An Assessment of the Occlusal Characteristics of Individuals With Growth Deficiencies

BY
NATALIA LINHARES RODRIGUES HODGE
D.D.S., Universidade Federal do Ceará, 2007
D.D.S., University of Illinois at Chicago, Chicago, 2011

THESIS

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Thesis Committee

Carla Evans, Chair and Advisor
Shahrbanoo Fadavi, Pediatric Dentistry
Grace Viana

This thesis is dedicated to my family. Especially my husband Rob, who has been by my side through this journey and has filled our years in Chicago with fond memories. To my parents, Arnaldo and Ana Tely Rodrigues, whose unconditional love and support are behind everything I have ever done in my life. To my grandfather, Edmo Linhares, my biggest example of hard work and dedication. I am forever grateful I have each one of you in my life.

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NH

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

LIST OF TABLES

LIST OF FIGURES

FIGURE PAGE

LIST OF ABBREVIATIONS

APSTI	Autoimmune Polyglandular Syndrome Type I
CAH	Congenital Adrenal Hyperplasia
GH	Growth Hormone
GHD	Growth Hormone Deficiency
IGFD	Insulin-like Growth Factor Deficiency
hGH	Human Growth Hormone
IRB	Institutional Review Board
ISS	Idiopathic Short Stature
IUGR	Intra-Uterine Growth Restriction
MaxAlig	Maxillary Alignment
MandAlig	Mandibular Alignment
OB	Overbite
OJ	Overjet
PHPT	Panhypopituitarism
RSS	Russell-Silver Syndrome
SGA	Small for Gestational Age

SUMMARY

Many conditions interfere with the general growth and development of children, as well as the craniofacial structures. Previous studies have shown that children with growth problems may present with underdevelopment of the cranial base, maxilla and mandible, increased prevalence of dental crowding and delayed development of the dentition. The purpose of this study was to perform an assessment of specific characteristics of occlusion in individuals with growth deficiencies.

All subjects in this study participated in dental screenings during the annual conventions of the Magic Foundation from 2010 to 2013. The Magic Foundation is a non-profit organization that gives assistance to families of children diagnosed with various medical conditions affecting growth.

A total of 58 subjects were included in the study. The charts of 33 subjects who participated in the screenings from 2010 to 2012 were analyzed and 25 subjects participated in a standardized orthodontic examination during the screenings performed in 2013. They presented with medical diagnoses of growth hormone deficiency, insulin-like growth factor deficiency, idiopathic short stature, small for gestational age, intra-uterine growth restriction, Russell-Silver syndrome, panhypopituitarism, optic-nerve hypoplasia/septo-optic dysplasia, congenital adrenal hyperplasia or autoimmune polyglandular syndrome type 1. The subjects were grouped by conditions with similar pathological processes. Subjects with primary, mixed and permanent dentitions were included in the analyses. The prevalence of maxillary transverse deficiency, dental

crowding, increased overjet, deep bite, Class II, and Class III molar relations were calculated for each group. For the Russell-Silver syndrome group, the mean overjet, overbite, maxillary and mandibular alignment scores were calculated and compared to the pooled mean of the general population according to the NHANES III study.

Due to the limited information available from the subjects' charts and the limited number of subjects examined in this study, the statistical analyses were mainly descriptive. The exception is the Russell-Silver syndrome group. This study found that Russell-Silver syndrome subjects presented statistically significant greater mean overbite, maxillary and mandibular alignment scores than the general population.

1. INTRODUCTION

1.1 Background

Many conditions interfere with the normal growth and development of children. The process of craniofacial growth and development is complex and can be affected by disturbances that interfere with normal growth.

Examples of conditions that present with short stature as a prominent feature are growth hormone deficiencies, idiopathic short stature, Russell-Silver syndrome, small for gestational age, intra-uterine growth restriction, panhypopituitarism, optic nerve hypoplasia/ septo-optic dysplasia, autoimmune polyglandular syndrome type I, and congenital adrenal hyperplasia. Some of these conditions present specific facial and dental characteristics (Keller et al., 1970; Kosowick and Rzymski, 1977; Bergman et al., 2003).

Growth deficiencies can be associated with underdevelopment of the cranial base, maxilla and mandible (Kosowick and Rzymski, 1977; Kjelberg et al., 2000). Studies have demonstrated that subjects with low levels of growth hormone have been reported with increased prevalence of dental crowding due to the small size of the jaws, as well as delayed development of the dentition (Keller et al., 1970; Takano et al., 1986; Krekmanova et al., 1997; Sarnat et al., 1988).

1.2 Significance

Diseases that interfere with the normal growth and development of children may influence the development of the craniofacial structures, including the jaws and the teeth. An investigation of the occlusal characteristics of children with growth

deficiencies is warranted to improve the understanding of the orthodontic needs of this population.

1.3 **Specific Aims**

The specific aims of this study are:

a) To determine the prevalence of selected occlusal characteristics in individuals with growth deficiencies.

b) To compare the prevalence and severity of selected occlusal characteristics in individuals with growth deficiencies to those of the general population.

1.4 **Hypothesis**

The null hypothesis of this study is:

a) There are no differences between occlusal characteristics of individuals with growth deficiencies and those of the general population.

2. REVIEW OF LITERATURE

2.1 Growth Hormone Deficiency and Idiopathic Short Stature

The prevalence of growth hormone deficiency (GHD) is estimated to be from 1:4,000 to 1:9,000 (Lindsay et al., 1994; Bao et al., 1992; Vimpani et al., 1977). GHD can happen in conjunction with other pituitary deficiencies or as an isolated deficiency. The diagnosis is based primarily on clinical assessment and auxology. Growth hormone level testing remains a controversial diagnostic tool due to variation in provocative agents, questionable validity and reproducibility. Routine GHD diagnosis is not based on genetic testing. However, numerous mutations leading to GHD have been identified and it is likely that the use of genetic testing become a more important tool in the diagnosis of GHD in the future (Stanley, 2012).

Growth hormone has direct effect on body structures and also functions as a regulating trophic hormone, which stimulates the productions of insulin-like growth factor I (IGF-I) amongst other peripheral hormones. IGF-I is an important mediator of GH and is essential for normal growth and development. Growth is impaired when the levels of IGF-I are low despite normal levels of GH. This condition is known as primary IGF-I deficiency (IGFD) (Ranke, 2006).

Another condition associated with reduced growth is idiopathic short stature (ISS). ISS is a disorder in which one's stature is at least 2 standards deviation below the norm, with normal body proportions and without evidence of nutritional deficiencies, endocrine abnormalities, chronic systemic or psychiatric diseases (Ranke, 1996). ISS children's birth weight falls within the normal range and they present normal levels of

GH. Despite normal GH levels, GH therapy has demonstrated to be beneficial and has been approved by the United States regulatory authorities for ISS children shorter than -2.25 standard deviations. The mean gain in adult height associated with GH therapy in ISS children is 3.5 to 7.5cm (Cohen et al., 2007).

Many authors have studied the dental and skeletal development of individuals with GHD and ISS. Keller et al. (1970) analyzed the skeletal development in GHD and ISS subjects as well as subjects with various other endocrine and metabolic diseases. Skeletal delay was observed in both GHD and ISS individuals. The delay was variable in the ISS group but steady in the GHD group. The skeletal examination was limited to a hand and wrist film and no evaluation of the skeletal craniofacial structures was performed in this study. Other studies focused on the craniofacial structures and showed that GHD and ISS individuals present underdeveloped maxillae and mandibles (Kosowick and Rzymski, 1977; Takano et al., 1986). Kosowick and Rzymski (1977) found that radiographs of the skulls of GHD individuals showed underdevelopment of the facial bones and normal or nearly normal cranial vault dimensions when compared to healthy control subjects. The maxillae were reduced in size and the sinuses were underdeveloped. The mandibles of GHD individuals were described as “small, delicate and with poorly developed angles” (p. 857). Takano et al. (1986) compared GHD to ISS children and found no difference in cephalometric analysis between groups. Kjelberg et al. (2000) performed cephalometric analyses of short individuals with varying GH levels and observed that most facial structures were significantly reduced in size and the cranial bases, maxillae and mandibles demonstrated disproportionate growth. As a consequence of the disproportionate growth, the faces were retrognathic and the

posterior facial height proportionally smaller than anterior facial height with an increased vertical inclination of the mandible.

