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LETTER TO THE EDITOR

An experimental challenge to bring the empirical study design a step closer to evidence-based medicine and quit ethically problematic situations

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Dear Editor:

Together with the authorized specialists in this field (Appendix), we would like to make some consideration concerning the use of decompressive cranioplasty in patients with mild trigonocephaly and psychomotor retardation aimed at favoring cognitive development as reported in your journal [1–3]. The efficacy of the procedure for developmental conditions is scientifically unproven [4], and mild cases of trigonocephaly are not candidates for surgery because of its mild morphological changes [5]. As an excuse for the long continuation of their non-controlled trial for the unproven intervention, it has been claimed for approximately 20 years that the deprivation of the chance to enjoy the promising intervention in the patients allocated to the control group is unethical and unacceptable [3]. This serious misunderstanding could not be corrected despite repeated explanation of the Declaration of Helsinki [6–9]. The huge performance bias in the field of developmental conditions results in a downward revision of the evidence ranking of observational studies to the lowest quality (level 5) [8]. Therefore, the only way that can promise the safety and efficacy of an unproven intervention is controlled study [8]. Although the authors firmly believe that "reducing the increased intracranial pressure (ICP) is the main surgeons' work (duty)" [3, 10], the mere presence of marked digital markings on 3D CT images, microcephaly, or elevated ICP never excuse the decompressive cranioplasty for developmental conditions [11–14]. There is little evidence of relationship between severity of trigonocephaly and cognitive development [15, 16] and raised ICP cannot be predicted by the presence of clinical signs including symptoms of high ICP, developmental delay, and ophthalmological or radiological findings in sagittal synostosis [14]. There is no correlation between CT-measured intracranial volume and ICP in craniosynostosis [11], and ICP is usually unrelated to cognitive functioning [12, 13]. In microcephalic children, there are no statistically significant differences in developmental scores and head sizes between children with high ICP and children with low ICP, and high ICP has decreasing tendency with age [17]. These results suggest that the presence of behavioral/cognitive delays may not be attributable to high ICP in craniosynostosis cases. Together with the important results of a multi-centered comparative study at postoperative 18 months [3, 18, 19], in which there is no significant developmental difference between the operated high-ICP trigonocephaly cases and non-operated controls, additional controlled studies may play a crucial role for ultimate benefit of patients.

In a clinical comparative study, most of the beneficial changes were manifested within a few months after the cranioplasty [20]. In the recent report, postoperative apparent improvements were also documented within 1 year [1]. Therefore, in order to confirm these beneficial results, postoperative changes should be compared with the natural developmental trajectory until at least one year postoperatively.

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As described above, the authors have declared that this unproven intervention is generally unaccepted for developmental conditions [1–4]. However, officers of the public insurance association and the Ministry of Health, Labour and Welfare received a tricky and misleading explanation that "the procedure itself is not a novel surgical technique at all and it is a generally accepted surgical procedure" [3]. This situation is tightly associated with a strong financial conflict of interest which influences the author's views, and the continuation of this trial is quite profitable for the hospital where the authors are employed. Therefore, the research costs should be paid using research funds without parents' economic burden [9]. In the multi-centered research, developmental evaluations and statistical analyses should be conducted by independent raters and statisticians who are blinded to the allocation information. In this continuing problematic situation where an unaccepted surgical procedure cannot be subjected to optimized scientific scrutiny for approximately 20 years, the significance and necessity of an experimental challenge should be tentatively considered by the institutional ethics committee. After detailed and explicit explanation of this experimentation to the parents, cases whose written informed consent was obtained are randomly assigned to two schedule groups, a treatment-placebo (A) and a placebo-treatment group (B) [8, 9]. Cases whose parents selected non-surgical options should be followed up as group C. In group A, the first hospitalization is for clinical evaluations, ICP monitoring, and the decompressive cranioplasty. In group B, the first hospitalization is just for clinical evaluations including ICP monitoring. At the short-term end-point (a year after the first hospitalization), group A patients are hospitalized for clinical evaluations including ICP monitoring, and group B patients are hospitalized for clinical evaluations, ICP monitoring, and cranioplasty. Developmental evaluations should be repeated every 6 months. In addition to the comparative analysis between groups, individual developmental changes after the first and second admissions provide important paired data. In the long-term follow-up, groups A and B can be compared with group C. Complete implementation of this experimental challenge might quit the problematic history of 20 years.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Appendix. The members of the Ethics Committee of Japanese Society for Child and Adolescent Psychiatry

Kazumasa Kimura, Satoshi Tanaka, Chiaki Abo, Arata Oiji, Yuji Okura, Kozo Ocho, Junichiro Ota, Tsunehisa Sakajiri, Yoshihiro Nakadoi, Kyoko Hazama, and Kiwamu Tanaka

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