Introduction

Craniofacial anomalies comprise approximately 30% of all congenital anomalies and are frequently associated with malocclusion, which often requires orthodontic treatment in order to obtain ideal occlusion[1]. Some craniofacial defects, such as facial clefting, have been relatively well studied regarding aspects ranging from their etiology to malocclusion and also the outcome of orthodontic treatment[2]. However, there are still many congenital disorders whose craniofacial features or orthodontic treatment outcome have not been well characterized.

Glucose transporter type 1-deficiency syndrome (GLUT1-DS) is a rare autosomal dominant genetic disorder caused by one or more mutations in the Solute Carrier Family 2, Facilitated Glucose Transporter Member 1 (*SLC2A1)* gene. Hallmarks of this transporter deficiency can include motor and mental developmental delays, seizures with infantile onset, deceleration of head growth that often results in acquired microcephaly, and movement disorders that include ataxia, dystonia, and spasticity[3]. The general

symptoms noted above are known to be caused by impaired brain energy metabolism resulting from a functional defect of SLC2A1, which is responsible for transporting glucose into the brain[4]. Although several reports have described the facial features of patients with GLUT1-DS using soft tissue analyses[3, 5], the overall craniofacial characteristics of these individuals including a description of their malocclusion and possible treatment options largely remains unreported. For this reason, we retrospectively examined the orthodontic treatment records of 9 GLUT1-DS patients and identified common malocclusion features, including excessive overjet and overbite.

Materials and methods

Study population

The samples used in this study consisted of samples from 9 Japanese GLUT1-DS patients (7 females and 2 males) aged from 8 to 49 years old,

retrospectively selected from the Department of Orthodontics and Dentofacial Orthopedics in Osaka University Dental Hopsital. None of the patients were biologically related to each other. All procedures performed in this study were in accordance with the ethical standards of Osaka University Graduate School of Dentistry (H30-E39) and in accordance with the declaration of Helsinki. A written understood consent was obtained from each participant and/or one of their patients.

Diagnosis of GLUT1-DS

Medical background and conditions associated with GLUT1-DS were assessed by a pediatric neurologist in Osaka University Medical Hopspital. Testing for genetic alterations within the *SLC2A1* gene was performed on DNA from each patient using conventional Sanger sequencing. Those patients who did not show any mutation in *SLC2A1* (cases 2, 3 and 6) were diagnosed by Erythrocyte 3-O-methyl-D-glucose uptake assay[6]. Both of these tests were performed in the Department of Pediatrics, Osaka University

Graduate School of Medicine. All of these information obtained from patients medical records.

Record analysis

Intraoral and facial photographs, dental casts and X-ray images for orthodontic diagnosis were utilized to assess craniofacial features. Cephalometric analysis as well as superimposition were performed using the Dolphin® imaging system version 11.8 premium (Dolphin Imaging & Management Solutions, Chatsworth, CA USA). Tooth material analysis was done by actual measurement using the patient's casts. All values were compared with Japanese standard values in a similar age group, which were established in the Department of Orthodontics and Dentofacial Orthopedics, Osaka University Graduate School of Dentistry.

Results

Diagnosis and etiology

A total of 9 patients (7 females and 2 males) aged between 8 and 49 years old participated in the study. The mean age was 19.6 years (mean for females, 19.8 years; for males, 19.0 years). Mutations in *SLC2A1* were detected in Cases 1 (c.227G>C, p.G76A), 4 (c.679+1G>A), 5 (c.517-2delA), 7 (c.1272T>A, p.Y424X), 8 (c.635G>A, p.R212H) and 9 (c.102T>G, p.N34K). While genetic variations in the SLC2A1 gene were not identified in the remaining three cases (Cases 2, 3 and 6), these cases were diagnosed with GLUT1-DS based on the results of a clinical erythrocyte 3-O-methyl-D-glucose uptake assay[6].

Facial and oral photographs of the 9 individuals are shown in Figure 1. As shown there, some of the patients exhibited a retrognathic facial profile with excessive overjet (OJ) (Cases 2, 3, 5, 6, 8 and 9). Lip incompetency with deep labiomental sulcus was observed in some of the patients (Cases 3, 5, 6 and 8). Two patients had a history of upper incisor injury (Cases 6 and 8), which is one of the representative risks which is increased by excessive OJ[7]. The oldest patient in this series was 49 years old, and had a low mandibular plane angle with excessive overjet and overbite (Case 9).