Dental development delay is commonly present in GHD and ISS individuals (Keller et al., 1970; Kosowick and Rzymski, 1977; Takano et al., 1986; Krekmanova et al., 1997). Takano et al. (1986) and Krekmanova et al. (1997) found no difference in dental delay between GHD and ISS individuals while Keller et al. (1970) found "mild but consistent dental delay" (p. 417) in ISS individuals and significant dental delay in GHD individuals.

GHD and ISS individuals present particular dental features such as small sized teeth and high prevalence of crowding (Kosowick and Rzymski, 1977; Sarnat el al., 1988; Krekmanova et al., 1997; Kjelberg et al., 2000). Kosowick and Rzymski (1977) found that the teeth of GHD individuals were somewhat smaller than those of healthy subjects but "proportional to the stunted growth" (p. 859). Krekmanova et al. (1997) found that the teeth of GHD and ISS individuals were significantly smaller than the teeth of healthy individuals and no difference in tooth size between the GHD and the ISS individuals. Kjelberg et al. (2000) found high prevalence (>40%) of dental crowding greater than 2mm in GHD and ISS individuals and no significant difference in the amount of crowding between them. Takano et al. (1986) evaluated dental abnormalities in GHD and ISS and found that malocclusion was present in 39.5% of the GHD individuals with GHD and in 16.1% of the ISS individuals. However, the study did not define the criteria used to determine the presence of malocclusion.

Kjelberg et al. (2000) speculated that GHD and ISS individuals “might be in greater need of orthodontic treatment due to the higher percentage of dental crowding” (p.359). In their study, they consider a misalignment of the teeth of at least 2mm as the presence of crowding. Brunelle et al. (1996) reported that the mean alignment score for the United States’ population is 2.4mm for the maxillary and 2.7mm for the mandibular arch. Therefore, it is debatable that ISS and GHD individuals present greater orthodontic needs based on the amount of crowding.

Medication therapy to improve the growth in GHD and ISS may affect the development of the craniofacial structures (Kosowick and Rzymski, 1977; Sarnat et al., 1988). Kosowick and Rzymski (1977) observed that treatment with anabolic drugs stimulated exfoliation of primary teeth and eruption of permanent teeth. Sarnat et al. (1988) observed that GH therapy did not accelerate dental age but enhanced bone age. They evaluated dental casts and found that GHD individuals not treated with GH presented significantly smaller mandibular arch length than the treated group, but there was no significant difference between the groups in regards to the size of the maxillary arches. They also observed a higher prevalence of crowding in individuals not treated than in those treated with GH (37.5% vs. 23.3%). No statistical analysis was performed to indicate if the difference in the prevalence of crowding between the groups was significant. One can speculate based on the results of this study that GH therapy may improve mandibular arch length, which, in turn, may lead to decreased prevalence of crowding. Richey et al. (1995) found that the arch dimensions of untreated ISS individuals were significantly smaller than those of the children of normal stature. They observed a statistically significant tendency for the arch dimensions of ISS children

treated with GH to increase over time. However, the arch dimensions of the control group also increased. Therefore, the influence of GH treatment on arch dimensions over time remains debatable based on the evidence from this investigation. A weakness of this study is that it did not have a control group of untreated ISS children. Kawala et al. (2007) observed a reduction in facial convexity associated with GH therapy. The profile changes were due to changes in the position of the mandible and mandibular anterior growth. The authors found a positive correlation between the duration of GH treatment and the amount of forward mandibular growth and increase in SNB angle, suggesting that GH therapy can lead the craniofacial structures towards a more favorable pattern of growth.

2.2 **Small for Gestational Age**

The term small for gestational age (SGA) refers to the size of the infant at birth, not to fetus growth (Hokken-Koelega, 2001). An individual is considered SGA when their birth weight and/or length falls at or below 2 standards deviations from the mean for gestational age. A diagnosis of SGA does not exclude growth hormone deficiency (Lee et al., 2003).

Most SGA children experience catch-up growth and achieve a height above 2 standard deviations below the mean by the age of 2 years (Lee et al., 2003; Albertson-Wikland et al., 1993; Tenovuo et al., 1987; Ounsted et al., 1982). A child who remains at least 2 standard deviations below the mean height by the age of 3 years is not likely to experience catch up (Lee et al., 2003).

SGA children are at increased risk of experiencing developmental and social problems throughout life. They are at risk of presenting significant height deficits as adults when compared to children of normal birth weight and height (Strauss, 2000; Karlberg and Albertson-Wikland, 1995). The head size of SGA children at 5 years of age is likely to be smaller than non-SGA children (Strauss, 2000). SGA children are at increased risk of developing neurologic disorders, poor academic performance and social issues (McCarton et al., 1996; Larroque et al., 2001; van der Reijden-Lakeman et al., 1996). In the long term, they present increased incidence of hypertension, cardiovascular diseases, cerebrovascular diseases and non-insulin dependent diabetes mellitus (Phipps et al., 1993; Lever and Harrap, 1992; Hales and Barker, 1992; Barker et al., 1989).

The treatment of SGA children often includes administration of growth hormone. Growth hormones are used to stimulate catch up growth in early childhood and maintain normal growth. The final goal is achievement of normal adult height. This therapy has shown to be effective (Lee et al., 2003).

No previous studies analyzing the facial development and dental findings of SGA individuals were found.

2.3 **Intrauterine Growth Restriction**

Intrauterine growth restriction (IUGR) is characterized by birth weight and/or length below the 10^{th} percentile for gestational age and the fetus experienced pathological restriction of growth (Wollmann, 1998). The failure in normal development

is a consequence of placental insufficiency and impaired placental nutrient transport from the mother to the fetus due to disturbances blood flow from the uterus and/or the fetus to the placenta (Ghidini, 1996). Those, in turn, can be caused by intra-uterine infections, chromosomal abnormalities, teratogens, fetal structure abnormalities, maternal medical complications or can be idiopathic. The cause is known in 40% of cases and idiopathic in 60% of cases (Hoffman and Bakketeig, 1984).

In pregnancies with impaired placental perfusion, fetal adaptations to overcome the deficient transfer of oxygen and nutrients are observed. In severe cases, absent or reserve end-diastolic flow in the umbilical artery may be present. The cardiac output may be redistributed to maintain oxygen supply to the heart, adrenal glands and brain at the expense of visceral organs, such as the gastrointestinal system. This phenomenon is known as the brain sparing effect. As a consequence, the gastrointestinal system can experience ischemia/hypoxia, resulting in impaired function after birth. IUGR infants are at risk for intestinal disturbances ranging from temporary enteral feeding intolerance to necrotizing enterocolitis (Bozzetti et al., 2013).

IUGR can present effects later in life. 50-60 % of children who present short stature subsequently to IUGR have GH anomalies (de Waal et al., 1994). IUGR with normal levels of GH also tend to present deficit in final height (Chaussain et al., 1994). IUGR has been associated with increased incidence of cardiovascular diseases and type II diabetes in adult life (Osmond et al., 1993; Rich-Edwards et al., 1997, Barker, 2006; Lithell et al., 1996; Forsén et al., 2000).

