Cervical characteristics of Noonan syndrome

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SUMMARY

BACKGROUND/OBJECTIVES A short neck and low posterior hairline are characteristics of Noonan syndrome (NS) and are hallmarks of basilar invagination/impression. However, it is seldom that NS has been directly linked with this symptom. Thus, this study aimed to investigate basilar impression in NS subjects compared with control subjects and individuals exhibiting Turner Syndrome (TS).

SUBJECTS/METHODS The degree of basilar impression and vertical positional differences of the third and fourth cervical vertebrae and hyoid bone in NS (n = 9, mean age: 12.1 years), TS (n = 9, mean age: 12.1 years), and control subjects (n = 9, mean age: 12.0 years) were investigated using lateral cephalometric radiographs. Differences between the three groups were compared using the Steel–Dwass test. Vertical positional differences in the anatomical structures within each group were compared using the Wilcoxon signed-rank test accompanied by a Bonferroni–Holm correction.

RESULTS The distance by which the odontoid tip extended past McGregor's line in subjects with NS was significantly greater compared with TS and control subjects. The third and fourth cervical vertebrae were positioned significantly superiorly in subjects with NS compared with TS and control subjects and, in NS, were also significantly superior to the hyoid bone. There was no difference in the position of the hyoid bone itself between the groups.

CONCLUSION/IMPLICATION These results suggest that basilar impression may be a frequently found symptom of NS.

Introduction

Noonan syndrome (NS; OMIM 163950) is an autosomal dominant condition in which approximately 50 per cent of cases are caused by missense mutations in the PTPN11 gene that encodes Shp-2, a regulatory component of the Ras-mitogen-activated protein kinase (Ras-MAPK) signalling network. In contrast, genetic anomalies in other Ras-MAPK pathway genes, such as KRAS, SOS1, and Raf-1, play only a minor role in the molecular pathogenesis of the disease (Ferrero et al., 2008). NS is characterized clinically by a pattern of typical facial dysmorphism, malformations including congenital cardiac defects, short stature, abnormal chest shape, a broad or webbed neck, and a variable learning disability (Turner, 2011; van der Burgt, 2007). Other characteristics are a short neck and low posterior hairline (van der Burgt, 2007). Reduced neck length and low hairline have been recognized as hallmarks of basilar invagination for several decades, and reduced neck length is considered a diagnostic feature of basilar invagination (Goel and Shah, 2009). In a previous study, patients with basilar invagination underwent atlantoaxial joint distraction as a putative treatment modality, with clinical and radiological analysis of the resultant physical and morphological changes in the neck. These experiments suggested that an asymptomatic short neck could be indicative of basilar invagination (Goel and Shah, 2009).

Another reported characteristic feature of NS is malocclusion (Collins and Turner, 1973; Horowitz and Morishima, 1974; Shaw et al., 2007). Thus, patients with NS often have need for orthodontic consultation. Several clinical reports describing such consultations have been published (Asokan et al., 2007; Emral and Akcam, 2009; Ierardo et al., 2010). Other orthodontic studies have reported abnormal radiographic findings in the cervical vertebrae, such as basilar invagination/impression (Vastardis and Evans, 1996; Soni et al., 2008). Such findings during cephalometric analysis were made possible because radiological diagnosis of basilar invagination/impression can be established using constructed lines on the lateral cephalogram (Soni et al., 2008).

It has been previously reported that the Arnold-Chiari malformation is also a characteristic of NS (Peiris and Ball, 1982; Gabrielli et al., 1990; Holder-Espinasse and Winter, 2003; Galarza et al., 2010), but there is only one case study directly linking NS with basilar invagination (Miyoshi et al., 2011). Thus, it is unclear whether basilar invagination/impression is a characteristic of NS.

Turner Syndrome (TS) is a phenotypically similar disorder to NS and shares several NS characteristics, such as short stature, webbed neck, low posterior hairline, and partially similar facial features (Gardner et al., 2007), although the presence of chromosomal defects in the
aetiology of TS distinguish it from NS (van Der Burgt and Brunner, 2000; Delgado-López et al., 2007). Therefore, the aim of this study was to systematically investigate basilar invagination/impression in NS compared with control subjects (lacking any congenital anomalies) and individuals with TS.

