Ommaya reservoir placement using ultrasound guidance via anterior fontanelle combined with frameless electromagnetic neuronavigation in patients with mucopolysaccharidosis type 2: case reports and review of the literature

Makoto Mizushima[1], Masahito Kawabori[1], Kazuyoshi Yamazaki[1], Kiyoshi Egawa[2], and Miki Fujimura[1]

[1]*Department of Neurosurgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan*

[2]*Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan*

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Running Title: Reservoir placement with ultrasound guidance through Anterior fontanelle in patients with MPS Ⅱ.

Corresponding author: Masahito Kawabori, MD, PhD
Department of Neurosurgery, Hokkaido University Graduate School of Medicine, North 15 West 7, Kita-ku, Sapporo 060-8638, Japan
Tel: +81-11-706-5987, Fax: +81-11-708-7737
E-mail: masahitokawabori@yahoo.co.jp

Introduction

Mucopolysaccharidosis type II (MPS II) is a rare genetic disorder attributed to the genetic absence or dysfunction of the lysosomal enzyme iduronate-2-sulfatase (IDS), which plays a pivotal role in the degradation of glycosaminoglycans (GAGs)[1]. The accumulation of GAGs causes enlargement and dysfunction of most organ-systems leading to shortened life expectancy[2]. Enzyme replacement therapy (ERT) utilizing idursulfase, delivered via intravenous administration, has emerged as an established therapeutic modality for managing MPS II[3, 4], However, intravenous administration is not effective for developmental delay due to the enzyme's incapacity to traverse the blood–brain barrier[5]. To address this challenge, intracerebroventricular (ICV) administration of idursulfase beta was explored, yielding favorable outcomes and obtained recent drug approval in Japan [6]. The implantation of an Ommaya reservoir is a prerequisite for periodic ICV administration, typically administered every 4 weeks. Nevertheless, MPS II infants frequently exhibit narrowed lateral ventricles owing to cerebral enlargement, thereby posing challenges for precise catheter placement. No study has previously reported technical insights into Ommaya reservoir placement for these patients. In this report, we document successful placements achieved by employing ultrasound guidance through the anterior fontanelle in conjunction with flameless electromagnetic neuronavigation in two infantile patients with MPS II.

Case presentation

We present two cases of MPS-II in Japanese boys, aged eleven and five months. The first child had an uneventful pregnancy and was born full-term. MPS-II was suspected following a newborn blood screening test and subsequently confirmed through biochemical analyses, revealing elevated urinary GAGs, and genomic analysis, which identified the pathogenic hemizygous IDS variant c.1180+1G > T. The data revealed that the patient is considered as severe case. At the time of diagnosis, the patient did not exhibit any disease-specific characteristics and was initiated on a regular follow-up regimen. Although there was no developmental delay, a notable feature of the disease became apparent at the age of 6 months: a prominent forehead along with a head circumference of 46.3 cm (+3.2 SD). Subsequently, the patient commenced weekly enzyme replacement therapy (ERT) with idursulfase (Elaprase®), and the placement of an Ommaya reservoir for intracerebroventricular (ICV) enzyme administration was scheduled for 11 months of age. The second child also had an uneventful pregnancy and was born full-term. The suspicion of MPS-II arose following newborn blood screening tests, which was later confirmed through biochemical analyses revealing elevated urinary GAGs and genomic analysis detecting a severe pathogenic IDS variant. While the patient did not display any signs of developmental delay, there was notable overgrowth in terms of height and weight, indicative of the onset of the disease. Consequently, the patients were promptly initiated on a weekly intravenous ERT. Furthermore, plans were made for Ommaya reservoir placement to facilitate intracerebroventricular (ICV) enzyme administration at the age of 5 months.

Preoperative magnetic resonance (MR) imaging revealed slit-like ventricles. Following induction of general anesthesia, the anterior fontanelle was detected by palpation (Fig. 1A). Subsequently U-shaped skin incision was made, along with the creation of a burr hole (Fig. 1B). To identify optimal puncture site and trajectory, electromagnetic (EM) image-guidance (StealthStation Synergy, Medtronic) was utilized. The trajectory was meticulously planned to ensure that it did not intersect with brain sulci during the procedure. The operator carefully inserted the catheter into the brain parenchyma, with a EM image-guidance navigational probe inside the catheter. Simultaneously, an assistant visualized the lateral ventricles and catheter tip by employing the convex probe of the Fujifilm ARIETTA 65LE ultrasound system via the anterior fontanelle. This real-time collaboration allowed the operator to confirm and make any necessary adjustments to the catheter tip (Fig. 2). Ultimately, the tip of the cannula was successfully positioned into the frontal horn of the lateral ventricle. The catheter was then securely attached to the Ommaya reservoir, and the skin incision was closed. Postoperative computed tomography confirmed the precise placement of the catheter (Fig. 3). The postoperative course was uneventful, and the patients were subsequently initiated on periodic ERT.