No previous studies analyzing the facial development and dental findings of IUGR individuals were found.

2.4 **Russell-Silver Syndrome**

Silver et al. (1953) first described two children with this condition in the literature. Russell (1954) independently described five children with similar features. The term Russell-Silver Syndrome (RSS) later became used to describe individuals who present intrauterine growth restriction, post-natal growth hormone deficiency, relative macrocephaly and triangular facial appearance with or without fifth finger clinodactyly and/or body asymmetry (Wollman et al., 1995; Price et al., 1999).

The diagnosis of RSS is based on clinical features, which are non-specific, vary in severity, and are more pronounced early in life. Therefore, the frequency of RSS is not easily determined. Abnormalities in chromosomes 7 and 11 have been found in around half of the individuals with the clinical diagnosis of RSS. There are still a significant number of individuals who present the clinical features of the syndrome in which the molecular cause is unknown (Wakeling, 2011).

RSS individuals have typical facial characteristics. Their overall facial dimensions are smaller, their mandibles and maxillae are steeply angled and their posterior facial height is diminished in relation to their anterior facial height (Bergman et al., 2003).

RSS individuals also present unique dental characteristics. Most of the evidence about dental characteristics of RSS individuals comes from case reports. Only one study comparing a cohort of RSS individuals to a cohort of healthy individuals was

found. In that study, Bergman et al. (2003) found that RSS individuals had greater prevalence of increased overjet, overbite and dental crowding than normal individuals. The authors did not perform a quantitative analysis of the amount of crowding of RSS individuals; they considered that crowding was present when 2mm of more of misalignment existed. The prevalence of Class II malocclusion showed no difference between groups. Dental maturity was found to be within normal limits and time of eruption was significantly delayed (1.1 years) for RSS individuals.

The dental characteristics of RSS individuals described in case reports generally reflect the findings of the above mentioned cohort study with some individual variations. Most case reports found the presence of severe crowding (Ioulia et al., 2012; Kulkarni et al., 1995; Rubenstein and Vitsky, 1988). Ioulia et al. (2012) also observed normal overjet, increased overbite and severe transverse discrepancy of the mandible in relation to the maxilla. Kulkarni et al. (1995) reported three cases of RSS who presented dental anomalies. One individual presented multiple missing teeth, a second individual presented a high arched palate, delayed dental eruption and discolored teeth of variable size, and a third individual presented microdontia. Cullen and Wesley (1987) observed microdontia of the primary dentition and congenital absence of second premolars. Cephalometric analysis revealed reduced ramus height and increased gonial angle, which is also in agreement with the skeletal findings of the study performed by Bergman et al. (2003).

2.5 **Panhypopituitarism**

Panhypopituitarism (PHPT) is a condition in which the production of hormones by the pituitary gland is deficient. It can be caused by malformations during the development of the gland or be secondary to tumors or trauma. Multiple genetic mutations have been identified in the congenital forms. However, the incidence of mutations in subjects with hypopituitarism is low, indicating that many genes remain to be identified (Mehta and Dattani, 2008).

The signs of hypopituitarism are a combination of individual hormone deficiencies. Growth failure and delayed bone maturation may occur due to low levels of growth hormones. Proper development and function of the pituitary assures the regulation of metabolic control, puberty, reproduction and stress response (Pfäffle and Klammt, 2011).

Prolonged undetected PHPT can result in significant deficit in final height, global developmental delay due to undetected hypoglycemia, untreated hypothyroirodism and severe sodium imbalance due to inadequate treatment in subjects with diabetes insipidus (Mehta and Dattani, 2008). Hypopituitarism can be associated with other midlines deformities such as single central incisor and cleft lip and/or palate (Rodriguez et al., 2011; Mehta and Dattani, 2008; Hall et al., 1997; Rappaport et al., 1977).

No previous study performing a comprehensive evaluation of the dental characteristics of individuals with PHPT was found.

2.6 Optic Nerve Hypoplasia and Septo-Optic Dysplasia

Optic nerve hypoplasia (ONH) is a congenital malformation that may exist as a single defect or combined with other optic, cranial or facial anomalies. It may occur a component of septo-optic dysplasia, which is associated with midline brain malformations and hypopituitarism (Kaur et al., 2013). However, the terms ONH and SOD are commonly used interchangeably (Vedin et al., 2011). These anomalies affect 1 in 10,000 live births with equal distribution between males and females (Patel et al., 2006). The major morbidities of these conditions are associated with vision loss and hypopituitarism (Parker et al., 2002).

The manifestations of hypopituitarism in ONH/SOD subjects are variable and may present as GH anomalies, diabetes insipidus, hyperprolactinemia, adrenal insufficiency and hypothyroidism. The overall prevalence of endocrinopathies is 71.7%. The most common single endocrinopathy is growth hormone deficiency, with a prevalence of 64.1% (Ahmad et al., 2005). ONH/SOD subjects with growth hormone deficiencies present similar stimulated peak of GH levels as subjects who are GHD without brain abnormalities (Vedin et al., 2011). However, they appear to present greater height, weight and body mass index despite GH axis abnormalities (Ahmad et al, 2005; Vedin et al., 2011). They also present similar response to GH therapy, with height outcomes within 1 standard deviation of the mean (Vedin et al., 2011).

No previous study evaluating the dental characteristics of ONH/SOD individuals was found.

2.7 **Congenital Adrenal Hyperplasia**

Congenital adrenal hyperplasia (CAH) is characterized by a defect in cortisol biosynthesis. The condition is autosomal recessive and has been associated with mutations on CYP21 gene. In 95% of cases, the cortisol deficiency is due to deficiency of 21-hydroxylase. It can present with or without aldosterone deficiency and androgen excess (Merke and Bornstein, 2005). In the United States, the incidence of CAH is 1 in 42,000 in African Americans and 1 in 15,500 in Caucasians (Therrell et al., 1998).

A deficit in cortisol synthesis causes an increase in corticotropin-releasing hormone due to abnormal negative feedback. In order to regulate the hormonal imbalances, supra-physiologic doses of glucocorticoid may be necessary. The consequent iatrogenic high levels of cortisol combined with excess sexual hormones have a negative impact on the development of CAH individuals. This combination of hormonal imbalances can stunt growth in children. In addition, it can cause insulin resistance, metabolic syndrome and infertility (Merke and Bornstein, 2005). High levels of sex hormones causes the epiphysis to close prematurely and high levels of glucocorticoid decreases growth (DiMartino-Nardi et al., 1986; Urban et al, 1978; Brook et al., 1974). The mean adult height of subjects with classic CAH is between 1 to 2 standard deviations below the mean normal population (Eugster et al., 2001; Muthusamy et al., 2010). Growth hormone alone or in combination with gonadropin releasing hormone analogs increases predicted final height (Quintos et al., 2001).

The consequences of hormonal imbalances associated with CAH manifest throughout life. Female infants with classic CAH can present ambiguous genitalia due to

high levels of androgens during intrauterine development. Male infants may present no signs but slight genital hyperpigmentation and enlargement (Merke and Bornstein, 2005). Chronic corticotropin stimulation may play a role in formation of adrenocortical tumors since subjects with CAH present higher frequency of such tumors compared with the general population (Jaresch et al., 1992). Subjects with non-classic CAH present 25-50% of normal 21-hydroxylase activity (Merke and Bornstein, 2005). They do not present cortisol deficiency, only hyperandrogenism that is generally not manifested until later in life (Lebovitz et al., 1984; Moran et al., 2000).

No previous study evaluating the craniofacial features and dental characteristics of individuals with CAH was found.