Subjects and methods

Subjects

Twenty-seven Japanese subjects participated after giving fully informed consent as required by the protocol, which was approved by the institutional ethics committee (approval #419). Participants were classified into three groups (n = 9 in each group): the NS group comprised subjects with NS (five males, four females; mean age: 12.1 ± 2.3 years), the TS group comprised subjects with TS, age-matched to the NS subjects (nine females; mean age: 12.1 ± 2.4 years), and the control group comprised subjects with no congenital anomalies and were age- and gender-matched with subjects in the NS group (five males, four females; mean age: 12.0 ± 2.2 years). Patients with NS and TS were diagnosed at hospitals containing a paediatric department. The karyotypes of TS subjects were unknown. All subjects were devoid of any missing erupted and successional permanent teeth (except for the third molars) and had no cleft lip and/or palate.

Cephalometric analysis

Lateral cephalometric radiographs were taken using a cephalostat (AXIOM Aristos MX/VX; Siemens, Tokyo, Japan). Patients were positioned with teeth in the intercuspal position and with a standing mirror-guided natural head position checked by dental radiologists, such that the degree of basilar impression and any vertical differences in the position of the third and fourth cervical vertebra and the hyoid bone could be simultaneously evaluated. In this study, we measured actual length. The magnification in the lateral cephalometric radiographs is 1.1 times and the results took into account the magnification.

The degree of basilar impression was measured as the distance by which the odontoid tip extended past McGregor’s line, drawn from the posterior hard palate to the lowest point on the midline occipital curve (Figure 1). Basilar impression is defined as odontoid tip migration of 4.5 mm or more past McGregor’s line (McGregor, 1948).

The vertical positions of the third and fourth cervical vertebra (C3 and C4, respectively) and the hyoid bone (H) were measured by extending a horizontal line from a reference point on each to intersect with a vertical (superior-inferior) line dropped from the sella turcica (S) (Figure 2). These reference points were derived from a previous report describing C3 and C4 references as being the most antero-inferior point of the body of these vertebrae, while the H reference was the most antero-superior point of the body of the hyoid bone (Kollias and Krogstad, 1999; Ricketts, 1989) (Figure 2).

To eliminate experimental errors, the same investigator traced all cephalometric radiographs, and the method error for each parameter was calculated by comparing duplicate tracings at an interval of at least 2 weeks. Errors for a single measurement of linear variables were calculated using the following formula (Dahlberg, 1940):

\[
\text{Method error} = \left( \frac{\sum d^2}{2n} \right)^{\frac{1}{2}}
\]

where \(d\) is the difference between measured pairs and \(n\) is the number of pairs.

Figure 1 Illustration showing the odontoid tip and McGregor’s line, which is used to assess superior odontoid migration. The dashed-dotted lines show McGregor’s line, and the distance by which the odontoid tip extends past McGregor’s line is indicated by an arrow.
Differences in linear measurements in the NS, TS, and control groups were examined using a Kruskal–Wallis test with post hoc Steel–Dwass analysis, a non-parametric multiple comparison procedure. Differences within each group with regard to the vertical positions of C3, C4, and H were statistically evaluated using the Friedman test and post hoc analysis using the Wilcoxon signed-rank test accompanied by a Bonferroni–Holm correction, a non-parametric statistical hypothesis test used when comparing two related or matched samples. A threshold of $P < 0.05$ was considered statistically significant for the Kruskal–Wallis, Steel–Dwass, and Friedman tests, and adjusted $P$-values were compared with 0.05 using a Wilcoxon signed-rank test with a Bonferroni–Holm correction (Chan et al., 2007).

Results

Representative lateral cephalometric radiographs from the NS, TS, and control groups are shown in Figure 3, with McGregor’s line and anatomical structures indicated on each. In the NS group, the odontoid tip, C3, and C4 were all located superiorly to their respective positions in the TS and control groups.

Clinical features of the subjects

Three NS subjects had a short neck and six had a low posterior hairline. In contrast no TS subjects had a short neck, but three TS subjects had a low posterior hairline. Two NS subjects had both symptoms.

Method error

Overall, the mean and standard deviation of the method error was $0.35 \pm 0.09$ mm for linear measurements. When compared with previous studies (Hiyama et al., 2001), no systematic errors were found.

