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Title: Monitoring Skull Base Abnormalities in Children with Osteogenesis Imperfecta – Review of Current Practice and a Suggested Clinical Pathway

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Abstract

Objectives

In the context of a lack of national consensus on the benefits of skull base imaging in children with osteogenesis imperfecta (OI), this study aims to analyse and correlate the clinical symptoms and radiological images of children with severe OI.

Methods

A retrospective case notes and image analysis was carried out on children with complex OI between 2012 and 2018 at a specialist tertiary centre. Data were collected on patient demographic factors, clinical data, imaging findings (presence of Wormian bones, platybasia, basilar impression (McGregor's technique) and basilar invagination (McRae's technique)), and clinical features at the time of imaging.

Results

Of the 127 patients in the OI database, 94 were included. A total of 321 radiographs, 21 CT scans and 39 MRI scans were analysed. Average frequency of radiographs was 8 per 10 years. Of the 94 patients, 58 (62%), 10 (11%), 1 (1%) demonstrated platybasia, basilar impression, and basilar invagination, respectively. Of the radiographs analysed, platybasia, basilar impression, basilar invagination, and the presence of Wormian bones, could not be evaluated in 71 (22.3%), 48 (15.2%), 61 (19.5%) and 28 (9.4%) radiographs respectively (due to poor positioning, anatomical abnormalities, and poor image quality). Of the 140 radiographs with platybasia, 17 (12%) also demonstrated basilar impression compared to only 3 (2.9%) out of the 99 without platybasia ($p=0.03$). No significant associations were seen between the presence of Wormian bones and basilar impression.

Of the 39 MRIs, additional information on CSF flow rate, spinal cord signal and cerebellar morphology was reported in 14 (36%). There was a lack of concordance between MRI and matched radiographs in 7.1% (1/14) and 36% (5/14) for platybasia and basilar impression respectively, with full concordance for basilar invagination.

Fewer than 5% had positive clinical symptoms/signs at the time of imaging; 2% (7/321) had macrocephaly, 0.6% (2/321) headache, all other neurological features were absent). Clinical features were not documented in >85% of patients.

Conclusion

The apparent low prevalence of clinical symptoms and signs and of radiologically identified cranio-cervical abnormalities, suggests that current levels of serial imaging may be excessive. Until larger prospective studies clarify these issues, we suggest a clinical pathway for base of skull imaging which proposes a risk stratification approach to radiographic frequency and suggests parameters for proceeding to MRI.

Keywords

Osteogenesis imperfecta
Skull base imaging
Cranio-cervical abnormalities
Clinical pathway

Abbreviations

OI- Osteogenesis imperfecta
D-M distance- Perpendicular distance of the tip of dens (D) to a line drawn through the most caudal point of occipital curve parallel to sella-nasion line (M)
MR- Magnetic resonance
LFMCSR- Lateral foramen magnum-centred skull radiographs
DI- Dentinogenesis imperfecta

Declaration of interest

NJB undertakes consultancy activity or clinical trial activity in the OI area for Amgen, Mereo Biopharma and Ultragenyx Pharmaceuticals. No other authors have any decelerations of interest.

1.0 Introduction

Osteogenesis imperfecta (OI) is a group of heritable genetic disorders which affect 1 in 15,000 to 20,000 births [1]. Genetic variants, most commonly *COL1A1* or *COL1A2*, lead to impaired type 1 collagen production and/or processing, resulting in altered bone material properties. These generally result in reduced bone mass and strength, which manifest as bone fragility and, in more severe disease, skeletal deformities [2].

Uncommonly, neurological complications are encountered in individuals with OI. These can be as a result of skull base abnormalities due to bony deformation, which can lead to serious complications and even death [2]. Basilar impression and invagination as well as platybasia are the most common skull base abnormalities in OI. These abnormalities have variable clinical presentations, from identification through screening asymptomatic individuals to acute neurological deterioration. Mostly, the only symptom present is headache, and this can pose a diagnostic challenge [3]. Importantly, whilst platybasia is mostly asymptomatic and its clinical significance uncertain [7], the early diagnosis of basilar invagination is important, as treatment is beneficial in symptomatic cases [5, 6]. Other abnormalities include compression of the structures of the posterior fossa, Chiari malformation, spinal cord syrinx, and hydrocephalus [4].

The current radiological modality used in screening for cranial base anomalies is lateral skull radiography; MRI is reserved for patients with abnormal or non-diagnostic radiographs or those with indicative neurological symptoms and/or signs [8]. However, the diagnostic criteria and terminology used is variable. Basilar invagination is identified by some authors (e.g., Cheung, Kovero and Arponen) as the protrusion of the odontoid into the foramen magnum based on a McRae measure at or above 0 [7, 9, 10]. Other authors (e.g., Janus) define basilar invagination as "protrusion of the odontoid above Chamberlain's or McGregor's line", while Sillence used a peg location of above McGregor's line by at least 7mm or above Chamberlain's line by at least 5mm [11, 12]. Basilar impression is defined by Arponen et.al as “relative lowering of the

cranial base with consequent positioning of the uppermost vertebral structures above the caudal border of the skull", and platybasia as "flattening of the cranial base" [7]. Basilar impression has also been described as "a condition in which the odontoid process is positioned far above the caudal borders of the skull". The radiographic criteria for basilar impression are fulfilled if the Chamberlain measure, the McGregor measure, or the D-M distance ('perpendicular distance of the tip of dens (D) to a line drawn through the most caudal point of occipital curve parallel to sella-nasion line (M)') are elevated by more than 3 SDs above the average of age-matched healthy controls, and platybasia as "a flat anterior cranial base angle (nasion-sella-basion angle)". Platybasia is diagnosed when the "anterior cranial base angle was more than 3 SDs above the average of healthy controls" [9, 10]. Given the variable definitions and parameters used, it is not surprising that the reported prevalence of skull base anomalies in children with OI is variable. One study showed a prevalence of platybasia and basilar impression of 16% and 4% respectively [9], while the reported prevalence of basilar invagination ranges from 6% to 25% [7, 9, 10, 13].

