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# *Long-term Outcomes of Non-syndromic and Syndromic Craniosynostosis: Analysis of Demographic, Morphologic, and Surgical Factors*

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## Abstract

**In this study, we analyzed the outcomes of patients (followed for 5–38 years, average 17.3 years) with craniosynostosis and evaluated their long-term prognosis. In all, 51 patients who underwent surgery for craniosynostosis between 1982 and 2015, including 12 syndromic and 39 non-syndromic cases, were included. The average age at the initial surgery was significantly lower in the syndromic group than that in the non-syndromic group (9.8 months old vs. 19.9 months, respectively). The surgical procedures did not significantly differ between the two groups, but repeat surgery was significantly more common in the syndromic group than in the non-syndromic group (4 children [30.8%] and 3 children [7.7%], respectively). The children requiring repeat surgery tended to be younger at the initial surgery than those who did not. Those patients who required repeat surgery did not have significantly different surgical procedures initially. The incidence of developmental retardation was 49.0% (43.5% in the non-syndromic group and 66.7% in the syndromic group), and only two children in the non-syndromic group displayed recovery. This study is the first to analyze the prognosis for patients who were followed for at least 5 years after cranioplasty. Repeat surgery was common, especially in syndromic patients. Severity of skull deformity and early initial surgery may be important factors determining the need for repeat surgery. Developmental retardation was also common, and improvement was rare even after surgery.**

Keywords: craniosynostosis, long-term outcome, syndromic, non-syndromic

## Introduction

The incidence of craniosynostosis is reported to vary between 1/1600 and 1/4000 live births[1–4] and is increasing gradually.[4,5] Of these cases, syndromic craniosynostosis constitutes between 12% and 31%.[1,4,6–8] Many surgical procedures have been introduced to treat craniosynostosis. Before 1980, only affected sutures were removed.[9–11] Tessier introduced craniofacial surgery.[12] In the 1980s, fronto-orbital advancement became standard treatment.[13] In the 1990s, a distraction technique to minimize operative invasiveness was introduced. Distraction osteogenesis was first introduced in cranio-maxillo-facial surgery of the mandible in 1992.[14] This technique was later applied to efficiently expand the intracranial volume in patients with craniosynostosis.[15,16] In 1998, Jimenez presented an endoscopic strip craniectomy with a molding helmet, especially for young infants younger than 4 months old.[17]

Although many surgical procedures have been introduced in the past four decades,[18] there are few reports on long-term postoperative outcomes in

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craniosynostosis.[19–27] Furthermore, there are almost no reports that denote the procedures for optimizing long-term outcomes in syndromic and non-syndromic cases, although outcomes may differ between the two types of the disease. Therefore, in this study, we retrospectively analyzed the long-term outcomes of children with craniosynostosis who were followed for at least 5 years after surgery and attempted to determine the prognosis in syndromic and non-syndromic groups.

## Materials and Methods

This study included 51 patients who underwent reconstructive surgery between 1982 and 2015. Of these patients, 39 had the non-syndromic type and 12 were syndromic, including Crouzon syndrome (n = 3), Apert syndrome (n = 3), Pfeiffer syndrome (n = 2), Saethre-Chotzen syndrome (n = 2), Munke syndrome (n = 1), and Beare-Stevenson-cutis-gyrata syndrome (n = 1). All syndromic cases were genetically confirmed. All subjects were carefully followed at our outpatient clinic for 5–38 years (average, 17.3 ± 9.1 years). Developmental retardation was defined as a developmental quotient less than 70 or an intelligence quotient less than 70 using the Wechsler Intelligence Scale for Children-Revised. We operated on patients with skull deformity confirmed with the early suture fusion on three-dimensional computed