Degree of basilar impression

Basilar impression is defined as extension of the odontoid tip 4.5 mm or more past McGregor’s line (McGregor, 1948). This was the case for seven subjects in the NS group, one subject in the TS group, and no subjects in the control group.
group. The median distance by which the odontoid tip extended past McGregor’s line in the NS, TS, and control groups was 7.0, 3.0, and 1.5 mm, respectively (Figure 4A). Statistical analysis using the Kruskal–Wallis test and Steel–Dwass post hoc test revealed significant differences between the groups, specifically between the NS and TS or NS and control groups. However, there was no significant difference between the TS and control groups. Between-group comparisons, adjusted for multiple testing by the Steel–Dwass test, are shown in Figure 4B.

**Vertical position of the third and fourth cervical vertebrae and the hyoid bone**

The Kruskal–Wallis test revealed significant differences between the groups with regard to the vertical position of C3 and C4 but not H. Steel–Dwass comparison showed that the vertical position of C3 was significantly more superior in the NS group compared with the TS and control groups. The same analysis demonstrated no significant difference between the TS and control groups. Between-group comparisons, adjusted for multiple testing by the Steel–Dwass test, are shown in Figure 4B.

Figure 4  Distance by which the odontoid tip extends past McGregor’s line in the NS, TS, and control groups. A, Individual data from all subjects. The horizontal line represents the criterion value of basilar invagination (4.5 mm). B, Data from A are represented as the median value enclosed by the 25th and 75th percentiles (box). Error bars represent 1.5 times the interquartile range of the lower and upper quartile. Data not included between the error bars are plotted as outliers (closed circle). *denotes a significant difference between the groups indicated ($P < 0.05$).

Discussion

The present study describes cephalometric analysis aimed at evaluating the position of the cervical vertebrae in NS, TS, and control subjects. The terms ‘basilar impression’ and ‘basilar invagination’ have been used synonymously. Kovero and colleagues defined basilar invagination as a protrusion of the odontoid process into the foramen magnum. This anomaly is apparent from the relation of the dens point to the foramen magnum line (McRae line). The area of the odontoid process that lies above one or several of the reference lines (Chamberlain line, McGregor line, or the baseline for the perpendicular distance from the tip of the odontoid process to a line parallel to the nasion-sella line and drawn through the lowermost point of the posterior cranial base) indicates basilar impression (Kovero et al., 2006). Thus, the term relevant to our results is specified as ‘basilar impression’, those used in a general sense are specified as ‘basilar invagination/impression’.

In the present study, there were three TS subjects with a low posterior hairline, but without basilar impression. Conversely, there were six NS subjects with a low posterior hairline and three with a short neck. Among them, two subjects had both symptoms. One subject with both symptoms and four subjects with a low posterior hairline had basilar impression. In this study, NS subjects with a low posterior hairline were associated with a high probability of basilar impression.

There are currently no reports describing basilar invagination/impression in TS patients. A previous study of basilar invagination/impression in osteogenesis imperfecta (OI) compared 54 OI patients with 108 healthy subjects (Kovero et al., 2006) and found a mean distance of odontoid tip extension past McGregor’s line of 2.3 mm in healthy subjects. In the present study, we calculated an equivalent...
median distance of 1.5 mm in the control group, in reasonable agreement with this previous study, suggesting that our results are comparable to published data.

There is currently only a single report directly linking basilar invagination with NS (Miyoshi et al., 2011). In the present study, the odontoid tip in seven out of nine subjects in the NS group extended 4.5 mm or more past McGregor’s line, and the distance by which the odontoid tip extended past McGregor’s line in this group was significantly greater compared with the TS and control groups. There are studies that have evaluated basilar invagination/impression using McGregor’s line as a reference line. Basilar invagination/impression has been variably defined as the tip of the odontoid process located more than 4.5 (McGregor, 1948), 5 (Soni et al., 2008), and 7 mm (Sillence, 1994) beyond McGregor’s line. In the present study, there were seven out of nine subjects (77.8 per cent) with odontoid tip migration of 4.5 mm or more in the NS group, six out of nine subjects (66.7 per cent) with migration more than 5 mm (except one subject with exactly 5 mm), and three out of nine subjects (33.3 per cent) with migration more than 7 mm (except two subjects with exactly 7 mm). In a previous study, it was stated that the odontoid apex should not lie above the criterion distance from McGregor’s line in 90 per cent of individuals (Yochum and Lindsay, 2005). In other words, only 10 per cent of subjects would have the odontoid apex below it in the general population. In this study, the percentages of NS subjects with the odontoid apex above it were higher with regard to any of the criteria above.