Although neurological symptoms are described in patients with OI, some studies have shown no difference between the prevalence of neurological symptoms amongst healthy populations and patients with OI [7, 13] and insufficient clinical data are available to determine the prevalence of neurological symptoms and their relation to skull base abnormalities in children with OI.

Apart from some suggestions that radiological studies should be performed every 2 to 3 years after the age of 5 in patients with severe OI [12], no agreed guidelines for radiological assessment of skull base abnormalities in these patients are available. Arponen suggests that in asymptomatic patients no further images are required, while an individual plan should be established for those who develop relevant symptoms [7]. However, no specific data are given on how often the follow-up studies should be performed. As a result of this lack of data, there is no consensus on the benefits of skull base imaging in children with OI. Therefore, this retrospective case note review aimed to analyse and correlate the clinical symptoms and radiological images of children with severe OI, with the objective of assessing the clinical impact of skull base imaging in this group.

2.0 Material and Methods

2.1 Patient Cohort

This retrospective case notes and image analysis was carried out on patients listed on the local osteogenesis imperfecta database of children with severe and/or complex OI between 2012 and 2018 at the <<BLINDED>>, a specialist tertiary centre in <<BLINDED>>.

Exclusion criteria included lack of a definitive diagnosis of osteogenesis imperfecta, inaccessibility to notes or images, and transfer of care from a different centre which had resulted in gaps in access to the necessary data. OI was diagnosed by clinical and radiological criteria with common genetic mutations identified in some cases. Severity of OI was classified according to the "expanded" Sillence classification [14] .

Data were collected on patient demographic factors (age and gender), clinical data (bisphosphonate therapy and severity/type of OI), imaging findings, and clinical features at the time of imaging.

2.2 Image Analysis

Data on the total number, frequency, and specific parameters for three imaging modalities (radiographs, CT scans and MRI scans) were collected.

The parameters measured included basilar invagination, basilar impression, platybasia and the presence or absence of an abnormal Wormian bone pattern. Basilar invagination was defined as the upward migration of the peg into the foramen magnum, i.e., the presence of the tip of the odontoid >0mm above McRae's line, a line joining the anterior to posterior margins of the foramen magnum (Figure 1a and b). Basilar impression was defined as the upward migration of the peg relative to the depression of the occiput, i.e., the presence of the tip of the odontoid >4mm above McGregor's line, a line joining the posterior hard palate to the most caudal point of the occiput (Figure 2). Platybasia was defined by the presence of a base of skull angle greater than 143 degrees. The base of skull angle is the angle created by the intersecting lines between the nasion and the tuberculum sellae, and the tuberculum

sellae and the anterior margin of the foramen magnum (Figure 3). Wormian bones are accessory bones along the sutures; an abnormal pattern was defined as greater than 10 Wormian bones in a mosaic distribution. If any relevant anatomical landmark could not be reliably identified, the radiograph was deemed as poor quality and the reason e.g., rotation, movement, poor penetration or position, excess coning etc was documented.

Additional parameters measured on the MRI scans included abnormal spinal cord signal, CSF flow rate around the foramen magnum and presence of cerebellar abnormalities.

Radiographic analysis was conducted using the tools of the PACS workstation by a trained research assistant and a specialist consultant radiologist working within the OI service. Radiographs analysed by the research assistant were randomly re-analysed by the consultant radiologist for quality assurance. MRI analysis was conducted by 1 of 2 paediatric neuroradiologists. Where the radiograph was absent, but a formal report of the above parameters was present, this was used.

Clinical features documented at the time of each image were collected (presence, absence, or no documentation) and included macrocephaly, headache, ataxia, lower cranial nerve palsy, paraesthesia, quadriparesis, hyperreflexia, Hoffmann's sign, clonus, nystagmus, dysphagia, subdural/extradural haemorrhage following trauma, respiratory compromise, stroke, and death.

2.3 Statistical Analysis

All statistical analysis was conducted using SPSS software (Version 26). A t-test or Mann-Whitney U test, depending on the distribution of data, was used to compare radiographic and clinical parameters between groups.

The study did not need formal Research Ethics Committee review but received local R&D approval before commencement.

Figure 1a: Measuring basilar invagination [defined as the upward migration of the peg into the foramen magnum, i.e., the presence of the tip of the odontoid >0mm above McRae line, a line joining the anterior to posterior margins of the foramen magnum]. In the image below, the odontoid is 10.8mm below McRae's line and therefore this patient does not have basilar invagination.