**Table 1 Repeat surgery in syndromic and non-syndromic groups**

| | | No. | Repeat surgery (+) | Repeat surgery (–) |
|---|---|---|---|---|
| **Syndromic** | | 12 | 4*[a] | 8 |
| Brachycephaly | | 8 | 3 | |
| Plagiocephaly | | 2 | 0 | |
| Oxycephaly | | 2 | 1 | |
| Scaphocephaly | | 0 | 0 | |
| Trigonocephaly | | 0 | 0 | |
| Clover leaf | | 0 | 0 | |
| Pancraniosynostosis | | 0 | 0 | |
| Age at 1st op | 3–36 (9.8*[b]) months | | 4.5 | 12.4 |
| Procedure | Conventional | 8 | 2 | 6 |
| | Distraction | 3 | 1 | 2 |
| | Suturectomy | 1 | 1 | 0 |
| **Non-syndromic** | | 39 | 3 | 36 |
| Brachycephaly | | 3 | 1 | 0 |
| Plagiocephaly | | 10 | 1 | 0 |
| Oxycephaly | | 1 | 0 | 1 |
| Scaphocephaly | | 8 | 0 | 8 |
| Trigonocephaly | | 14 | 0 | 14 |
| Clover leaf | | 2 | 1 | 1 |
| Pancraniosynostosis | | 1 | 0 | 1 |
| Age at 1st op | 2–66 (19.9) months | | 3.7*[c] | 21.2 |
| Procedure | Conventional | 23 | 2 | 21 |
| | Distraction | 16 | 1 | 15 |
| | Suturectomy | 0 | 0 | 0 |

Repeat surgery was significantly more common in the syndromic group than in the non-syndromic group (a) ($p = 0.0254$). The incidence of repeat surgery was compared among the various skull shapes in the syndromic and non-syndromic groups. The skull shape did not affect the repeat surgery ratio. The age at the 1st operation was significantly lower in the syndromic group (b) ($p = 0.0153$). The age at the 1st operation was compared between those with or without repeat surgery in each group. In the non-syndromic group, the age was lower in the repeat surgery group (c) ($p = 0.014$). The incidence of repeat surgery among the various surgical procedures was compared. In the syndromic group, 2 of 8 children with conventional cranioplasty, 1 of 3 with distraction osteogenesis, and 1 of 1 suturectomy needed repeat surgery. In the non-syndromic group, 2 of 23 children with conventional cranioplasty and 1 of 16 with distraction osteogenesis needed repeat surgery. The ratio of repeat surgery was not significantly affected by the surgical procedures in each group.

tomogram. For trigonocephaly, we operated patients with trigocephalic deformity associated with orbital deformity. For the patients who showed the signs of intracranial pressure elevation and/or incomplete eye closure, we operated on as early as possible. And for other patients who need bone transfer, we wait until their weight getting over 5 kg. The repeat surgery was performed for patients who showed the sign of intracranial pressure elevation, and cranio-facial deformity due to advanced bone backslide and poor bone growth.

In this study, we compared the following clinical data between the syndromic and non-syndromic groups: skull shape, age at the initial surgery, surgical procedures, and incidence of repeat surgery during the follow-up period. Postoperative developmental recovery was also studied in both groups. The intergroup differences were analyzed using a t-test or chi square test as appropriate.

## Results

### Initial presentation and surgery

The following skull shapes were observed in the non-syndromic group: brachycephaly (n = 3), plagiocephaly (n = 10), oxycephaly (n = 1), scaphocephaly (n = 8), trigonocephaly (n = 14), clover leaf skull (n = 2), and pancraniosynostosis (n = 1). Skull shapes in the syndromic group included brachycephaly (n = 8), plagiocephaly (n = 2), and oxycephaly (n = 2). There was a significant difference in the phenotype between the two groups ($p$ = 0.0001).

Initial reconstructive surgery was performed at ages ranging from 2 to 66 months old (average, 19.9 ± 17.2) and 3 to 36 months old (average, 9.8 ± 10.3) in the non-syndromic and syndromic groups, respectively. Therefore, age at the initial surgery was significantly lower in the syndromic group than that in the non-syndromic group ($p$ = 0.0153).

