Title: INTRODUCING THE TURRICEPHALY INDEX: a validated method for analyzing the natural history of turricephaly in Apert syndrome.

Institution: Great Ormond Street Hospital for Sick Children, London, UK

Authors: O'Hara J (FRACS Plast); Way B; Borghi A (PhD), Knoops P, Chua D, Hayward R (FRCS Neurosurg).

Abstract:

Introduction: We present the CT scan-derived turricephaly index (TI) as a quotient of the maximal occipito-frontal length of the skull to the distance from the centre of the sella to the highest point on the vertex as a validated tool for assessing turricephaly and evaluating surgical techniques.

Materials and Methods: TI measurements were taken from CTs from non-operated children with Apert syndrome and age-matched controls and analysed using *Centricity PACS* system (from the lateral scout image) and Osirix (the thick-sliced Osirix tool). CTs from non-operated children with Apert syndrome were used to investigate the natural history of turricephaly.

Results: There was statistically significant agreement between measurements taken from the CT scout and Osirix for 42 control children (R^2 =0.97) and 42 children with Apert syndrome (R^2 = 0.98) and between two separate observers. There was a statistically significant difference ($p<0.001$) between CT scout-derived TI value between controls (1.73±0.12, range 1.46 – 1.99) and Apert children (1.42±0.15, range 1.13 – 1.73).

Analysis of 113 CTs of 65 non-operated children with Apert syndrome showed a decrease in turricephaly with age (positive spearman correlation: $r = 0.50$, $p<0.001$). Analysis of 37 CTs of those with multiple (>2) CT's showed a decrease in turricephaly in the individual child ($p<0.001$).

Conclusions: TI derived from the CT scout view provides a simple, objective and validated method for assessing turricephaly.
We recommend it for monitoring and for the prospective evaluation of reconstructive techniques in children with complex/syndromic craniosynostosis.

240/250 words!

Introduction:

Turricephaly (*Tower Head*) is a descriptive term for a distinctive head shape often observed in children with syndromic forms of craniosynostosis and, in particular, those with Apert syndrome[1]. As an anthropometric measurement however it is poorly defined[1] and this has resulted in craniofacial surgeons relying on subjective assessments both when describing its severity and when evaluating its natural history and the effects of surgical intervention.[2] [3] Quotients of anthropometric measurements of skull dimension are already used to describe certain head shapes (the cranial index - CI - in scaphocephaly, for example) but vertical height has been omitted because reliable reference points can be difficult to define.[4]

There is a need therefore for a simple, objective and validated method for assessing turricephaly similar to the CI that is now frequently used as a proxy measure for evaluating scaphocephaly.[4] [5] CI is simple to derive and can be used both to record the severity of scaphocephaly and to compare the effectiveness of surgical techniques used to reduce it.[6] [7] [8] [9] The turricephaly index (TI) is, like the CI, a quotient derived from two simple radiologically determined measurements but substituting vertical height[10] for width.

To be accepted, a new index should be validated for the methodology used, for inter-observer variation and for its clinical utility. This study deals with both these issues. In Part 1 we have calculated TI using two different imaging techniques – one simple, one more complex – and (a) compared the results obtained from each; (b) recorded consistency between observers and (c) compared TI of children with Apert syndrome with those of normal controls. In Part 2, the clinical utility of TI has been tested on a predictably affected model – the child with Apert syndrome – to (a) examine variations in TI with age in a cohort of non-operated children with Apert syndrome and (b) investigate variations in TI in the individual child with Apert syndrome.

Methodology:

The retrospective review of patient data for this study was approved by the hospital's research and audit department (audit registration number 1544).

For Part 1 of the study, CT scans of patients with Apert syndrome presenting to the craniofacial unit at Great Ormond Street Hospital for Sick Children, London, UK between 2000 and 2017 were retrieved from the craniofacial unit database. Age- and sex-matched controls who had CT scans (on the same equipment and at the same settings) for computer navigation-guided epilepsy surgery planning were recruited from the neurosurgical unit database. No control patient had conditions affecting their intracranial pressure or head shape.
For Part 2, non-operated children with Apert syndrome who had undergone multiple CT scans were selected.