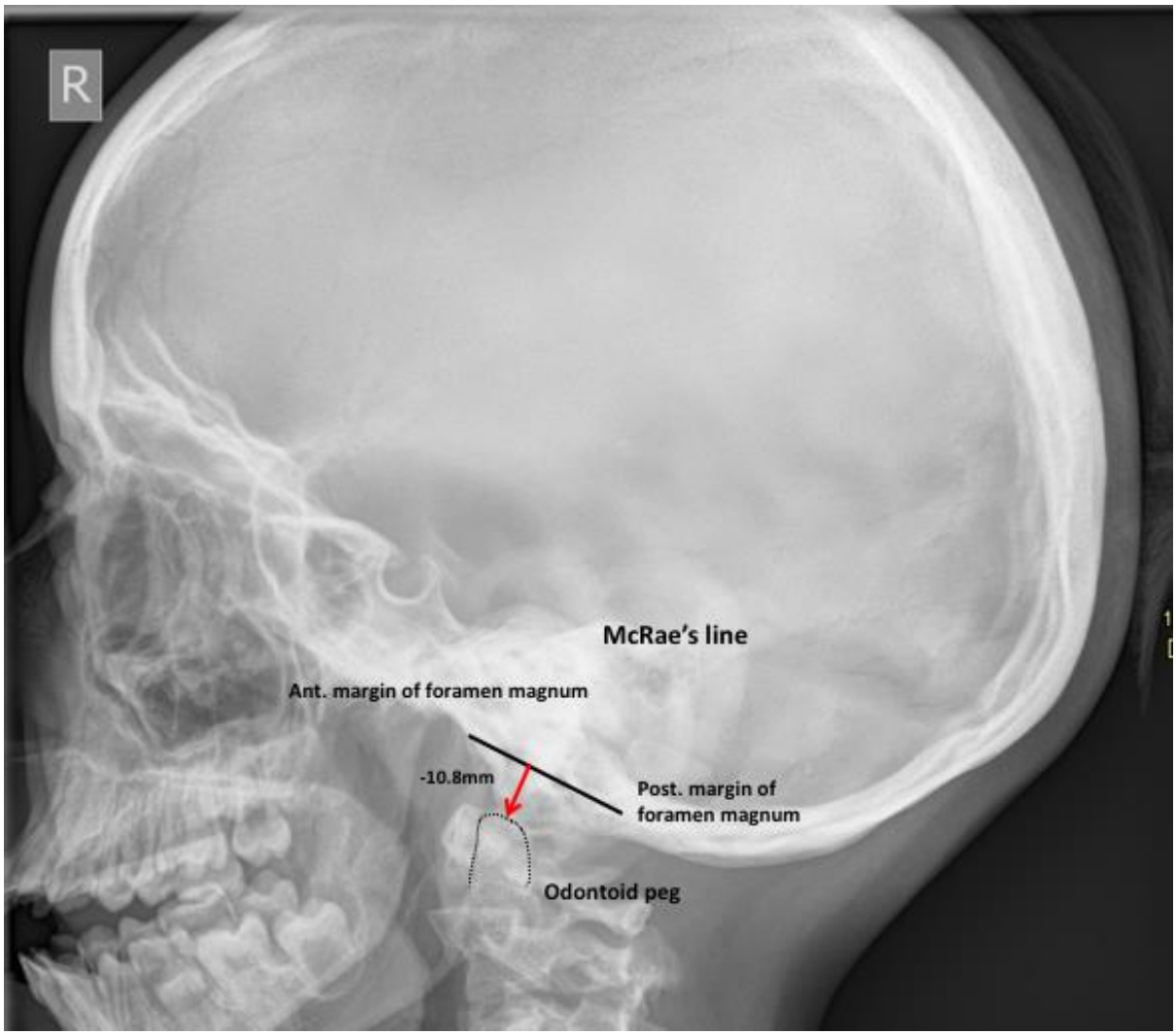


Figure1b:

Sagittal T1 Volume MRI demonstrating basilar invagination. The tip of the odontoid lies 3.2mm above McRae's line.