In the non-syndromic group, conventional cranioplasty was performed in 23 children between 1982 and 2015, and distraction osteogenesis was completed in 16 children between 1999 and 2013. In the syndromic group, conventional cranioplasty was performed in eight children between 1985 and 2014, distraction osteogenesis was performed in three children between 2003 and 2011 and suturectomy was completed in one patient in 2001. The initial surgical procedures did not significantly differ between the two groups ($p$ >0.05).

### Repeat surgery during follow-up

As shown in Table 1, repeat surgery during the follow-up period was performed in 7 of 51 children (13.7%). A second surgery was required in 3/39 non-syndromic children (7.7%) and 4/12 syndromic children (33.3%). The phenotypes observed in syndromic children included Pfeiffer syndrome (n = 2), Crouzon syndrome (n = 1), and Apert syndrome (n = 1). Therefore, repeat surgery was more common in the syndromic group than in the non-syndromic group ($p$ = 0.0254). As shown in Table 2, all three non-syndromic children required a second surgery due to forehead backslide (Fig. 1a). In the syndromic

**Table 2 Children needing repeat surgery**

| Case No. | Skull type | 1st procedure | Age at 1st op (m.o.) | 2nd procedure | Age at 2nd op (m.o.) | Reason for repeat surgery | Genetic mutation | Syndrome |
|---|---|---|---|---|---|---|---|---|
| **Syndromic** | | | | | | | | |
| 1 | Oxycephaly | FOA | 5 | FOA (D) | 15 | Backslide | *FGFR2* | Pfeiffer |
| 2 | Brachycephaly | FOA (D) | 3 | FOA (D) | 9 | Backslide | *FGFR2* | Pfeiffer |
| 3 | Brachycephaly | Suturectomy | 5 | Monoblock adv. | 133 | Backslide | *FGFR2* | Crouzon |
| 4 | Brachycephaly | FOA | 5 | Occipital expansion | 73 | High ICP | *FGFR2* | Apert |
| **Non-syndromic** | | | | | | | | |
| 5 | Plagiocephaly | FOA | 4 | FOA | 50 | Backslide | None | |
| 6 | Brachycephaly | FOA (D) | 5 | FOA | 72 | Backslide | None | |
| 7 | Clover leaf | Total cranioplsaty | 2 | Total cranioplasty | 36 | Backslide | None | |

In the syndromic group, a child with Apert syndrome needed repeat surgery due to ICP elevation, and the other three children needed a second surgery due to backslide. In the non-syndromic group, all three children needed repeat surgery due to backslide. FOA: fronto-orbital advancement, FOA (D): FOA by distraction osteogenesis, ICP: intracranial pressure, *FGFR*: fibroblast growth factor receptor.