Spiral CT scans were carried out on a Somatom Sensation Spiral computed tomographic scanner, Siemens, Munich, Germany with 0.75mm collimation (slice thickness). Standardization of head position was maintained by established protocol[4] of laser light positioning, position maintenance with restraints and optimization of gantry. Scan data were stored as Digital Imaging and Communications in Medicine Files (DICOM, Rosslyn, Va. USA) and exported to both Centricity GE Healthcare IT, (Version 3.1.4, United Kingdom) and open-source software *Osirix* v5.8 (Pixmeo, Geneva, Switzerland). Scan data in *Osirix* was viewed in 3D multiplanar reconstructions (MPR) with the thick-slab tool set to the maximum of 100mm (giving a composite view of 100mm depth in each plane), in the maximum intensity projection setting.

The maximal occipito-frontal length (OFL) of the skull (from outer cortex to outer cortex) and the distance from the centre of the sella to the highest point on the vertex (SVD) were measured on the calibrated scout image using the calibrated line ruler tool (Figure 1A – 1B)

The same measurements were made in *Osirix* using the vertically orientated gridlines to mark the most anteriorly and posteriorly projecting points of the skull when viewed

laterally in thick-slice mode, and measuring the distance between them with the ruler tool. The center of the sella turcica was identified using the point tool (viewed in all three planes), and the highest point on the vertex identified from a horizontally orientated gridline viewed on the thick-slab image (figure 1C).

All measurements were repeated twice and performed independently by two investigators (JOH, BW) at separate times. The data was entered into a spreadsheet and statistical analysis undertaken in *SPSS* and *Matlab (MathWorks, MA).*

Statistical analysis

Intraclass Correlation Coefficient (ICC) and Pearson correlation coefficients were used to assess the TI measurements performed using CT scout and Osirix as well as by different observers. Pearson correlation was used to assess age dependence of TI in the Apert population. ANOVA was used to compare mean TI in the three subgroups; paired T-test was used to assess difference between the TI at the time of first CT with that at the time of the last CT available for a subgroup of Apert patients. Shapiro-Wilk test was used to assess normality of distributions.

Results:

Part 1 (Validation)

The CT scans of 42 children with Apert syndrome (average age 8.5 years, range 0.05-20.6 years) and of 42 age and sex-matched controls (average age 9.9 years, range 1.7-17.8 years) were used for this part of the study.

Comparison of the two methods of measurements showed extremely good correlation between those performed on CT scout and Osirix both for control subjects ($R^2 = 0.969$, $p<0.0001$) and Apert patients ($R^2 = 0.994$, $p<0.0001$) (see figure 2).

OFL and SVD measurements performed by two separate observers showed excellent correlation (ICC above 0.9) when measured on the CT scout view and when using Osirix (see table 1).

The mean TIs derived from these measurements by the CT scout method were 1.42±0.15 for children with Apert syndrome (range 1.13 to 1.73) and for the controls 1.73±0.12 (range 1.46-1.99)– a statistically significant difference ($p<0.001$). Figure 3 shows TI versus age distribution for the two populations.

Part 2. (Clinical application)

To investigate variations in TI with age, 113 CT scans of 65 Apert patients (average age at scans 4.29 years, range 0-18 years) who had undergone neither cranial vault surgery nor CSF diversion were analyzed after the population had been subdivided into three clinical age groups. TI's ranged from 1.26±0.11 (for children <1 year of age) to 1.41±0.16 (for children >5years of age) (figure 4). Table 2 reports all values for each subgroup.

ANOVA showed significant difference between the three subgroups ($p<0.0001$). TI increased with age as shown by positive spearman correlation ($r = 0.50$, $p<0.001$) (Figure 5).

To investigate changes in TI in the individual non-operated Apert child the CTs of 37 patients who had undergone more than one CT (number 2-3) with no intervening cranial

surgery were analyzed. There was a statistical increase in TI from first to last scan ($p<0.001$) as shown in figure 6.

Discussion

Turricephaly, despite often responsible for a major component of the craniofacial deformity affecting children with syndromic/complex forms of craniosynostosis, has proven difficult to quantify reliably.[2]

To address this issue we have derived a Turricephaly Index (TI) from simple measurements taken from the lateral scout view of a CT.

As evidence of its validity as a reliable tool for the craniofacial surgeon we have:

- Demonstrated that measurements taken from the scout view of a CT scan are as reliable as those derived from a more complex and more precise tool – *Osirix*.
- Established from separate measurements made at separate times (and repeated) by two observers the inter-observer consistency of these CT scan derived measurements.