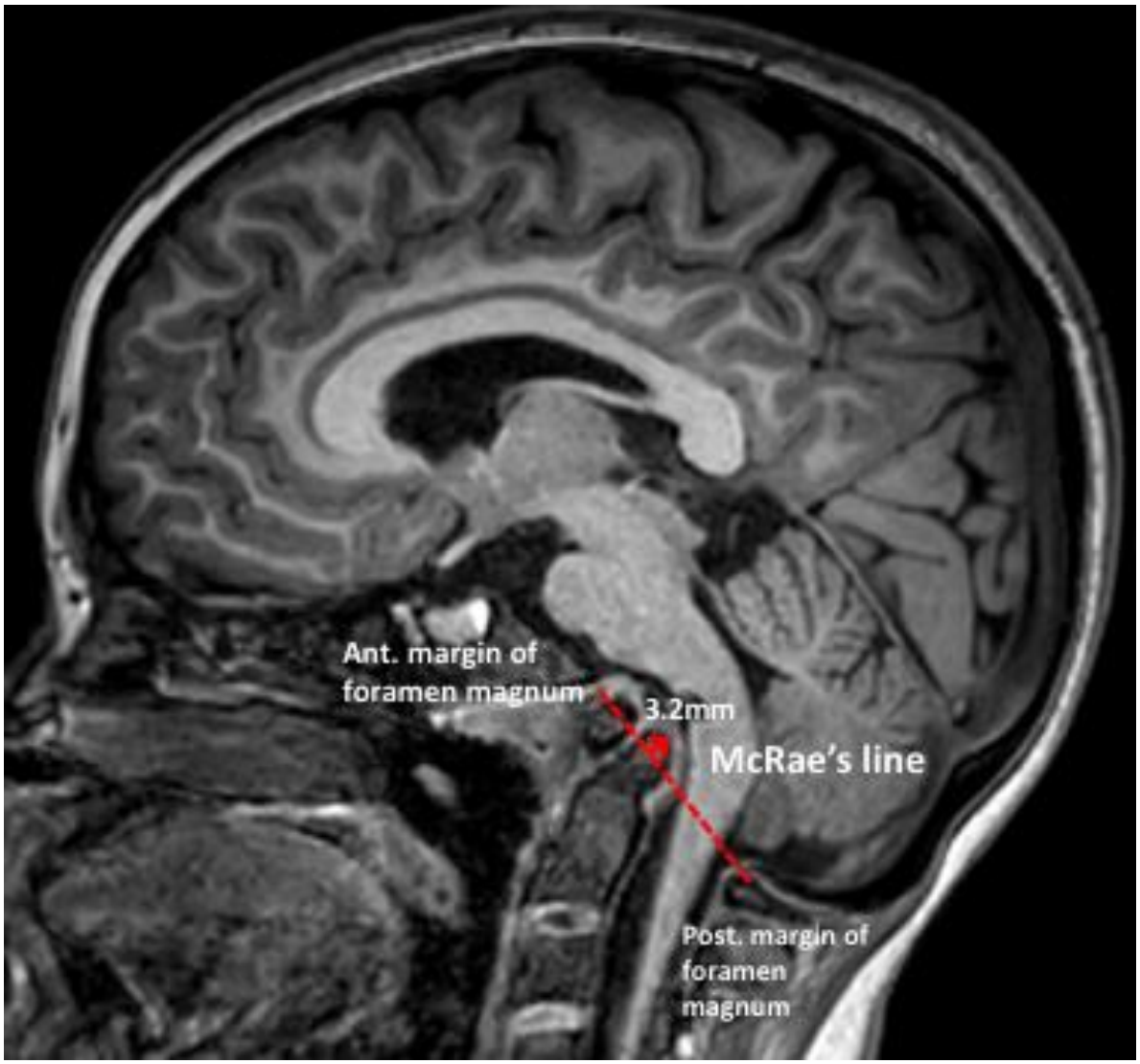


Figure 2: Measuring basilar impression (defined as the upward migration of the peg relative to the depression of the occiput, i.e., the presence of the tip of the odontoid > 4mm above McGregor's line, a line joining the posterior hard palate to the most caudal point of the occiput). In the image below, the odontoid is 6mm above McGregor's line, and therefore this patient has basilar impression.