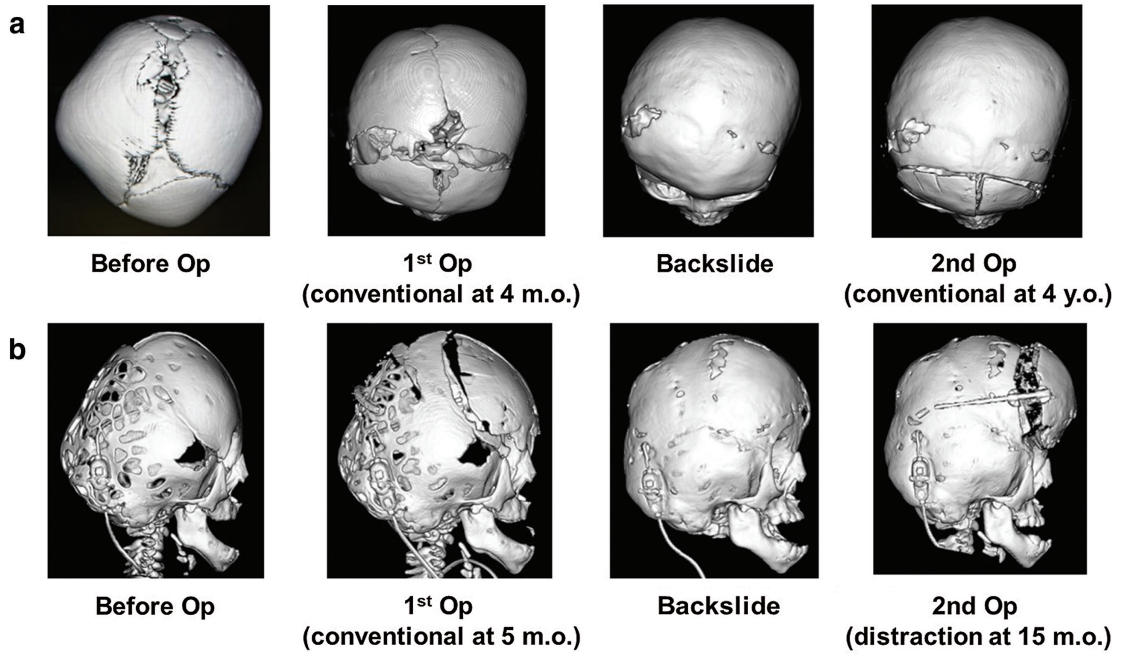


**Fig. 1 (a) Case 5. A non-syndromic child with plagiocephaly had the 1st operation using conventional fronto-orbital advancement at the age of 4 months. At 4 years, she had the 2nd operation using conventional cranioplasty due to forehead backslide and flattening. (b) Case 1. A child with Pfeiffer syndrome with oxycephaly had the 1st operation using conventional fronto-orbital advancement at the age of 5 months. At the age of 15 months, she had the 2nd operation using fronto-orbital advancement by distraction osteogenesis due to the backslide of the forehead and orbital bandeau.**

group, forehead backslide was also the reason for repeat surgery in three children (two cases with Pfeiffer syndrome and one with Crouzon syndrome) (Fig. 1b). Another case with Apert syndrome underwent occipital expansion surgery due to increased intracranial pressure. No children required a third surgery. The interval between the initial and repeat surgeries was 55.7 ± 57.8 months and 54.3 ± 12.7 months in the non-syndromic and syndromic groups, respectively ($p$ >0.05).

In the non-syndromic group, the age at initial surgery was 2, 4, 5 months (average 3.7 ± 1.5 months, median 4 months) and 3–66 months (average 21.2 ± 17.2 months, median 16 months) in the children who underwent repeat surgery and those who did not, respectively. Therefore, the children requiring repeat surgery underwent the initial surgery earlier ($p$ = 0.0142). In the syndromic group, the age at initial surgery was 3–5 months (average 4.5 ± 1.0 months, median 5 months) and 3–36 months (average 12.4 ± 11.9 months, median 7.0 months) in the children who underwent repeat surgery and those who did not, respectively. Likewise, the syndromic children requiring repeat surgery tended to be younger at the initial surgery than those who did not ($p$ = 0.0563).

The procedures of the initial surgery in children who required repeat surgery included conventional cranioplasty (n = 2) and distraction osteogenesis (n = 1) in the non-syndromic group. The procedures of the initial surgery did not significantly differ between the children who had repeat surgery and those who did not ($p$ >0.05). In the syndromic group, the procedures of the initial surgery in children who required repeat surgery included conventional cranioplasty (n = 2), distraction osteogenesis (n = 1), and suturectomy (n = 1). Likewise, the procedures of the initial surgery did not significantly differ between the children who had repeat surgery and those who did not ($p$ >0.05).