2.8 **Autoimmune Polyglandular Syndrome Type 1**

Autoimmune polyglandular syndrome type I (APSTI) is an autosomal recessive condition associated with autoimmune regulator gene mutations (Nagamine et al., 1997). The typical clinical phenotype presents as chronic mucocutanoeous candidiasis, chronic hypoparathyroidism and autoimmune adrenal insufficiency (Ahonen et al., 1990; Neufeld et al., 1980). The condition is associated with various other clinical autoimmune endocrinopathies, autoimmune or immunomediated gastrointestinal disturbances, autoimmune skin diseases, keraconjuctitis, chronic active hepatitis, defects in the immune system, ectodermal dystrophy, asplenia and cholelithiasis (Ahonen et al., 1990; Neufeld et al., 1981;).

There are reports of growth hormone insufficiency in subjects with APS (Pun and Chandurkar, 2011; Franzese et al., 1999). However, no previous comprehensive study about growth deficit in individuals with APSTI was found. Studies evaluating the craniofacial structures and dental characteristics of individuals with APSTI were also not found.

3. METHODOLOGY

3.1 Study Design

This study consists of a retrospective component and a prospective component. The retrospective component consists of data about the dental occlusion of subjects with growth deficiencies obtained from orthodontic screening notes. The prospective component consists of data about the dental occlusion of subjects with growth deficiencies collected using a standardized clinical evaluation. The control group used in this study was the sample of the U.S. population examined during the National Health and Nutrition Surveys (Kelly et al., 1973; Kelly and Harvey, 1977; Brunelle et al., 1996)

3.2 Sample Selection

The Magic Foundation is a non-profit organization that helps families of individuals diagnosed with numerous medical conditions affecting growth. The organization provides support primarily through education, networking and medical referrals. The organization hosts a yearly convention where an extensive educational program is presented to the families of individuals with growth deficiencies. During the convention, many individuals with growth deficiencies including, but not limited to, GHD, IGFD, SGA, IUGR, RSS, PHPT, ONH/SOD, CAH and APSTI present for dental screening and counseling

The subjects of the retrospective component participated in the dental screenings of the Magic Foundation conventions from 2010 to 2012. One orthodontist participated in all the screenings and collected data about the occlusion of those subjects. The

subjects of the prospective component were participants of the 2013 Magic Foundation convention who volunteered to participate in study. The participation in the study was independent from the participation in the dental screening and counseling. No treatment was delivered to either cohort of subjects.

Only subjects who fulfilled the following inclusions and extrusion criteria were included in the study:

3.2.1 **Inclusion Criteria**

a) At least one set of opposing permanent molars or central incisors
b) Present a condition that is associated with growth deficiency- This information was obtained from the parent or legal guardian.

3.2.2 **Exclusion Criteria**

a) Individuals who presented uncooperative behavior such as refusal to let the examiner look into their mouth
b) Individuals who were unable to follow commands (e.g. open or close mouth) due to developmental delay and/or neuromuscular dysfunction

3.3 **Retrospective Component**

The primary examiner analyzed the screening notes of subjects screened from 2010 to 2012. The charts were de-identified so that no personal health information was available to the examiner.

The following information was recorded from the screening notes:

a) Medical diagnosis
b) Age
c) Growth hormone therapy: Yes or No
d) Dentition:
    a. Primary - No permanent tooth erupted
    b. Mixed - Presence of primary and permanent teeth
    c. Permanent: No primary tooth remaining - Permanent teeth may be congenitally missing or impacted, therefore presence of all permanent teeth is not used as criterion for determining permanent dentition.
e) Maxillary transverse deficiency - Determined by the presence of lingual crossbite and/or history of orthodontic maxillary expansion.
f) Overjet (OJ): Within normal limits, increased, edge-to-edge or negative. In cases where a millimetric measure was available, OJ between 0 and 2mm was considered within normal limits and OJ greater than 2mm was considered as increased.
g) Overbite (OB): Within normal limits, deep bite, edge-to-edge, negative overbite (open bite). In cases where a millimetric measure was available, OB

between 0 and 3mm was considered within normal limits and OB greater than 3mm was considered increased.

h) Crowding of at least 2mm or spacing

i) Molar and classification: Class I, II or III

3.4 **Prospective Component**

The primary examiner evaluated all the subjects who volunteered to participate in the study. The examination consisted of completion of a medical questionnaire by the subject's parent or legal guardian and a clinical examination of the subject.

3.4.1 **Medical Questionnaire**

The medical questionnaire consisted of the following questions:

a) What is the subject's age (in years and months)?

b) What is the subject's medical diagnosis?

c) Is the subject currently receiving GH replacement therapy?

d) If the subject is not currently receiving GH replacement therapy, has he/she ever taken GH replacement therapy?

e) Has the subject ever received orthodontic treatment?

f) Is the subject currently receiving GH replacement therapy?

g) If the subject is not currently receiving GH replacement therapy, has he/she ever taken GH replacement therapy?

h) Has the subject ever received orthodontic treatment?

i) If yes, how old was the subject when the most recent orthodontic treatment was started?

j) If yes, what was the reason for orthodontic treatment?

3.4.2 **Clinical Examination**

The examiner used a disposable mouth mirror, a periodontal probe and a disposable tongue blade to evaluate the following occlusal traits:

a) Incisor alignment score

The examiner measured with a periodontal probe, to the nearest whole millimeter, the bucco-lingual linear displacement of anatomic contact points of each maxillary and mandibular incisors. The alignment score was calculated by adding the displacements of each contact point. A score of zero was given when there was perfect alignment from the mesial surface of one canine to the mesial surface of the contralateral canine. Only teeth erupted to the level of the occlusal plane were included. The mesio-distal separation of contact points was ignored. For example, the displacement was zero if a diastema existed between incisors but the teeth were aligned and there was no labiolingual displacement between the adjacent contact points. If teeth were missing, the adjacent surfaces were excluded (Little, 1975; Brunelle, 1996).

b) Presence or absence of maxillary midline diastema

The presence of a maxillary midline diastema was defined as a mesio-distal separation of at least 2mm between the maxillary incisors. If at least one central incisor was missing or restored, the individual was excluded from the diastema assessment. Any space smaller than 2 mm was not considered a maxillary midline diastema (Brunelle, 1996).

c) Presence or absence of crossbite

Only primary and permanent teeth distal to the canines and erupted to the level of the plane of occlusion were considered for the evaluation of crossbites. A positive finding was defined as at least two teeth, either one on each side or at least two teeth on the same side, displaced past cusp to cusp either facially or lingually (Brunelle, 1996).

d) Overjet

The examiner measured with a periodontal probe, to the nearest whole millimeter, the horizontal overlap of the incisors when the posterior teeth were in occlusion. This measurement consisted of the distance between the mid-point of the labial surface of the most anterior lower central incisor to the mid-point of the labial surface of the most anterior upper central incisor, parallel to the occlusal plane. When the upper incisor was anterior to the lower incisor, the overjet was positive. When the lower incisor was anterior to the upper incisor, the overjet was negative. If there was no horizontal overlap of incisal edges, the relation was described as edge-to-

edge. No assessment was made when opposing central incisors were not present (Brunelle, 1996).

e) Overbite

The examiner measured with a periodontal probe, to the nearest whole millimeter, the vertical overlap of the incisors when the posterior teeth were in occlusion. When the incisors overlapped vertically, the overbite was positive. When there was a vertical separation between incisal edges (*i.e.* open bite), the overbite was negative. When there was no vertical overlap of incisal edges, the relation was described as edge-to-edge. The assessment was made on the upper right central incisor. If at least one right central incisor was not fully erupted, missing, fractured or restored, the left central incisors were used. If the left central incisors could not be used as substitution, no overbite assessment was performed (Brunelle, 1996).

f) Molar Classification

The examiner determined the permanent molar classification of the right and left sides when the posterior teeth were in contact. Class II molars presented the mesio-buccal cusp of the maxillary first molar occluding at or mesially to the mesio-buccal cusp of the mandibular first molar. Class III molars presented the mesio-buccal cusp of the maxillary first molar occluding at or distally to the disto-buccal cusp of the mandibular first molar. Class I molars presented the mesio-buccal cusp of

the maxillary first molar occluding between the mesio-buccal and disto-buccal cusps of the mandibular first molar.