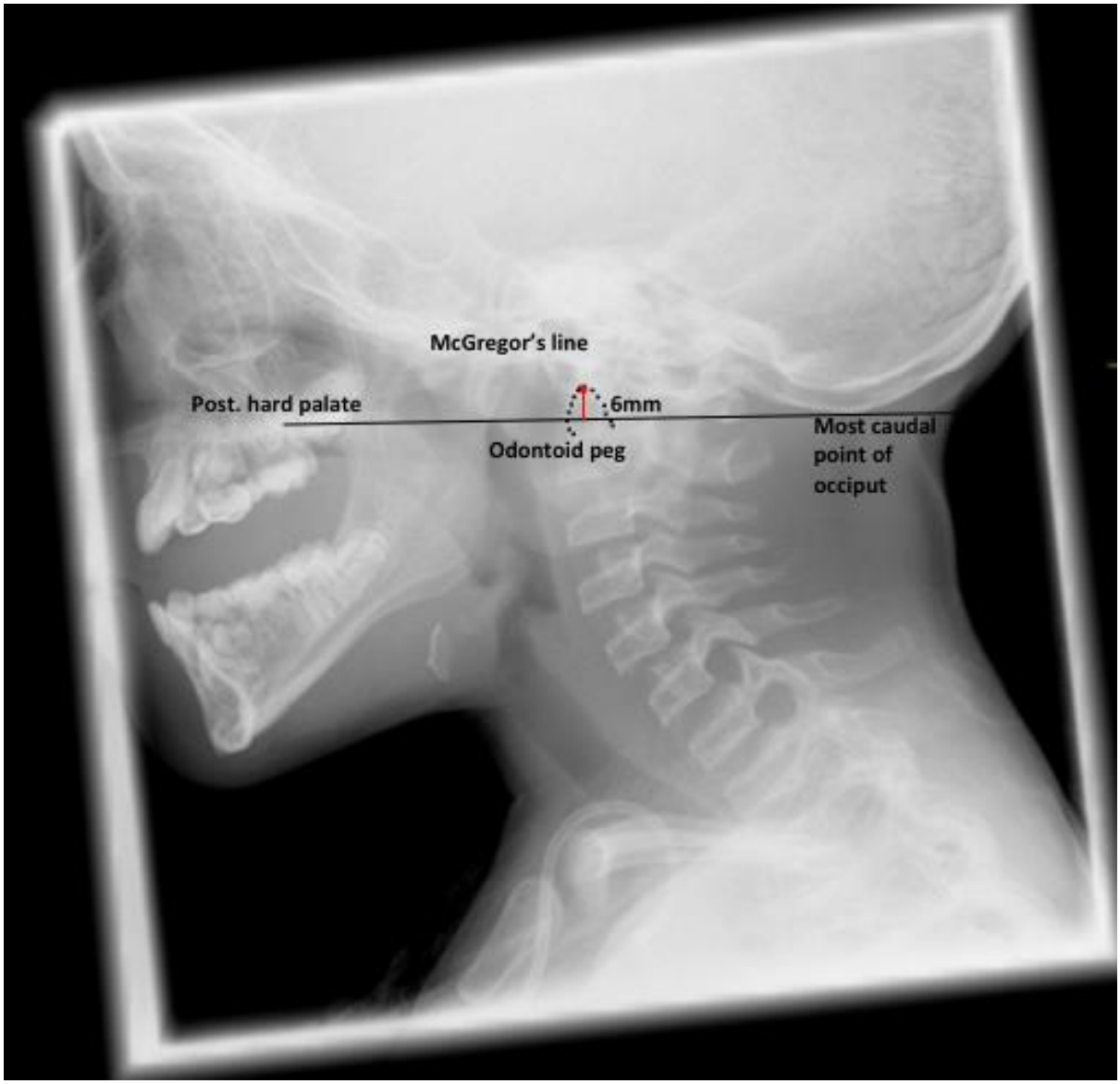
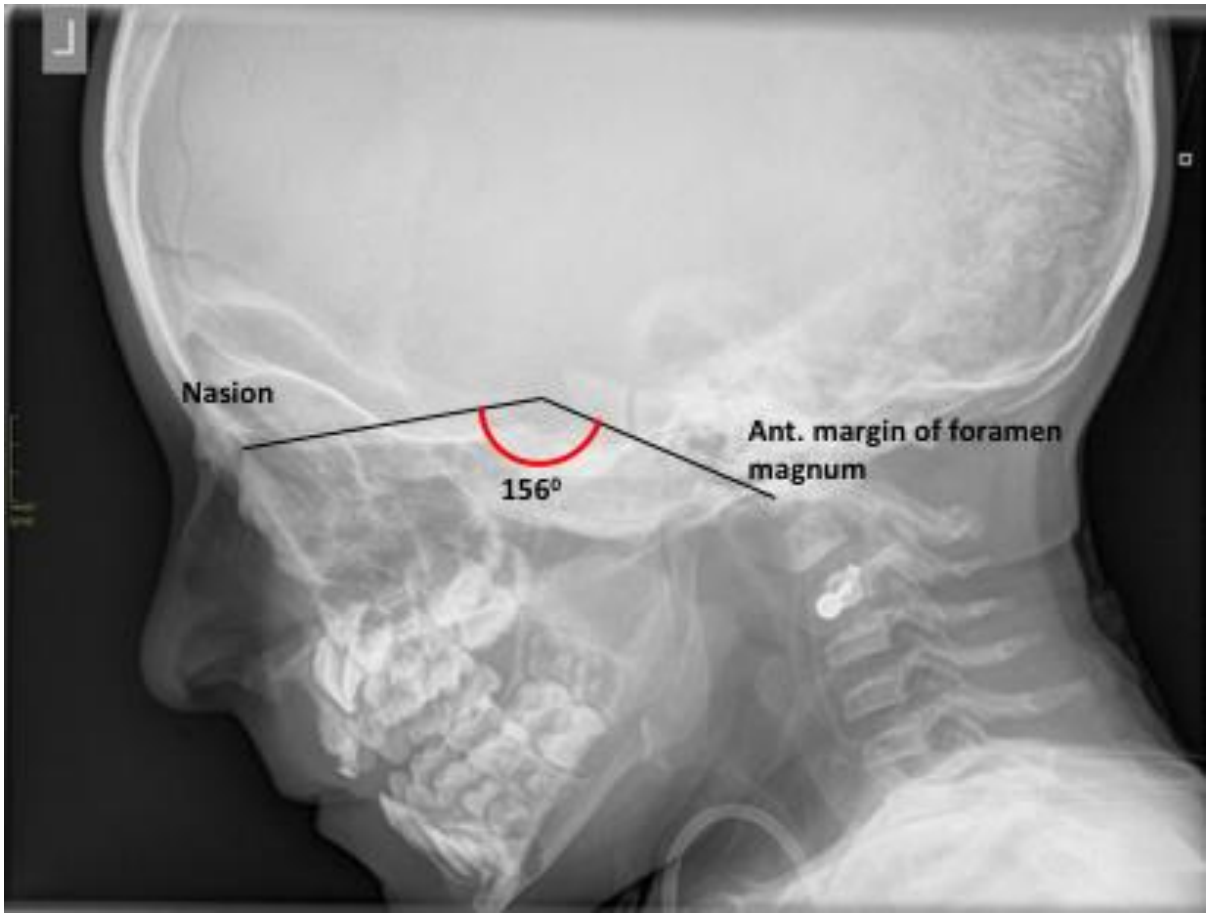


Figure 3: Measuring platybasia (defined by a base of skull angle >143°. This is the angle created by the intersecting lines between the nasion and the tuberculum sellae, and the tuberculum sellae and the anterior margin of the foramen magnum). The angle measured below is 155°, therefore the patient has platybasia. Note the abnormal Wormian bone pattern.



3.0 Results

3.1 Patient demographics

Of the 127 patients in the OI database, 94 were included. Of these, the average age was 9 years (range 5months-18years 6months) and 49 (52%) were female. The most common OI subtype according to the expanded Sillence classification was III (n=40, 42.6%) (Figure 4). Almost all patients (>95%) were on some form of bisphosphonate therapy; 43 (45.7%) on zoledronate, 43 (45.7%) on pamidronate, 5 (5.3%) on risedronate and only 3 (3.2%) on no treatment.

3.2 Image analysis

A total of 321 radiographs, 21 CT scans and 39 MRI scans were analysed for the patient cohort.

Average frequency of radiographs was 8 per 10 years. Of the 94 patients with radiographs 58 (62%), 10 (11%), 1 (1%) demonstrated platybasia, basilar impression, and basilar invagination, respectively. Platybasia, basilar impression, basilar invagination, and presence of Wormian bones were evaluated or commented on in 318, 315, 313 and 299 radiographs, respectively. Of these radiographs analysed, platybasia, basilar impression, basilar invagination, and the presence of Wormian bones could not be evaluated in 71 (22.3%), 48 (15.2%), 61 (19.5%) and 28 (9.4%) radiographs, respectively. Documented reasons for not evaluating the above radiographs included poor positioning, anatomical abnormalities, and poor image quality.