Basilar invagination/impression is indicative of a cephalad position of the upper cervical vertebra relative to the base of the skull (Guebert et al., 2005). Common signs and symptoms include muscle weakness, neck pain, posterior column dysfunction, bowel and bladder disturbance, and paraesthesia (Goel et al., 1998). However, a large proportion of deformities of the craniovertebral junction, particularly skeletal anomalies, are asymptomatic. Indeed, symptoms were absent in 60 per cent (of 52 cases) of radiologically demonstrable cases of basilar impression (Burrows, 1981), and in 100 per cent of the NS subjects in the present study. The lack of literature reporting coincident NS and basilar invagination/impression may stem from the fact that most NS patients with basilar invagination/impression, being asymptomatic, fail to consult a neurologist.

We found that the positions of C3 and C4, but not the hyoid bone, in the NS group were significantly superior to those in the TS and control groups, suggesting that...
basilar impression might be a frequently found symptom of NS. Although the relationship between the positions of the cervical vertebrae and the hyoid bone has not been reported in TS, it has been investigated in healthy subjects (Moore and Dalley, 1999; Standring, 2008). We found that in the control group using the horizontal line, C3 was significantly superior to the hyoid bone, whereas C4 was significantly inferior to the hyoid bone. In a previous study using CT images and the FH plane as a reference, the centre of the body of the hyoid bone was most often at the level of C4, despite the hyoid bone being consistently described in contemporary anatomy textbooks as being level with C3 (Mirjalili et al., 2012). The authors postulated that this disparity might relate to the use, by anatomy textbooks, of both the body and greater horn of the hyoid bone to describe its vertebral level, whereas they measured only from the centre of the body of the hyoid bone. The authors also pointed out that the vertebral level of the body of the hyoid bone seen in tracings of the lateral cervical radiograph varies depending on which reference plane is used (Figure 6). We measured the orientation of a horizontal reference line and FH plane in the control group according to Madsen's method (Madsen et al., 2008) and confirmed that the average orientation was $-3.28 \pm 4.01$ degrees similar to that reported in Madsen et al ($-4.82 \pm 4.63$ degrees in that study). In agreement with the Mirjalili study, there was no difference in the statistical results when the FH plane was used instead (data not shown) or in the centres of both the hyoid bone and C4 as references, the reference point H in eight control subjects was located approximately level with the fourth cervical vertebra (data not shown). However, because in the present study we used alternative reference points for C3 and C4 (i.e. their most antero-inferior points) and the hyoid bone (i.e. its most antero-superior point) (Figure 6), the reference point of H was located significantly superior to the reference point in C4, despite the anatomy being demonstrably normal and in agreement with previous studies. We believe that this accounts for any discrepancy between our data and previous studies.

In this study, the number of subjects was small. However, it is difficult to recruit sufficient numbers of NS and TS subjects because they are rare syndromes. Further studies should investigate the results found here in a larger number of NS subjects. However, most previous studies listing cervical spine malformations commonly found in a variety of syndromes (Vastardis and Evans, 1996; Soni et al., 2008) did not include NS in their analysis, depriving clinicians of an easy reference for recognizing and diagnosing NS in relation to other conditions affecting the cervical vertebrae. Our findings may help orthodontists recognize NS through the detection of basilar impression, a frequently found symptom of this syndrome, using cephalograms when patients attend orthodontic clinics for correction of malocclusion.

Conclusion

In the current study, we found that the odontoid tip extended significantly further past McGregor's line in the NS group compared with the TS and control groups, and that the positions of the third and the fourth cervical vertebrae in the NS group were significantly superior to those in the TS and control groups. Together, these data support a conclusion that basilar impression may be found frequently as a characteristic feature of NS.

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