3.5 Data Analysis

Data analysis was performed using SPSS vs.20.

3.6 Institutional Review Board Approval

This study was approved by the University of Illinois at Chicago Institutional Review Board on June 19, 2013 (IRB Protocol #2013-0501).

4. RESULTS

4.1 **Retrospective and Prospective Studies**

This study analyzed the charts of 33 subject screened during the 2010, 2011 and 2012 Magic Foundation convention. Twenty-five subjects fulfilled the inclusion and exclusion criteria and were examined during the 2013 Magic Foundation convention. The subjects were grouped by medical diagnoses. The data of the retrospective and the prospective cohorts were combined for all groups. The data from the prospective cohort RSS was also analyzed separately for comparison of the mean OB, OJ and alignment scores with those of the control groups.

The data from the combined cohorts is summarized on tables I and II.

Table I

SUMMARY DENTITION STAGE, MTD AND CROWDING

Variables / Groups	N	Primary Dentition	Mixed Dentition	Permanent Dentition	MTD	Crowding
GHD+ISS	16	1 (6%)	8 (50%)	6 (37%)	4 (25%)	9 (56%)
SGA	8	5 (62%)	3 (38%)	0 (0%)	1 (12%)	2 (25%)
RSS	20	3 (15%)	11 (55%)	6 (30%)	2 (10%)	17 (85%)
PHPT+ONH/SOD	12	5 (42%)	4 (33%)	3 (25%)	2 (17%)	2 (17%)

Table II

SUMMARY OJ, OB AND MOLAR CLASSIFICATION

Variables / Groups	N	Increased Overjet	Deep Overbite	Class II	Class III
GHD+ISS	16	6 (37%)	6 (37%)	5 (31%)	1 (6%)
SGA	8	3 (38%)	2 (25%)	1 (12%)	0 (0%)
RSS	20	10 (50%)	15 (75%)	8 (40%)	0 (0%)
PHPT+ ONH/SOD	12	3 (25%)	0 (0%)	0 (0%)	1 (8%)

4.2 **Growth Hormone Deficiency and Idiopathic Short Stature**

A total of 16 subjects reported GHD, IGHD or ISS. From the charts available, 8 subjects reported GHD, 1 subject reported IGFD and 1 subject reported ISS. From the subjects examined for this study, 4 reported GHD and 2 reported IGFD. The mean age of those subjects was 12 years and 9 months (range: 5 years – 14 years 11 months). From this cohort, 11 (68.8%) subjects were receiving or have received GH therapy. Subjects in all dentition stages were present in this cohort: 1 (6.3%) subject presented primary dentition, 8 (50%) subjects presented mixed dentition and 6 (37.5%) subjects presented permanent dentition. The information about the stage of dentition of 1 subject was not available. Maxillary transverse deficiency was present in 4 (25%) subjects. The OJ was increased in 6 (37.5%) subjects, edge-to edge incisor relation present in 1 (6.3%) subject and negative OJ in 1 (6.3%) subject. The OB was increased in 6 (37.5%) and 9 (56.3%) subjects presented crowding. The molar classification of 5 (31.3%)

subjects was class II and 1 (6.3%) subject was Class III. Some of the subjects examined, 2 GHD and 2 IGFD, have had or were having orthodontic treatment. All of those subjects reported crowding as one of the reasons for treatment, 1 subject reported increased OJ and late eruption and 2 subjects reported maxillary transverse deficiency in addition to crowding.

4.3 Small for Gestational Age

A total of 8 subjects reported SGA: 6 from the charts available and 2 examined for this study. The mean age of those subjects was 4 years and 4 months (range: 1 year and 9 months - 7 years). From this cohort, 2 (25%) subjects were receiving or have received GH therapy. None of the subjects in this cohort presented permanent dentition, 5 (62.5%) presented primary dentition and 3 (37.5%) presented mixed dentition. Maxillary transverse deficiency was found in 1 (12.5%) subject. The OJ was increased in 3 (37.5%) subjects, the OB was increased in 2 (25%) subjects and crowding was present in 2 (25%). Only 1 (12.5%) subject presented class II molar relation. Out of 5 subjects in the primary dentition, 4 (80%) presented no interdental spaces in the lower arch.

4.4 Russell-Silver Syndrome and Intra-Uterine Growth Restriction

A total of 20 subjects reported RSS: 6 from the charts available and 14 examined for this study. Two subjects examined for this study reported a diagnosis of SGA, a third subject reported IUGR and a fourth subject reported SGA and IUGR in addition to RSS. The data obtained from the prospective cohort about OJ, OB and crowding was

analyzed separately for statistical comparison with the values published by the NHANES III study (Brunelle et al., 1996). The prevalence of diastema of this cohort was also analyzed separately because this variable was not observed in the retrospective cohort.

The mean age of these subjects was 9 years and 8 months (range: 5 years -16 years and 7 months). From this cohort, 16 (80%) subjects were receiving or have received GH therapy. All stages of dentition were found in these subjects: 3 (15%) presented primary dentition, 11 (55%) presented mixed dentition and 6 (30%) presented permanent dentition. Maxillary transverse deficiency was found in 2 (10%) subjects and 1 (5%) subject presented buccal crossbite. The OJ was increased in 10 (50%) subjects and the OB was increased in 15 (75%) subjects. From the retrospective cohort, 3 (15%) subjects presented 100% deep bite and 5 (25%) subjects from the prospective cohort presented OB greater than 7mm. Crowding was present in 17 (85%) subjects. The molar classification was class II in 8 (40%) subjects. One subject presented a repaired cleft palate.

One subject from the prospective cohort did not present permanent central incisors. Therefore, the subject was not included in the diastema, OJ, OB and alignment scores. The mean age for the remaining prospective cohort (N=13) was 10 years and 11 months (range: 7 years and 1 month-16 years and 7 months). From this cohort, 3 subjects reported having had orthodontic treatment: 1 subject for overbite, 1 for overbite and crowding and 1 for crowding. The prevalence of diastema was determined from 11 subjects that were younger than 11 years of age and presented both permanent

maxillary incisors at examination. From this cohort, 4 (36.3%) subjects presented maxillary diastema. OJ and OB were measured in all 13 subjects. The mean OJ was 4.3mm (range: 0-10mm, SD- 2.5mm). The mean OB was 6.7mm (range- 0- 12mm, SD- 3.3mm).

The mean OJ and OB of the RSS cohort was compared to the values of the general population as determined by the NHANES III study (Brunelle et al., 1996). In that study, the population was distributed by age group. The pooled mean of OJ and OB values from the age groups 8-11 years and 12-17 years was used for comparison because the age range for the RSS cohort is from 6 years and 9 months to 16 years and 7 months. The mean OJ for the general population (8-17 years) was determined to be 3.2mm, (N=2,243). One-Sample T- test revealed no statistically significant difference (p=0.140) between the mean OJ of the RSS cohort (4.3mm) and the mean OJ of the general population (3.2mm). The mean OB for the general population (8-17 years) was determined to be 3.0mm, (N=2,266). One-Sample T-test revealed statistically significant difference (p=0.001) between the mean OB of the RSS cohort (6.7mm) and the mean OB of the general population (3mm).