From the cephalometric analysis, large overjet (Cases 1, 2, 3, 5, 6, 8 and 9), small lower facial height (Me-PP) (Cases 2, 3, 4, 5, 6, 7 and 9), and low mandibular plane angle (FH-Mp) (Cases 4, 6, 7, 8 and 9) were observed at high frequency (Figures 1, 2 and Table 1).

None of the patients showed abnormal tooth number or developmental defects in any dentition except the wisdom teeth (Figure 3). The rate of occurrence of other manifestations, such as systemic abnormalities and behavioral features, including dysarthria, epilepsy, hypoalgesia, and need for growth hormone replacement therapy, was based on diagnoses by a pediatric neurologist and are shown in Table 1.

Treatment progress

The treatment objectives for two growing patients who showed large overjet and overbite with skeletal Class II tendency were to reduce the overjet and improve the convex facial profile. For these reasons, we treated these patients with Class II FKO in order to correct the malocclusion. The appliances were

used in these cases for 1 year and 8 months (Case 2) and 2 years and 6 months (Case 3), which resulted in reduced overjet and overbite (Figure 4, Table 1). Cephalometric superimposition for case 2 revealed vertical growth of the mandible with molar extrusion and lower incisor labial inclination after the treatment (Figure 4A). For case 3, we used a bite plate for daytime and Class II FKO for night-time. Substantial improvement of the retrognathic facial profile as well as overjet was observed by examining facial and oral photographs (Figure 4B). From the cephalometric superimposition, both molar extrusion and forward growth of the mandible were detected and resulted in reduced overjet and overbite with improved facial profile (Figure 4B).

The treatment objective for one adult patient with large overjet, skeletal Class II and maxillary spaced arch (Case 8) was to reduce the overjet and improve the maxillary spaced arch. For these purposes, a removable appliance with a labial bow was used to incline the upper incisors in order to reduce the overjet. Successful palatal inclination of the upper incisors could

be observed by superimposition (Figure 5A).

For one adolescent patient who showed large overjet, skeletal Class II, and severe crowding in the maxilla (Case 5), we decided to extract two upper bicuspids and use edgewise appliances with TADs. Treatment progress showed successful incisor retraction which resulted in reduced overjet (Figure 5B). The crowding was corrected and the current treatment is a detailing phase that aims to obtain mutually protected occlusion.

One of the patients (Case 6) with the most severe malocclusion, with large overjet and overbite with low angle mandibular plane, was diagnosed as a case that required orthognathic surgery. The treatment outcome will be described elsewhere.

All of the patients underwent the diagnostic procedures, and a possible treatment plan was suggested for each of them. Some of the patients were left untreated because of a minor problem they had, and/or because they had less need of orthodontic treatment.

Discussion

GLUT1-DS is inherited in an autosomal dominant manner by mutation in the *SLC2A1* gene, which encodes a protein responsible for transporting glucose from the bloodstream across the blood–brain barrier to the central nervous system[3, 4]. It is well known that various genetic as well as environmental factors influence individual craniofacial features[8]. For this reason, it is sometimes challenging to identify the craniofacial features in a rare syndrome when one has information about only a limited number of patients. The incidence/prevalence of GLUT1-DS patients has been estimated to be rather low (around 1:90000)[9, 10]. In the present study, we successfully collected 9 cases of GLUT1-DS patients and analyzed their medical records and summarized general craniofacial features in this syndrome.

Regarding craniofacial structures, it is known that GLUT1-DS patients exhibit acquired microcephaly as a result of abnormally slow growth of the brain and skull[11]. The morphological features of facial soft tissue in multiple GLUT1-DS patients have also been reported[5]. In the present study, we

described some characteristic craniofacial and occlusal features in GLUT1-DS patients based on the results of multiple analyses, which were compared with Japanese average values; these features included large overjet, small lower facial height (LFH), low mandibular plane angle (FH-Mp), and small mandible size (Go-Pg) (Table 1). We found that large OJ (greater than 5 mm), had a substantially higher prevalence in the GLUT1-DS patient group (77.8%) compared to the general Japanese population (22.4%) described in Surveys of Dental Diseases in Japan in 2016 (https://www.mhlw.go.jp/toukei/itiran/eiyaku.html). The prevalence of other features, such as small lower facial height (LFH), low mandibular plane angle (FH-Mp), and small mandible size (Go-Pg), in the general Japanese population are not available and will thus require further investigation in the future.

By genetic testing we identified multiple positions and types of mutation in the *SLC2A1* gene (shown in the Results section). There was a report that described types of mutation that were related to the severity of general

symptoms such as mental retardation in GLUT1-DS patients[12]. However, we could not find a clear correlation between the type of mutation and the craniofacial features, such as malocclusion severity in this study. This failure could be due to the small sample size and it may be possible to find a genotype and craniofacial phenotype correlation in the future by increasing the number of samples and performing detailed craniofacial analysis.