Platybasia was more common in those with basilar impression than in those without ($p=0.03$). Of the 140 radiographs with platybasia, 17 (12%) also demonstrated basilar impression compared to only 3 (2.9%) out of the 99 without platybasia. No significant associations were seen between the presence of Wormian bones and basilar impression. The small sample size for basilar invagination made any statistical tests unreliable.

Of the 39 MRIs, additional information on CSF flow rate, spinal cord signal and cerebellar morphology was reported in 14 (36%). Of the 39 MRIs, base of skull angle was reported in 26 (platybasia present in 23 (88%), basilar impression was evaluated in 19 (basilar impression present in 9 (47%) and basilar invagination in 20 MRIs (basilar invagination present in 3 (15%)). When the MRI findings were compared against findings of radiographs matched to the individual and time, 1/14 (7.1%) contradicted findings of platybasia (i.e., showed platybasia on the MRI while the radiograph did not or vice versa), 5/14 (36%) contradicted findings of basilar impression, whereas there was full concordance between the two modalities for basilar invagination. Concerning image quality, platybasia and basilar invagination could not

be assessed on 4 and 2 radiographs respectively; no MRI scans were non-diagnostic for any of the measured base of skull parameters (Table 1).

Table1: Incidence of platybasia, basilar impression and basilar invagination on MRIs and matched radiographs

		Platybasia on radiographs			
		Yes	No	Indeterminate (poor quality)	Matched radiographs unavailable
Platybasia on MRI (n=26)	Yes (n=23)	11	1	4	7
	No (n=3)	0	2	0	1
		Basilar impression on radiographs			
		Yes	No	Indeterminate (poor quality)	Matched radiographs unavailable
Basilar impression on MRI (n=19)	Yes (n=9)	0	4	0	5
	No (n=10)	1	9	0	0
		Basilar invagination on radiographs			
		Yes	No	Indeterminate (poor quality)	Matched radiographs unavailable
Basilar invagination on MRI (n=20)	Yes (n=3)	0	0	1	2
	No (n=17)	0	12	1	4

The 21 CT scans were conducted for the following reasons: 4 (20%) as part of inflicted injury surveillance, 1 (5%) for better visualisation of the cranio-cervical junction, 4 (20%) due to an alternative clinical indication, and 11 (55%) for miscellaneous reasons

including history of head injury and for neurosurgical follow-up. The indication was not documented for 1 (5%) CT scan.

3.3 Clinical signs and symptoms

The presence or absence of the various listed clinical features at the time of imaging were not specifically documented in 277-300/321 (86%-92%) of cases, as illustrated in Table 2. Of those features documented, the most common was macrocephaly 7/321 (2%), followed by headache 2/321 (0.6%), while the presence of any other features was not recorded in either the clinical notes or imaging request form, and may (or may not) have been entirely absent in the study population.

Figure 4: Distribution of types of osteogenesis imperfecta

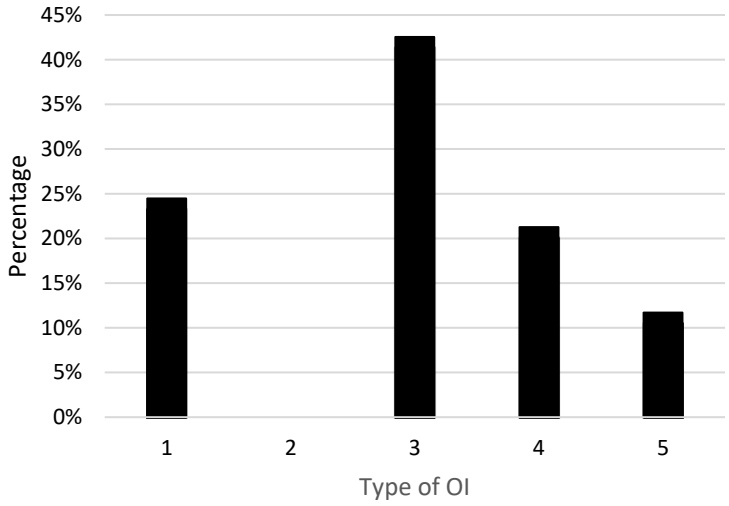


Table 2: Summary of clinical signs and symptoms

Clinical sign or symptom	**Present**	**Not commented on**	**Absent**
Headache	2 (0.6%)	289 (90%)	10 (3.1%)
Macrocephaly	7 (2.1%)	277 (86%)	25 (7.7%)
Ataxia	0	285 (89%)	20 (6.2%)
Lower cranial nerve palsy	0	294 (92%)	11 (3.4%)

Paraesthesia	0	297 (93%)	6 (1.9%)
Quadriparesis	0	287 (89%)	21 (6.5%)
Hyperreflexia	0	294 (92%)	11 (3.4%)
Hoffman's sign	0	300 (93%)	5 (1.6%)
Clonus	0	296 (92%)	8 (2.5%)
Nystagmus	0	292 (91%)	13 (4%)
Dysphagia	0	295 (92%)	10 (3.1%)

4.0 Discussion

We study observed a low prevalence of skull base abnormalities and neurological symptoms and signs among children with osteogenesis imperfecta. The incidence of basilar invagination reported in the literature (4-25%) is much higher than in our cohort (1%), even though we have reviewed data from a cohort with relatively severe disease. Nonetheless, comparison is challenging due to variations in the definitions of the radiographic parameters used. McRae et al identified 25% (7/28) of their patient cohort with basilar invagination using a collection of definitions including the Boogard's angle, foramen magnum line, Chamberlain's and McGregor's lines [15]. Charnas and Marini described basilar invagination in 11% of their paediatric and adult patients [13]. Sawin et al with a broader definition of basilar invagination to include protrusion of the odontoid above the McRae line, 2.5mm above the Chamberlain's or 4.5mm above McGregor's line, identified all their 18 OI patients with basilar invagination [16]. The differences observed were likely due to the utilization of different parameters/definitions in these studies, which may have led to an increased diagnosis of basilar invagination, thus the establishment of uniform definitions would pave way for reliable comparisons.