**Functional outcome**

Intellectual outcome was assessed at the final follow-up. Developmental retardation was present in 25/51 children (49.0%). There was no significant difference between the non-syndromic (17/39, 43.5%) and syndromic groups (8/12, 66.7%). In non-syndromic patients, the average age at initial surgery was 23.4 ± 15.0 months in the developmentally retarded group and 17.4 ± 18.4 months in the non-retarded group; surgery was significantly later in the retarded group ($p$ = 0.0372). In the syndromic group, the average

**Table 3 Developmental retardation**

| | With retardation | Motor | Mental | Both | Improve |
|---|---|---|---|---|---|
| Syndromic (12) | 8 (66.7%) | 8 | 5 | 5 | 0 |
| Non-syndromic (39) | 17 (43.5%) | 12 | 14 | 9 | 2 |

Developmental retardation was observed in 8 of 12 children in the syndromic group, and 17 of 39 children in the non-syndromic group. Some children had both motor and mental delays. No child in the syndromic group showed improvement in their delays after cranioplasty. In contrast, 2 children, 1 with gait delay and 1 with hyperactivity, showed improvement after cranioplasty.

age at initial surgery was 5.4 ± 2.0 months in the retarded group and 18.5 ± 15.0 months in the non-retarded group; the difference was not significant. In the non-syndromic group, motor developmental delay was observed in 12 children, mental retardation in 14, and both in 9. Of these cases, one child with trigonocephaly having a gait delay and another with scaphocephaly having hyperactivity improved after the initial surgery. In the syndromic group, motor developmental delay was observed in eight children, mental retardation in five, and both in five. None of them experienced recovery in their developmental delays even after surgery (Table 3).

## Discussion

### Repeat surgery

In this study, non-syndromic children were followed for 5–35 years (average, 13.5 years), whereas syndromic children were followed for 5–38 years (average, 18.3 years). The incidence of repeat surgery was 7.7% in the non-syndromic group and 30.8% in the syndromic group. According to previous reports, the incidence of repeat surgery widely varied from 0% to 39% (Table 4).[19,20,22–27] However, the previous reports included short-term follow-up of patients, and the average follow-up period was 4.4–13.2 years, which is much shorter than that in this study. It is difficult to conclude the incidence of repeat surgery for craniosynostosis according to such short-term follow-up studies. Furthermore, the difference in the aggressiveness for repeat surgery at each institute may also influence the difference in the incidence of repeat surgery. Because there is no consensus on scientific criteria for repeat surgery except for increased intracranial pressure, repeat surgery may be performed only for cosmetic reasons in many patients.

In this study, repeat surgery was more common in the syndromic group. Earlier initial surgery may be associated with higher incidence of repeat surgery. Syndromic patients have more severe skull deformities and may require early initial surgery. In this study, the average age at the initial surgery was 19.9 months and 9.8 months in the non-syndromic and syndromic groups, respectively. Based on previous reports, the patients who underwent initial surgery before 6 months of age were more likely to undergo repeat surgery compared with those aged 6 months or older (18–62% vs. 11–12%, respectively).[19,24] Actually, Utria et al. (2015) recommended that the initial surgery should be performed between 6 and 9 months of age in syndromic patients.[23] These findings are consistent with our results. In our study, the initial surgery was performed before 5 months of age in all 7 patients who underwent repeat surgery. And in both syndromic and non-syndromic groups, the children requiring repeat surgery tended to be younger at the initial surgery than those who did not. But the number of patients in each group are limited, and this result is not highly reliable statistically.

Skull shape did not influence the incidence of repeat surgery. This finding may be because of the limited number of patients in each group in this study. Similarly, the operative procedures did not affect the incidence of repeat surgery. Teichgraeber et al. (2002) reported that the incidence of repeat surgery was higher in patients with plagiocephaly and trigonocephaly when treated with an endoscopic minimally invasive technique.[20] However, Bennet et al. (2019) recently reviewed previous reports and concluded that there were no reports denoting the impact of surgical procedures on the incidence of repeat surgery during long-term follow-up.[28]

### Functional outcome

This study clearly showed a very high incidence of long-term developmental retardation especially in syndromic patients, which correlates with previous reports.[29,30] Early surgery has been recommended to avoid retardation in some reports. Some reports insist on cranial expansion before 1 year of age.[30,31] As mentioned above, the initial surgery before 6 months of age is reported to yield a better full-scale IQ and performance IQ at 10 years of follow-up compared to later surgery.[21] In an animal study using a rabbit brachycephalic model, early suturectomy prevented