We propose that the TI so derived provides the craniofacial surgeon with a useful tool for assessing and comparing the effectiveness of surgical maneuvers designed to address a complex skull deformity.

We would not suggest that TI describes the head shape of the affected child in anything but simple terms. The deformity of the child with sagittal synostosis is often more complex than scaphocephaly alone – a description that omits the pterional indrawing and low posterior vertex important in the deformity. Similarly, the head shape of the child with Apert syndrome presents an appearance more complex than turricephaly alone, with shallow and externally rotated orbits and hypertelorism, for example. Nevertheless, the cranial index (CI) has become an accepted proxy for scaphocephaly within the craniofacial community and has been regularly used for evaluating techniques aimed at restoring a more regular head shape. It is in this context that we propose the TI as a suitable tool for the assessment of turricephaly correction.

TI deployed in combination with CI could also provide the craniofacial surgeon with a method for describing in three as opposed to two dimensions the head shape of a child affected by both simple or syndromic craniosynostosis than those dependent upon complex analytic techniques such as, for example, principal component analysis.[11 12 13]

To demonstrate the clinical use of TI we have focused on the turricephaly of children with Apert syndrome and shown how their TI differs from that of age-matched controls (1.42 for children with Apert syndrome versus and 1.73 for controls (p 0.001)) while both populations display a similar tendency for TI to increase with age.

Although it has been suggested that untreated turricephaly is likely to worsen with age (a possible indication for early intervention[6 14]) our study shows the opposite – there is a tendency for TI, over time, to decrease and approach more normal proportions (an increase in TI from 1.25 under 1year old to 1.41 over age 5 years against a mean TI of our control population of 1.73). The craniofacial surgeon must therefore be careful not to suggest to parents of children with Apert syndrome that a predictable worsening of turricephaly is a reason for early reconstructive surgery. Many procedures, a posterior vault expansion, for example,[6 9 15 16] may indeed reduce turricephaly but, our data shows, they are not needed for prophylaxis alone.

What accounts for this decline in the severity of turricephaly in Apert syndrome? In the young Apert child the sagittal and metopic sutures are often widely open with the coronals and lambdoids wholly or partially closed – a combination that constricts the skull base in the antero-posterior axis and predisposes to the development of turricephaly. But when within two or three years all vault sutures are likely to have fused subsequent skull growth becomes more evenly distributed with an accompanying reduction in the drive towards further upward extension.

Conclusion

We propose the TI as a tool as simple, reliable and repeatable as the CI as a proxy for describing one element of the calvarial deformity seen particularly in children with Apert syndrome but also in other complex forms of craniosynostosis. Like the CI for scaphocephaly it can be used both to track the progress of turricephaly in the individual patient and to evaluate the effects of surgical procedures designed to improve it.

In addition we have demonstrated how, for the unoperated child with Apert syndrome, there is a statistically significant tendency for this particular proportion of their complex craniofacial deformity to improve with time.

1806/3000 words!

TABLES

ICC (p-value)	Scout	Osirix
OFL	0.962 (p<0.0001)	0.929 (p<0.0001)
SVD	0.943 (p<0.0001)	0.871 (p<0.0001)

Table 1: ICC of OFL and SVD for measurements performed on Scout and Osirix, showing

	Apert		
Age	n	MEAN	SD
<1	55	1.26	0.11
1 to 5	34	1.37	0.11
>5	25	1.41	0.16

Table 2: TI value for the different subpopulations

FIGURE LEGENGS

Figure 1 A) Measurements used to calculate TI from CT scout image in a "control" child B) Measurements used to calculate TI from CT scout image in a child with Apert syndrome C) TI measurement performed on Osyrix.

Figure 2: Correlation between TI measurements performed on Osirix and extracted from CT scout for the control group (left) and Apert group (right).

Figure 3: Age distribution for the Apert and control populations.

Figure 4: Average TI values for three subpupulations: younger than 1 year old; between 1 and 5 year old; over 5 year old.

Figure 5: TI increase with age ($r = 0.5$, $p<0.001$)

Figure 6: Turrichephaly Index between first and last CT for 37 unoperated patients Grey lines indicate change for each patient between the first and last CT. Boxplots indicate mean, as well as first and third quartiles.