The incidence of basilar impression in our study, 11%, is similar to that previously quoted. Janus el al described basilar impression as "protrusion of the odontoid above Chamberlain's or McGregor's line" on lateral skull radiographs, reporting 10% of

children to have the abnormality [11]. Apronen, using the D-M distance ('perpendicular distance of the tip of dens to a line drawn through the most caudal point of occipital curve parallel to sella-nasion line'), identified 15% of their study population with basilar impression [7].The terms basilar invagination and impression are sometimes used interchangeably while the definitions often overlap. The definition for basilar invagination used by Sawin et al, presence of the odontoid >4.5mm above the McGregor's line [16], encompasses the definition used in this study for basilar impression, presence of the odontoid >4mm above McGregor's line and may explain the much higher incidence of basilar invagination quoted in the literature compared to our cohort.

Nevertheless, even studies utilising the same diagnostic parameters as our study report a higher prevalence of basilar invagination between 4-22% [7, 9, 10]. Such differences may be explained due to disparities in the distribution of age in the patient cohorts, acknowledging that the incidence of basilar invagination may increase with age [9]. Cheung et al and Kovero et al reported a mean age of 12 and 36 years respectively [7, 9, 10], compared to an average age of 9 years in our patient cohort.

The most common skull base anomaly identified in our patient cohort was platybasia (62%) and its prevalence was found to be higher than those previously reported in the literature. However, platybasia is usually asymptomatic and is of uncertain clinical significance [7].

Our study reveals a very low recorded prevalence of neurological signs and symptoms, supporting clinical neurological manifestations as an uncommon phenomenon in OI [7, 13]. The most common sign or symptom reported was macrocephaly (2%), followed by headache (0.6%), while all other features were absent/not recorded. Similarly, Charnas and Marini found the average head circumference to be close to that of the normal population in most patients with OI [13]. Arponen et al demonstrated that most of their patients with radiological anomalies remained asymptomatic apart from two patients who reported mild headache and upper limb numbness. Only one patient had symptoms severe enough to warrant surgery [7].

An important limitation of our retrospective study is that in >85% of records, clinical signs and symptoms of relevance to this study were not specifically recorded. Although this may be due to the absence of such symptoms and signs, this cannot be reliably concluded due to the lack of documentation and is a limitation that would need to be addressed in future prospective studies. Such studies should focus on reporting the neurological features/complications of OI that are specific to childhood. Other limitations include exclusion of 25% of patients due to lack of access to images, and reliance on radiological reports in some cases.

In our patient cohort, patients underwent skull radiographs at an average frequency of 8 over a 10-year period. At present, there is no consensus on the optimum frequency for monitoring base of skull abnormalities, although Sillence advises every 2-3 years from the age of 5 for those with severe forms of OI [12]. Others argue that further imaging is unnecessary in asymptomatic patients if the baseline radiograph is normal [7].The low prevalence of both skull base abnormalities and clinical features on the one hand and the relatively high frequency of imaging on the other, suggests that we may be over-investigating the patients in our cohort.

Although radiographs are established as the first line of imaging, MR is considered the optimal imaging modality [7]. The added detail enables more accurate identification of cerebellar abnormalities, changes in the foramen magnum including signal changes in the cord and CSF flow rate. Presence of any of these signs is of clinical significance, being indications for possible neurosurgical intervention, to achieve cranio-cervical junction decompression [16].

Our study observed discrepancies in findings between MRI and radiographs (i.e., presence of abnormality observed in one modality and not in the other) for platybasia, and basilar impression in 7.1% and 36% respectively. Janus et al, when investigating the presence of basilar impression with radiographs and MR imaging found similar discrepancies where out of the 13 suspected cases on radiographs, basilar impression could not be confirmed on MRI in 5. This was attributed to severe osteopenia and extreme changes in anatomical structures making radiographic interpretation difficult [11]. Similarly, in our study, extreme changes at the cranio-cervical junction made distinction of the anatomical structures on conventional radiographs difficult to

determine. Differences in patient positioning may also play a role. Poor image quality through rotated images or overenthusiastic coning led to inability to determine the cranio-cervical parameters in about 20% of radiographs. MR imaging with the added detail, provided more accurate measurements. However, MR is not widely available, is relatively expensive, and may require general anaesthetic in some cases. For these reasons, MR cannot replace radiographs as the initial imaging modality of choice and should be reserved for those cases with abnormal or non-diagnostic radiographs.