The mean maxillary anterior alignment score was 7.1mm (range: 0-21mm, SD- 6.2mm). The mean mandibular anterior alignment score was 10.1mm (range: 2-35mm, SD – 9.3mm). The mean anterior alignment scores of the RSS cohort were compared to the values of the general population as determined by the NHANES III study (Brunelle et al., 1996). The pooled mean of maxillary and mandibular alignment indexes from the age groups 8 to 11 years and 12-17 years was used for comparison. One-Sample T-

test revealed statistically significant difference (p= 0.011) between the mean maxillary alignment score of the RSS cohort (7.1mm) and that of the general population (3mm, N= 2.275). One-Sample T- test also revealed statistically significant difference (p=0.008) between the mean mandibular alignment index (10.1mm) and that of the general population (3.1mm, N=2,301).

A summary of the dental findings of the RSS prospective cohort and those of the general population is presented on table III. The results of descriptive statistics and one-sample t-tests are presented on table IV.

Table III

SUMMARY RSS ($\bar{x}$ ± SD) AND CONTROL GROUP ($\bar{x}$)

Variables / Groups	Diastema (8-11 yrs)	Overjet (mm)	Overbite (mm)	MaxAlig (mm)	MandAlig (mm)
RSS	36%	4.31 ± 2.52	6.77 ± 3.29	7.15 ± 6.18	10.15 ± 9.30
Control	19%	3.20	3.00	3.00	3.10

Table IV

RSS DESCRIPTIVES AND ONE-SAMPLE T-TEST

Variables	N	Mean (mm)	SD (mm)	p-value	MeanDiff (mm)	CI (95%)
Overjet	13	4.31	2.52	0.140	1.10	-0.42 - 2.64
Overbite	13	6.77	3.29	0.001	3.79	1.78 - 5.76
MaxAlig	13	7.15	6.18	0.011	5.15	1.41 - 8.89
MandAlig	13	10.15	9.30	0.008	8.15	2.52-13.77

4.5 **Panhypopituitarism and Optic Nerve Hypoplasia/ Septo-Optic Dysplasia**

Since of growth hormone deficiency in ONH/SOD is due to malfunction of the pituitary gland, these conditions were analyzed together. A total of 12 subjects reported either PHPT or ONH/SOD: 1 PHPT examined for this study, 6 SOH/NOD and 5 PHPT from the charts available.

The mean age of these subjects was 7 years and 4 months (range: 2 years - 13 years and 4 months). 3 (25%) were receiving or have received GH therapy. A subject with PHPT presented unusual maxillary central incisors crown morphology, which were straight, small with a protuberance on the center of the incisal edge (Figure 1). Another subject presented a single maxillary central incisor. That same subject was undergoing orthodontic treatment at the time of examination for this study. The reported reasons for treatment were crowding, missing tooth (maxillary central incisor) and maxillary transverse deficiency. All stages of dentition were found in these subjects: 5 (41.7%)

presented primary dentition, 4 (33.3%) presented mixed dentition and 3 (25%) presented permanent dentition. Maxillary transverse deficiency was present in 2 (16.7%) subjects. The OJ was increased in 3 (25%) subjects. All subjects presented OB within normal limits. Crowding was present in 2 (16.7%) subjects and spaces were present in 6 (50%) subjects. One (8.3%) subject presented class III molar relation.

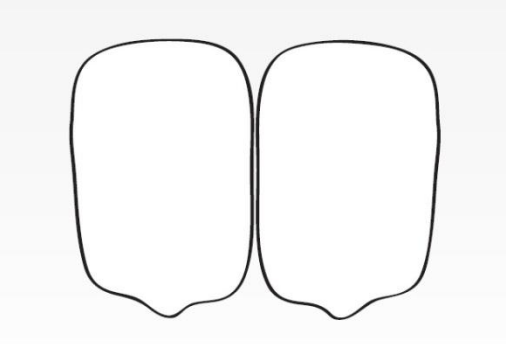

Figure 1: Unusual morphology of permanent central incisor crowns in a PHPT subject.

4.6 **Congenital Adrenal Hyperplasia**

One subject examined for this study reported CAH. This subject was 8 years and 4 months old at the time of examination. The subject was undergoing orthodontic treatment and the reported reason for treatment was crowding. The subject presented OJ of 4mm, OB of 7mm, maxillary and mandibular incisors irregularity index of 5mm and 12mm, respectively, and bilateral class I molar relationship.

4.7 **Autoimmune Polyglandular Syndrome Type I**

One subject examined for this study reported APSTI. This subject was 16 years and 3 months old at the time of examination and had never had orthodontic treatment. This subject presented OJ of 7mm, OB of 6mm, maxillary and mandibular incisors irregularity index of 12mm and 9mm, respectively, and bilateral class II molar relationship.

5. DISCUSSION

5.1 Discussion

This study analyzed the prevalence and severity of specific occlusal characteristics of individuals with different conditions that present with growth deficit as a common feature. Due to the heterogeneity of the conditions found in the sample, the subjects were divided into groups of conditions with similar pathologic processes.

5.1.1 Growth Hormone Deficiency and Idiopathic Short Stature

GHD and ISS subjects were included in the same group. These conditions may not present the same pathologic processes since ISS is, by definition, the presence of height deficit without evidence of systemic pathology (Ranke, 1996). In GHD, however, the diagnosis is based primarily on clinical assessment and auxology because GH level testing remains a controversial tool (Stanley, 2012). Besides, both conditions present similar treatment since ISS subjects have been shown to respond successfully to treatment with GH (Cohen et al., 2007).

The prevalence of MTD on our sample was 25%, which is higher than the prevalence of crossbite in the U.S. population (8.5% for individuals from 6 to 11 years of age and 7.9% for individuals from 12 to 17 years of age) (Brunelle et al., 1996). However, our sample was small (N=16) and it is possible that MTD in children with GHD or ISS is not as prevalent as found in this study.

Crowding was present in 56% of the subjects in this group. Kjellberg et al. (2000) found that 44% of children with GHD or ISS presented dental crowding

greater than 2mm. The studies cannot be directly compared because we did not determine the amount of crowding for our sample. However, both studies show a significant prevalence of dental crowding in GHD and ISS subjects.

Increased OJ was found in 37% and increased OB was also found in 37% of these subjects. These are higher than the prevalence reported by Kjellberg et al. (2000) who looked at 48 subjects with either GHD or ISS and found a prevalence of 14% increased OJ and 5% increased OB. Differences in methodology are likely the reason for such discrepancies. In our study, an OJ greater than 2mm and OB greater than 3mm was considered increased while Kjellberg et al. (2000) considered and OJ equal or greater than 6mm and OB equal or greater than 5mm as increased.

The prevalence of Class II molar classification in our sample was 31%. That is similar to the prevalence of Class II molar classification in the U.S. population, which is 35% for individuals 6 to 11 years of age (Kelly et al., 1973) and 32% for individuals 12 to 17 years of age (Kelly and Harvey, 1977). Kjellberg et al. (2000) found a prevalence of Class II malocclusion of 29% on his GHD and ISS sample, which is also similar to our findings.

5.1.2 **Small for Gestational Age**

The subjects who were SGA were analyzed in a separate group. None of the subjects in this cohort presented permanent dentition. They presented either primary or mixed dentitions.

Due to the small sample size (N=8) and young mean age (4 years and 4 months), the results are merely descriptive and no attempt was made to compare the prevalence and severity of occlusal characteristics to those of the general population. No previous study about malocclusion in SGA children was found for comparison.

Of the on this cohort, 5 presented primary dentition. Four of those subjects did not present interdental spaces in the lower arch and 1 presented crowding. The lack of interdental spaces in the primary dentition has been associated with increased risk of developing crowding in the permanent dentition (Baume, 1950b). However, only one of the subjects in the mixed dentition presented crowding.