Some muscles in these patients are known to show spasticity[13]. For this reason it is possible to think that abnormal myofunctional activities of craniofacial muscle(s) could influence the growth of the craniofacial complex, and thus in turn cause malocclusion, similarly to how muscle hypertrophy or muscular dystrophy causes patients to exhibit skeletal discrepancy[14, 15]. However, the exact reasons for these craniofacial features and malocclusions in GLUT1-DS patients are still largely elusive and requires further investigation by increasing the sample size and performing biological basic research.

After the orthodontic diagnostic procedures, we used conventional treatment

methods such as functional or edgewise appliances. In many cases, the purpose of the orthodontic treatment was to reduce the overjet. Excessive overjet is known to result in increased risk of upper incisor trauma, and orthodontic treatment in children with overjet is effective for reducing the incidence of the trauma[7, 16]. Our study group indeed included two adult patients with large overjet who had already experienced upper incisor enamel fracture. The present results indicate that GLUT1-DS patients who exhibit excessive overjet could be treated efficiently and effectively using conventional orthodontic protocols in order to reduce their risk of incisal trauma.

Another problem which was exhibited in some cases was deep bite. In some cases, deep bite was associated with low mandibular plane angle, which could have increased the overbite due to short face pattern growth[17]. Two adult patients exhibited low mandibular plane angle and severe deep bite with lower incisors touching the palatal gingiva (Cases 6 and 9). Both of the children with deep bite that was treated with functional appliances showed

reduction of overbite due to skeletal and dental growth modification. One adolescent patient was treated with maxillary bicuspid extraction in order to correct the crowding and excessive overjet. TADs were inserted to reinforce the anchorage and overjet was substantially decreased by incisor retraction.

We speculated that GLUT1-DS patients might show different craniofacial growth patterns or reactions to orthodontic/orthopedic force for two reasons. The first is because of specific movement defects, including spasticity, which could influence craniofacial growth and orthodontic treatment[18]. The second is based on the defect of cellular glucose uptake, which could impact osteoblast differentiation and in turn could affect craniofacial growth as well as tooth movement[19]. However, all of the cases treated in this study showed reasonable orthopedic and/or orthodontic movement from the cephalometric superimposition without any major complication. Altogether, the present findings suggested that orthodontic treatment of GLUT1-DS patients with malocclusion could be performed in an effective manner. Our clinical experience indicated that some patients with hypoalgesia, which is one of the

symptoms of GLUT1-DS, could suffer injury of the mucosa by the orthodontic appliances that they did not report and thus it remained unnoted until the next visit for orthodontic treatment, which is one thing that should be noted and guarded against. Brushing their own teeth could be challenging due to the patients' ataxia, and thus professional tooth cleaning at each dental visit and careful tooth brushing instructions for the parents are also essential. It is also important to follow present treated cases in order to assess the stability of obtained occlusion since these patients exhibit muscle spasticity which could influence the position of dentition[20].

CONCLUSION

We summarized characteristic craniofacial features and malocclusion in this syndrome, such as excessive overjet, skeletal Class II and low mandibular plane angle. Orthodontic treatment of patients with GLUT1-DS both during childhood and during adulthood had beneficial results and contributed to improve the occlusion.

Ethical Approval

All the patients consented to publication of the study in writing.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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FIGURE LEGENDS

Figure 1 Initial facial and oral photographs of the patients before treatment.

Facial and oral photographs of 9 patients are shown. White letters in the upper left corner indicate the case number of the individual and white letters in the lower right corner indicate the age and sex. M: Male, F: Female.

Figure 2 Initial lateral cephalogram of the patients before treatment.

Lateral cephalograms of 9 patients are shown. Letters in the upper left corner indicate the case number of the individual.

Figure 3 Initial orthopantomogram of the patients before treatment.

Orthopantomograms of 9 patients are shown. Letters at the upper left indicate the case number of the individual.

Figure 4 Treatment outcome of two cases with Class ll functional appliance

Left panels show pre-treatment and post-treatment facial and oral photographs. Right panel shows superimposition of initial (black) and post-treatment (red) tracing of lateral cephalogram.

Figure 5 Treatment outcome of removable appliance and edgewise appliance with TADs

Left panels show pre-treatment and post-treatment facial and oral photographs. Right panel shows superimposition of initial (black) and post-treatment (red) tracing of lateral cephalogram.