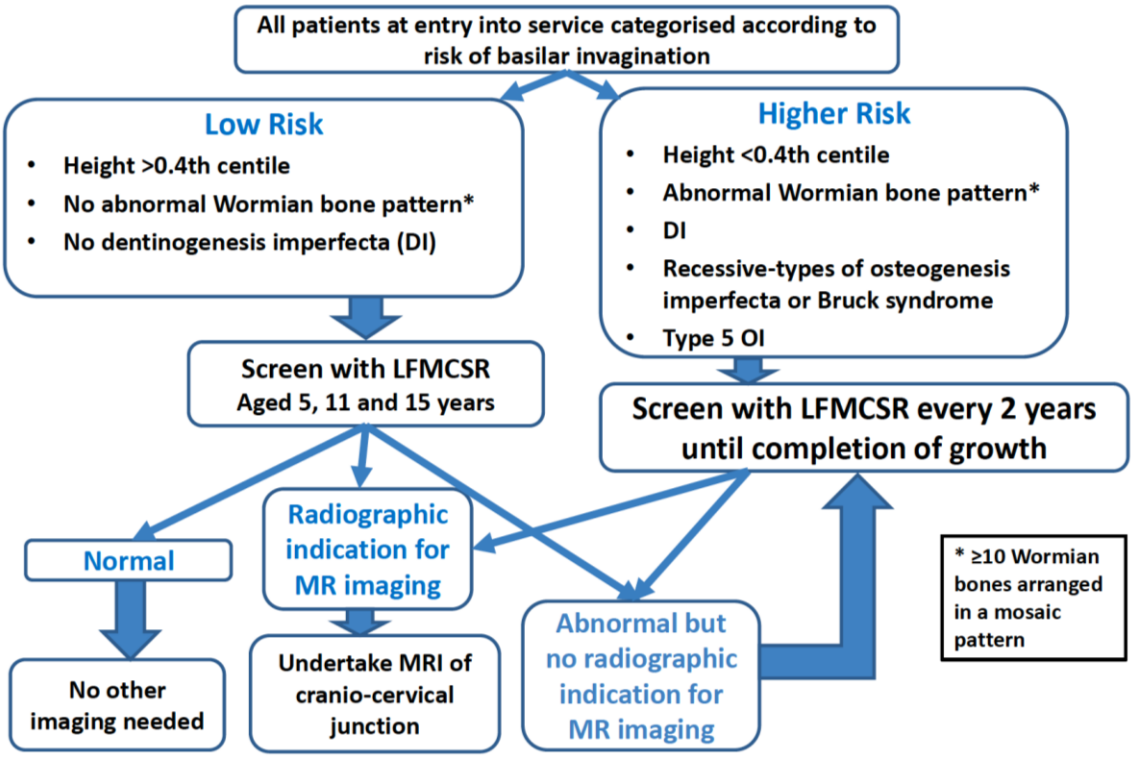
The frequency and timing of MR imaging is debated. Commonly, when basilar invagination is suspected on radiographs, MR imaging is done to obtain greater detail and evaluate the effect on surrounding structures. Cranio-cervical abnormalities are often asymptomatic [7, 11, 15, 17] and of the three measurements, basilar invagination is most commonly symptomatic [15]. Symptoms that can occur include headache, weakness, numbness, lower cranial nerve dysfunction, ataxia, and hyperreflexia. These have been recorded in varied frequencies in the literature [7, 15, 16, 18]. Causes and/or effects of all of these are better depicted on MR than on radiographs. There is also debate on the clinical significance of asymptomatic cranio-cervical abnormalities, as surgical intervention for such cases is controversial [9, 18, 19]. In our opinion, these arguments may support a role for MR imaging only in symptomatic cases, but larger scale studies are required. We do not identify a routine role for CT in this context.

A risk of the current practice of serial imaging in asymptomatic cases, such as in our centre, is that it may represent excessive imaging with associated “unnecessary” radiation exposure. Arponen *et al*, investigating the progression of cranio-cervical abnormalities with time, found no statistically significant association, favouring the argument against serial imaging [7]. However, their study only involved a small sample size with a low prevalence of cranio-cervical abnormalities. Further investigation is required before the optimal approach for screening may be determined.

5.0 Conclusions

Neurological symptoms and signs play a vital role in the clinical decision-making process when evaluating cranio-cervical abnormalities and prompting more detailed imaging such as MRI. However, in our cohort these were not recorded in a large majority of cases; maintaining a robust and explicit record of the presence or absence of child-focused neurological symptoms/signs is important. There appears to be a low prevalence of clinical symptoms and signs and of radiologically identified cranio-cervical abnormalities. Routine serial imaging may be leading to more skull base imaging than is needed. Additionally, inadequate radiographs for the evaluation of the cranio-cervical junction (with rotated imagery and overenthusiastic coning) are common and initiatives should be undertaken to minimise this. MR imaging provides more detailed and accurate evaluation of the skull base but may be better targeted in symptomatic cases or when radiographic parameters are abnormal. Until larger prospective studies clarify these issues, based on the results of our study and clinical experience across all <BLINDED> centres of the <BLINDED> (<BLINDED>: funded by <BLINDED>), we suggest the clinical pathway outlined in Figure 5, which has been developed within the context of and adopted by the <BLINDED>. This proposes a risk stratification approach to radiographic frequency and suggests parameters for proceeding to MRI.

Figure 5: Flow diagram showing radiographic screening of asymptomatic children with OI using lateral foramen magnum-centred skull radiographs (LFMCSR) as undertaken by the <BLINDED>. Radiographic indications for MRI of the cranio-cervical junction are 1) basilar invagination (odontoid >0mm above McRae's line) 2) basilar impression (odontoid >4mm above McGregor's line) PLUS unclear McRae's measure 3) high risk group with unclear McRae's measure 4) Patients with scoliosis having MRI spine for surgical planning. Radiographic abnormalities not in themselves warranting MRI include platybasia and abnormal Wormian bone pattern.



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