5.1.3 **Russell-Silver Syndrome and Intra-Uterine Growth Restriction**

The RSS cohort was the largest (N=20) due to the significant presence of RSS individuals at the Magic Foundation conventions.

The prevalence of MTD (10%) in RSS subjects was similar to that of the U.S. population. Brunelle et al. (1996) found that 8.5% of people from 8 to 11 years of age and 7.9% of people from 12 to 17 years of age presented posterior crossbite. The prevalence of Class II molar relation in RSS subjects was 40%, also similar to that of the U.S. population, which is 35 % for people from 6 to 11 years (Kelly et al., 1973) and 32% for people from 12 to 17 years of age (Kelly and Harvey, 1977). The prevalence of increased OJ was 50% and increased OB

was 75%. Bergman et al. (2003) also investigated the occlusal characteristics of 15 RSS subjects and found that 25% presented OJ equal or greater than 6mm and 31.3% presented OB equal or greater than 5mm. In our study, an OJ equal or greater than 2mm and an OB equal or greater than 3mm was considered increased. This explains our higher prevalence of increased OJ and B. Bergman et al. (2003) also showed no difference in the prevalence of Class II molar relation between their RSS and control groups. The prevalence of Class II malocclusion in their sample (25%) was lower than on our sample (40%).

14 subjects of the prospective cohort were RSS. The severity of OJ, OB, maxillary and mandibular alignment, as well as the prevalence of maxillary diastema for these subjects were calculated. Statistical analyses revealed that RSS subjects present increased OB, maxillary and mandibular alignment scores when compared to the U.S. population ($p<0.05$). The difference in mean OJ is not statistically significant ($p>0.05$).

Evaluation of the presence of diastema in subjects younger than 11 years was performed for 11 subjects and revealed a prevalence of 36.3%. That is higher than the 19.3% found in the U.S. population from 8 to 11 years of age (Brunelle et al., 1996). Since there is a higher severity of crowding in the RSS population, a reduced prevalence of diastema could be expected. The high prevalence of diastema in this population could be due to the sample size. Another explanation could be that RSS subjects could present delayed development of the dentition as previously described in the literature (Bergman et

al., 2003). The presence of diastema, which is commonly present in the early mixed dentition, could persist at a later age in these subjects.

The most prominent features of malocclusion found in RSS subjects were deep bite and crowding. The deep bite found in RSS subjects was often 100% or greater. Deep bites that severe can compromise the periodontal health of the palatal surface of the upper incisors and the labial surface of the lower incisors. Gingival stripping associated with deep bite was observed in some patients. All individuals presented with at least 2mm of crowding. The most severe case presented with 35 mm of crowding. The crowding was worse in the mandible than in the maxilla. Case reports found in the literature (Ioulia et al., 2012; Rubenstein and Vitsky, 1988) present similar findings.

Based on our observations and the literature consulted in this study, RSS individuals present significant orthodontic needs. Orthodontic evaluation should be part of the multidisciplinary needs of RSS individuals.

5.1.4 **Panhypopituitarism and Optic Nerve Hypoplasia / Septo-Optic Dysplasia**

In PHPT and in ONH/SOD, normal growth can be impaired due to functional problems or malformations in the pituitary gland. Therefore, these conditions are analyzed in the same group.

The prevalence of MTD on our sample was 17%, which is higher than the prevalence of crossbite in the U.S. population, 8.5% for individuals from 6 to 11

years of age and 7.9% for individuals from 12 to 17 years of age (Brunelle et al., 1996). However, our sample was small (N=12) and it is possible MTD in subjects with PHPT or ONH/SO is not as prevalent as found in this study.

Crowding was present in 17% of the subjects in this group. That prevalence is lower than that of other groups analyzed in this study. One explanation for this finding could be that 42% of these subjects were in the primary dentition, when interdental spaces are commonly present (Baume, 1950a).

It appears that ONH/SOD that are growth hormone deficient present greater height, weight and BMI than GHD subjects without brain abnormalities (Ahmad et al., 2005; Vedin et al., 2011). That suggests a course of development that deviates less from the norm, possibly associated with better growth potential for the maxilla and mandible, which could also explain the lower prevalence of crowding.

Increased OJ was found in 25% of those subjects. None of these subjects presented increased overbite nor did they present Class II molar classification. One PHPT subject presented Class III molar. This same subject presented a single maxillary central incisor. Other authors have reported cases of PHPT associated with single maxillary central incisor and other midline malformations (Rodriguez et al., 2011; Mehta and Dattani, 2008; Hall et al., 1997; Rappaport et al., 1977).

5.1.5 Congenital Adrenal Hyperplasia and Autoimmune Polyglandular Syndrome Type 1

Only 1 CAH and 1 APST1 were examined for this study. Both of these subjects presented increased OJ, increased OB, significant maxillary and mandibular alignment scores. Due to the small sample size for these conditions, no attempt to compare these findings to those of the U.S. population was attempted. However, it was observed that the characteristics of the malocclusion of these subjects are also found in other conditions associated with growth deficiencies.

5.2 Limitations of the Study and Future Research

There are limitations in regards to the sample size and methodology of this study. A larger sample size would yield a better understanding of the occlusal characteristics of individuals with growth deficiencies. The sample size of this study was limited by the availability of data from dental charts and the number of subjects who presented to participate in the standard clinical exam. Future research can be performed to increase the number of subjects in this study. Future studies should focus on performing standard exams on subjects for more homogeneous data.

In this study, the subjects were not separated by stages of dental development. Future studies could focus on each stage of development: primary, mixed and permanent dentition, separately.

This study was limited to clinical evaluation of individuals. Evaluation of findings on panoramic radiographs and cephalometric analyses would yield a more thorough analysis of the orthodontic needs of this population. Future studies could also compare the sizes of teeth between individuals with growth deficiency and the general population.

This study did not perform a detailed examination of the subjects' medical records and it did not attempt to evaluate the effect of growth hormone therapy on dental and craniofacial development. Future studies could focus on performing a thorough review of the subjects' medical records to evaluate the gestational history and birth weight of the subjects since these factors can present consequences that interfere with normal craniofacial development. They should also evaluate the effects of growth hormone therapy on the craniofacial structures and the possible consequences of GH overuse.

6. CONCLUSIONS

1- Due to the limited information available for the retrospective cohort and the limited number of subjects examined for this study, it was only possible to perform statistical comparison of the severity of occlusal characteristics between the RSS group and the control group (U.S. population).

2- RSS subjects presented statistically significant greater mean OB compared to the control group.

3- RSS subjects presented statistically significant greater mean maxillary and mandibular alignment scores compared to the control group.

4- Orthodontic evaluation should be part of the multidisciplinary needs of RSS individuals particularly due to the high prevalence of severe deep bite and crowding.