**Table 4 Summary of reports including long-term results**

| Author | Year | Case No. | Type | Follow-period (yrs) | Repeat surgery | Developmental recovery after cranioplasty |
|---|---|---|---|---|---|---|
| Wagner JD[19] | 1995 | 22 | Non-synd (bicoronal) | 0.5–14 (mean 4.4) | 2nd op 36%<br>3rd op 18% | NM |
| Teichgraeber JF[20] | 2002 | 180 | Non-synd (microsopic vs conv) | 3–14 (mean 7.3) | Micro 14.9%<br>conv. 7.1% | NM |
| Nishimoto H[22] | 2014 | 133 | Synd and non-synd | 1–28 (ave 13.2) | Synd 25.7%<br>non-synd 11.2% | NM |
| Utria A[23] | 2015 | 52 | Synd | 1–24 | 36.9% (Whitaker 3,4) | NM |
| Utria A[24] | 2016 | 413 | Non-synd | 3–26 (ave 5) | 14% (Whitaker 3,4) | NM |
| Morrison KA[25] | 2018 | 81 | Synd and non-synd | 2–22 | 2.50% | NM |
| Persad A[26] | 2020 | 32 | Non-synd (sagittal) | 4.5–9 (mean 5.8 ) | 0% | NM |
| Massenburg BB[27] | 2020 | 3924 (national deta base) | Synd and non-synd | 3–7 | 2.40% | NM |
| Akai T | 2021 | 56 | Synd and non-synd | 5–38 (ave 17.3) | Synd 30.8%<br>non-synd 7.7% | 2/25 (8%) |

In previous reports, the follow-up period was 0.5–28 years. All those reports included patients with short-term follow-up. The proportion of those who had repeat surgery was 0–39%. Syndromic patients were more likely to need repeat surgery than non-syndromic patients. No previous report mentioned recovery of developmental retardation after cranioplasty. Synd: syndromic, non-synd: non-syndromic, conv: conventional, ave: average, micro: microscopic, NM: not mentioned, op: operation.

white matter degeneration.[32] In our study, the average age at initial surgery was 19.9 ± 17.2 months in the non-syndromic patients and 9.8 ± 10.3 months in the syndromic patients. In the non-syndromic patients, the age was significantly later in the retarded group. This delay in surgery may have resulted in the high incidence of developmental retardation. Most patients first visit a pediatrician if there are developmental concerns. Therefore, there should be tight cooperation with pediatricians to provide earlier interventions.

Even after surgery, however, improvement in intellectual function is uncommon. This issue is still being debated in the clinical setting. In our study, a motor delayed child with trigoncephaly and a mental delayed child with scaphocephaly in non-syndromic group recovered after surgery. It is difficult to determine whether this improvement was induced by the surgery or normal child growth. To prevent mental developmental aggravation, some reports have supported the beneficial effect of reconstructive surgery.[21,30,33] Shimoji reported the importance of frontal opercular decompression by decompressive cranioplasty to improve mental developmental delay.[34] However, other reports have concluded that reconstructive surgery cannot improve cognitive function and can only improve cosmetics.[31,35–38] However, we have no high-quality evidence yet.[39,40]

This study has limitations because of long-term follow-up and variety of patients' symptoms. During the follow-up period, patients were not treated base on a single-standard strategy. Patients were not operated by a single surgical team, and new technique such as distraction osteogenesis and occipital expansion has been introduced, and the strategy has changed.

## Conclusion

Repeat surgery for craniosynostosis during long-term follow-up was common, especially in syndromic patients. The severity of skull deformity and early initial surgery may be important factors for subsequent need for repeat surgery. Developmental retardation is also very common in both non-syndromic and syndromic patients, and improvement in motor and mental function is rare even after surgery. However, the conclusions should be confirmed with a larger cohort. For this purpose, we are planning a nationwide prospective case registration study that will determine the optimal operative procedure and its timing.

## Conflict of Interest Disclosure

The authors declare that they have no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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