REFERENCES

1. Ferguson MWJ. Turricephaly. *Int J Oral Surg*. 1980;9(5):343-350.
2. Sonstein WJ, Hall CD, Argamaso R V., Goodrich JT. Management of secondary turricephaly in craniofacial surgery. *Child's Nerv Syst*. 1996;12(11):705-712. doi:10.1007/BF00366155
3. Weber J, Collmann H, Czarnetzki A, Spring A, Pusch CM. Morphometric analysis of untreated adult skulls in syndromic and nonsyndromic craniosynostosis. *Neurosurg Rev*. 2008;31(2):179-188. doi:10.1007/s10143-007-0100-x
4. Waitzman AA, Posnick JC, Armstrong DC PG. Craniofacial skeletal measurements based on computed tomography: Part I. Accuracy and reproducibility. *Cleft Palate-craniofacial J*. 1992;29(2):112-117.
5. Fearon JA, McLaughlin EB, Kolar JC. Sagittal craniosynostosis: Surgical outcomes and long-term growth. *Plast Reconstr Surg*. 2006;117(2):532-541. doi:10.1097/01.prs.0000200774.31311.09
6. Nowinski D, Di Rocco F, Renier D, Sainterose C, Leikola J, Arnaud E. Posterior cranial vault expansion in the treatment of craniosynostosis. Comparison of current techniques. *Child's Nerv Syst*. 2012;28(9):1537-1544. doi:10.1007/s00381-012-1809-6
7. Saiepour D, Nilsson P, Leikola J, Enblad P, Nowinski D. Posterior cranial distraction in the treatment of craniosynostosis - Effects on intracranial volume. *Eur J Plast Surg*. 2013;36(11):679-684. doi:10.1007/s00238-013-0874-8
8. Derderian CA, Bastidas N, Bartlett SP. Posterior cranial vault expansion using distraction osteogenesis. *Child's Nerv Syst*. 2012;28(9):1551-1556. doi:10.1007/s00381-012-1802-0
9. Goldstein J a, Paliga JT, Wink JD, Low DW, Bartlett SP, Taylor J a. A craniometric analysis of posterior cranial vault distraction osteogenesis. *Plast Reconstr Surg*. 2013;131:1367-1375. doi:10.1097/PRS.0b013e31828bd541
10. Waitzman AA, Posnick JC, Armstrong DC PG. Craniofacial skeletal measurements based on computed tomography: Part II. Normal values and growth trends. *Cleft Palate-craniofacial J*. 1992;29(2):118-128.
11. Rodriguez-Florez N, Göktekin ÖK, Bruse JL, et al. Quantifying the effect of corrective surgery for trigonocephaly: A non-invasive, non-ionizing method using three-dimensional handheld scanning and statistical shape modelling. *J*

Cranio-Maxillofacial Surg. 2017;45(3):387-394. doi:10.1016/j.jcms.2017.01.002

12. Pluijmers BI, Ponniah AJT, Ruff C, Dunaway D. Using principal component analysis to describe the Apert skull deformity and simulate its correction. *J Plast Reconstr Aesthetic Surg*. 2012;65(12):1750-1752. doi:10.1016/j.bjps.2012.07.007
13. Staal FCR, Ponniah AJT, Angullia F, Ruff C, Koudstaal MJ, Dunaway D. Describing Crouzon and Pfeiffer syndrome based on principal component analysis. *J Cranio-Maxillofacial Surg*. 2015;43(4):528-536. doi:10.1016/j.jcms.2015.02.005
14. Allam KA, Wan DC, Khwanngern K, et al. Treatment of apert syndrome: A long-term follow-up study. *Plast Reconstr Surg*. 2011;127(4):1601-1611. doi:10.1097/PRS.0b013e31820a64b6
15. Arnaud E, Marchac A, Jeblaoui Y, Renier D, Di Rocco F. Spring-assisted posterior skull expansion without osteotomies. *Child's Nerv Syst*. 2012;28(9):1545-1549. doi:10.1007/s00381-012-1843-4
16. De Jong T, Van Veelen MLC, Mathijssen IMJ. Spring-assisted posterior vault expansion in multisuture craniosynostosis. *Child's Nerv Syst*. 2013;29:815-820. doi:10.1007/s00381-013-2033-8