APPENDIX

RAW DATA

GHD, IGFD, ISS

Age (months)	Dentition Stage[1]	MTD[2]	OJ[3]	OB[4]	Crowding [5]	Molar[6]
108	2	0	0	0	1	-
164	3	0	1	0	-	1
144	3	0	0	0	1	2
102	2	0	1	0	-	1
76	2	0	0	0	1	1
144	2	0	1	1	2	-
86	2	1	0	0	-	1
132	-	0	0	0	1	1
60	1	0	1	1	-	-
141	2	0	0	0	1	1
179	2	1	0	0	-	2
107	2	0	2	1	1	1
160	3	0	1	1	1	1
158	3	1	3	1	1	0
161	3	1	0	0	-	1
151	3	0	1	1	1	1

[1-] 1- primary; 2- mixed; 3- permanent

[2-] 0- no maxillary transverse deficiency; 1- lingual crossbite or history of maxillary expansion

[3-] 0- within normal limits (0-2mm); 1- increased (>2mm); 2- edge to edge; 3- negative

[4-] 0- within normal limits (0-3mm); 1- deep (>3mm); 2- edge to edge; 3- open bite

[5-] 1- crowding; 2- spacing

[6-] 1- Class I; 2- Class II, Class III

SGA

Age (months)	Dentition Stage[1]	MTD[2]	OJ[3]	OB[4]	Crowding [5]	Molar[6]
84	2	1	2	0	1	-
26	1	0	0	0	2	1
52	1	0	0	2	2	2
48	1	0	0	0	2	1
21	1	0	2	2	2	1
31	1	0	2	0	1	-
73	2	0	0	0	-	1
81	2	0	0	0	-	1

PHPT, SOD/ONH

Age (months)	Dentition Stage[1]	MTD[2]	OJ[3]	OB[4]	Crowding [5]	Molar[6]
120	2	0	0	0	2	1
72	1	0	0	0	-	1
48	1	0	0	0	2	-
24	1	0	0	0	-	-
49	1	0	1	0	2	-
24	1	0	1	0	2	1
72	2	0	0	0	2	1
141	3	1	0	0	-	3
120	2	0	0	0	-	1
122	3	1	0	0	1	1
160	3	0	0	0	2	1
105	2	0	1	0	1	1

[1-] 1- primary; 2- mixed; 3- permanent
[2-] 0- no maxillary transverse deficiency; 1- lingual crossbite or history of maxillary expansion
[3-] 0- within normal limits (0-2mm); 1- increased (>2mm); 2- edge to edge; 3- negative
[4-] 0- within normal limits (0-3mm); 1- deep (>3mm); 2- edge to edge; 3- open bite
[5-] 1- crowding; 2- spacing
[6] 1- Class I; 2- Class II, Class III

RSS

Age (months)	Dentition Stage[1]	MTD[2]	OJ[3]	OB[4]	Crowding [5]	Molar[6]
60	1	0	0	0	-	1
100	2	0	0	2	-	1
117	3	0	0	0	1	-
75	1	0	2	2	1	1
128	2	0	0	0	1	1
72	1	0	0	2	-	2
129	2	0	2	2	1	2
86	2	0	2	2	1	-
81	2	0	0	0	-	1
108	2	1	0	0	1	1
95	2	0	2	2	1	2
127	2	0	2	2	1	1
129	2	0	2	2	1	2
126	2	0	1	2	1	1
140	3	0	2	2	1	2
121	3	0	1	2	1	1
85	2	1	2	2	1	2
199	3	0	2	2	1	2
179	3	2	1	2	1	-
181	3	0	2	2	1	2

[1-] 1- primary; 2- mixed; 3- permanent
[2-] 0- no maxillary transverse deficiency; 1- lingual crossbite or history of maxillary expansion
[3-] 0- within normal limits (0-2mm); 1- increased (>2mm); 2- edge to edge; 3- negative
[4-] 0- within normal limits (0-3mm); 1- deep (>3mm); 2- edge to edge; 3- open bite
[5-] 1- crowding; 2- spacing
[6-] 1- Class I; 2- Class II, Class III

RSS- MAX ALIG, MAND ALIG, OJ AND OB (mm)

MaxAlig	MandAlig	OJ	OB
0	2	7	6
0	3	5	4
4	7	0	0
8	7	5	6
11	8	10	6
5	7	3	11
8	5	2	9
21	21	4	7
10	12	2	11
16	16	6	6
5	35	3	12
2	1	4	5
3	8	5	5

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VITA

NAME:	Natalia Linhares Rodrigues Hodge
EDUCATION:	Specialty certificate in orthodontics, University of Illinois at Chicago, Chicago, IL, 2014
	Master of Science in Oral Sciences, University of Illinois at Chicago, Chicago, IL, 2014
	Doctor of Dental Surgery, University of Illinois at Chicago, Chicago, IL, 2011
	Doctor of Dental Surgery, Universidade Federal do Ceará, Fortaleza, CE, Brazil, 2007
AWARDS AND HONORS:	Omicron Kappa Upsilon, Sigma Chapter,Honor Dental Society, 2011
	James R. Havera Scholarship in recognition of top ranking graduate student, 2011
	Magna Cum Laude, Universidade Federal do Ceará, 2007
	Scientific Initiation Research Scholarship awarded by the Ministry of Education of Brazil, 2005 to 2007
PROFESSIONAL MEMBERSHIPS:	American Dental Association
	American Association of Orthodontists
	Illinois Society of Orthodontists
	Chicago Dental Society

IRB NOTIFICATION

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Initial Review (Response To Modifications)

June 20, 2013

Natalia Hodge, DDS
Orthodontics
801 S. Paulina Street, Room 131
M/C 841
Chicago, IL 60612
Phone: (312) 996-7138 / Fax: (312) 996-0873

RE: Protocol # 2013-0501
"An Assessment of the Occlusal Characteristics of Individuals with Growth Deficiencies"

Dear Dr. Hodge:

Your Initial Review (Response to Modifications) was reviewed and approved by the Expedited review process on June 19, 2013. You may now begin your research.

Please note the following information about your approved research protocol:

Protocol Approval Period: June 19, 2013 - June 19, 2014
Approved Subject Enrollment #: 400 Total
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites: UIC, The Magic Foundation
Sponsor: None
Research Protocol(s):

a) An Assessment of the Occlusal Characteristics of Individuals With Growth Deficiencies, Version 2, dated 5/29/13

Recruitment Material(s):

a) Recruitment email "An Assessment of the Occlusal," vs3 - 6/16/13
b) Flyer "An Assessment of the Occlusal Characteristics of Individuals with Growth Deficiencies" vs. 2 -5/29/13

Informed Consent(s):

a) Consent "An Assessment of the Occlusal," Version 2 - 5/29/13
b) Waiver of Informed Consent for the retrospective portion of the research study granted under [45 CFR 46.116(d)]

Assent(s):

a) Verbal Assent "An Assessment of the Occlusal" (7-11 years of age), V2 - 5/29/13
b) Written Assent, "An Assessment of the Occlusal" (12-17 years of age), V2 - 5/29/13

Parental Permission(s):

a) Parental Permission "As Assessment of the Occlusal" Vs2 - 5/29/13

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific categories):

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving X-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)
Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.,
(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).,
(7) Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
05/13/2013	Initial Review	Expedited	05/28/2013	Modifications Required
06/03/2013	Response To Modifications	Expedited	06/11/2013	Modifications Required
06/17/2013	Response To Modifications	Expedited	06/19/2013	Approved

Please remember to:

→ Use your **research protocol number** (2013-0501) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
"UIC Investigator Responsibilities, Protection of Human Research Subjects"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 355-1404. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Sheilah R. Graham, MPH
IRB Coordinator, IRB # 3
Office for the Protection of Research Subjects

Enclosure(s):

1. **Informed Consent Document(s):**
   a) Consent "An Assessment of the Occlusal," Version 2 - 5/29/13
2. **Assent Document(s):**
   a) Verbal Assent "An Assessment of the Occlusal" (7-11 years of age), V2 - 5/29/13
   b) Written Assent, "An Assessment of the Occlusal" (12-17 years of age), V2 - 5/29/13
3. **Parental Permission(s):**
   a) Parental Permission "As Assessment of the Occlusal" Vs2 - 5/29/13
4. **Recruiting Material(s):**
   a) Recruitment email "An Assessment of the Occlusal," vs3 - 6/16/13
   b) Flyer "An Assessment of the Occlusal Characteristics of Individuals with Growth Deficiencies" vs. 2 -5/29/13

cc: Carlotta A. Evans, Faculty Sponsor, Orthodontics, M/C 841
Philip T. Marucha, Associate Dean for Research, College of Dentistry, M/C 621