absence of congenital heart disease had no effect on the final outcome.

The females in the sample did not reach expected height with the same frequency as the males and tended to be a bit shorter than their peers, but less than one standard deviation. Of the females in the adult sample, 74% were within 3 cm of calculated expected height (just over one inch), and of those who were not, the majority was shorter than expected height. None were of severe short stature, but 16% of the sample were at or below the 10th percentile for general population norms, and were well below their predicted heights.

Is the Data Perfect?

The growth curves shown in the appendix are revised versions of the initial curves constructed on a slightly smaller sample of individuals with VCFS. The curves were constructed from individual data points on 1682 people with VCFS, not all of whom had annual measurements, and most of whom did not reach adulthood at the time the curves were constructed. These data were obtained retrospectively rather than prospectively. As a result, it was not possible to use standardized techniques or instrumentation to ascertain measurements. Although many of the subjects had annual measurements and weights, most did not have them available for every year so that there were some gaps in the data points for individual subjects. Although the growth statistics from this sample is a large data set for a rare disorder, the sample is still relatively small for constructing a growth curve compared to the CDC growth charts used for the general population. For many of the age levels, we had more than a thousand data points whereas the CDC charts are based on tens of thousands of such points. For birth weight, we had over 1,500 data points and the early years of

life provided large numbers per month of age. Late adolescent and adult measures were fewer with some months having 100 or slightly fewer entries that might make the calculations less robust. When dealing with retrospective data of this type, we have to take what is available. We may also be dealing with a biased sample. It is possible that the mildest cases of VCFS, in other words, the most normal people, are never diagnosed, or if they are diagnosed but are not symptomatic for any major problems, they may have no reason to be called to the attention of researchers or clinicians. It may also be true that less significantly stigmatized people with VCFS may not grow differently than the general population.

Another issue that could affect linear growth is scoliosis. Scoliosis is found in nearly 30% of individuals with VCFS. Scoliosis can dramatically reduce linear growth measurements. Although the subjects with scoliosis were essentially equally divided between males and females, the relative severity and effect on height for each case is not known from the data available. It is also true that scoliosis impairs height in a progressive manner. In other words, at the outset of scoliosis, there is little effect on height, but over time the curvature worsens and impairs height increasingly over time.

Interpreting the Growth Curve

We now have evidence that children with VCFS grow at a different pace than other children and also grow to adult heights that are generally considered to be normal. However, with rare exception, children with VCFS are not extremely small to the point where they are considered to be so far from population norms that their height calls attention to them. Given the common nature of VCFS, one would expect that if very short stature were a common finding in the syndrome that cases would have been detected by scientists who study syndromes of short stature. This has not been the case. It can be surmised that most adults with VCFS are of normal stature and they begin life at normal birth weights. Although they reach adult height at a different velocity than children who do not have VCFS, according to our data, they cannot be considered to have prenatal or postnatal growth deficiency as is seen in skeletal dysplasias, lysosomal storage diseases, and other metabolic disorders. Although there are cases with VCFS that can be considered to have short stature even when compared to the curves shown in the appendix, it is also true that in the general population, there are people who are of short stature compared to the CDC growth charts. It can not be stated definitively that the frequency of short stature in people with VCFS is greater than that seen in the general population; at this point in time, it would seem that most, if not almost all people with VCFS do reach heights within the normal range even when compared to normative data for the general population.

Summary

Growth in VCFS is different than it is for children who do not have the syndrome. Linear growth velocity and weight gain are both different than in the general population because of effects that are related to the deletion from chromosome 22. Superimposed on top of the genomic deletion, secondary effects related to congenital heart disease, sleep disturbance, and abnormal muscle growth may also occur and enhance growth velocity differences. Although growth differences have multifactorial causes, the most important factor is the deletion that sets all of these wheels into motion. Without the deletion, none of these other issues would be present. Therefore, having separate growth charts for people who have the deletion is imperative so that children with VCFS are not compared to the general population, thus avoiding unnecessary and inappropriate treatments. In part 2 of our review of cases that will follow this article in this journal, we will discuss the impact of misinterpretation of growth velocity in VCFS, including the application of alternative feeding techniques, hyperalimentation, quality of life issues, and how the use of procedures such as tube feedings and surgical enteric feedings can have an effect on development and family dynamics.

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