Discussion

Owing to the degenerative nature of the disease, the secure and precise placement of catheters is inherently vital for the management of MPS II. However, data from the prior clinical trial involving infant MPS II patients indicated that one patient (16.7%) experienced post-procedural hemorrhage, and another patient (16.7%) developed contusion, both of which were attributed to the reservoir placement procedure[6]. While it is challenging to draw definitive conclusions due to the limited number of patients involved in the clinical trial, a safer method for reservoir placement is of paramount importance.

In contrast to patients with hydrocephalus, the majority of individuals necessitating Ommaya reservoir placement present with normal to slit-like ventricles, rendering the catheter placement procedure challenging. Gerber et al. reported the surgical outcomes of Ommaya reservoir placement in pediatric patients with malignant tumors, identifying catheter malpositioning in 3 out of 31 procedures (9.7%)[7]. In recent times, image-guided placement techniques have advanced and encompassed a range of modalities, including fluoroscopy, frame-based and frameless stereotaxy, ultrasound, neuroendoscopy, C-Arm, O-Arm, smartphone applications, and neurosurgical robots, catering to both adult and pediatric patient populations (Table 1) [8-22]. Among these methods, stereotaxy is currently the most popularly adopted technique. Pre-operative analysis to prevent the catheter from entering or exiting adjacent sulci can reduce the risk of hemorrhagic complications. However, this method does not provide real-time visualization of the catheter tip, which can result in misplacement due to registration errors and intraoperative anatomical changes caused by cerebrospinal fluid leakage and brain shifting. Shamir et al. reported a mean localization error at the target of 5.9 ± 4.3 mm in Ommaya reservoir catheter placement using stereotaxy with a neuronavigation system[19]. To address this limitation, the combination of stereotaxy with real-time observation devices such as ultrasound, neuroendoscope, C-Arm, and O-Arm presents a potential solution. Neuroendoscope requires additional equipment which pushes up the cost[10], and both C-Arm and O-Arm are associated with radiation exposure concerns. In this study, we opted to employ ultrasound for real-time observation, proving to be highly valuable in fine-tuning the positioning of the catheter tip. However, it is imperative to note that ultrasound alone may not suffice for ensuring the secure placement of the catheter. This limitation arises from the restricted visual field provided through the anterior fontanelle, which only covers the region proximate to the ventricle and does not offer insight into the subpial trajectory of the catheter.

The rapid expansion of therapeutic modalities, which includes enzyme replacement therapy (ERT), molecularly-targeted therapy, and gene therapy, exemplified by cerliponase alfa for CLN2 disease and tralesinidase alfa for Sanfilippo syndrome type B, has led to a rising demand for Ommaya reservoir placement in infantile patients[15, 17].

Consequently, the need for the development of dependable catheter placement techniques for infantile patients with slit-like ventricles becomes increasingly critical. The ultrasound guidance via anterior fontanelle combined with frameless electromagnetic neuronavigation can be one good option for safe implantation procedure.

Conflicts of interest

All authors have no conflict of interest.

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Figure legends

Fig. 1. Intraoperative scenes

A: The anterior fontanelle identified by palpation (white arrow) and the entry point decided based on preoperatively considered trajectory (white arrowhead).

B: intraoperative ultrasound guidance was used during the catheter insertion procedure.

Fig. 2. Intraoperative ultrasound guidance enabled catheter tip and the ventricle. Ultrasound guidance via anterior fontanelle showing the anterior horns of lateral ventricles (yellow dotted line) and catheter (red dotted line) in real time.

Fig. 3. Postoperative computed tomography

A: Catheter is placed in the planned ventricle

B: Ommaya reservoir is placed posterior to the burr hole.

Table. 1 Recent studies of Ommaya reservoir placement into the lateral ventricle.

Leading author	Year	Patients (n)	Technique	Real-time observation	First pass rate	Malposition*	Complications*[2]
Unal [20]	2023	9	Ultrasound	Possible	100%	0%	
Liu*[3] [13]	2021	10	Robot	Impossible	100%	0%	NA
Ozerov [12]	2018	60	Smartphone	Impossible	97%	5.8%	6.7%
Xu [22]	2016	24	EM navigation	Impossible	100%	0%	4%
Wang [10]	2016	25	EM navigation + Neuroendoscope	Possible	96%	16%	4%
Morgenstern [8]	2016	57	Fluoroscopy	Possible	NA	NA	1.8%
		88	Frameless stereotaxy	Impossible	NA	NA	6.8%
Filis [16]	2016	48	Navigation	Impossible	NA	NA	83%
Kennedy [9]	2015	41	Frame-based stereotaxy	Impossible	100%	NA	9.8%
		68	Frameless stereotaxy	Impossible	97%	NA	10%
Weiner [21]	2015	12	EM navigation	Impossible	NA	17%	0%
		16	Optical navigation	Impossible	NA	31%	6.3%

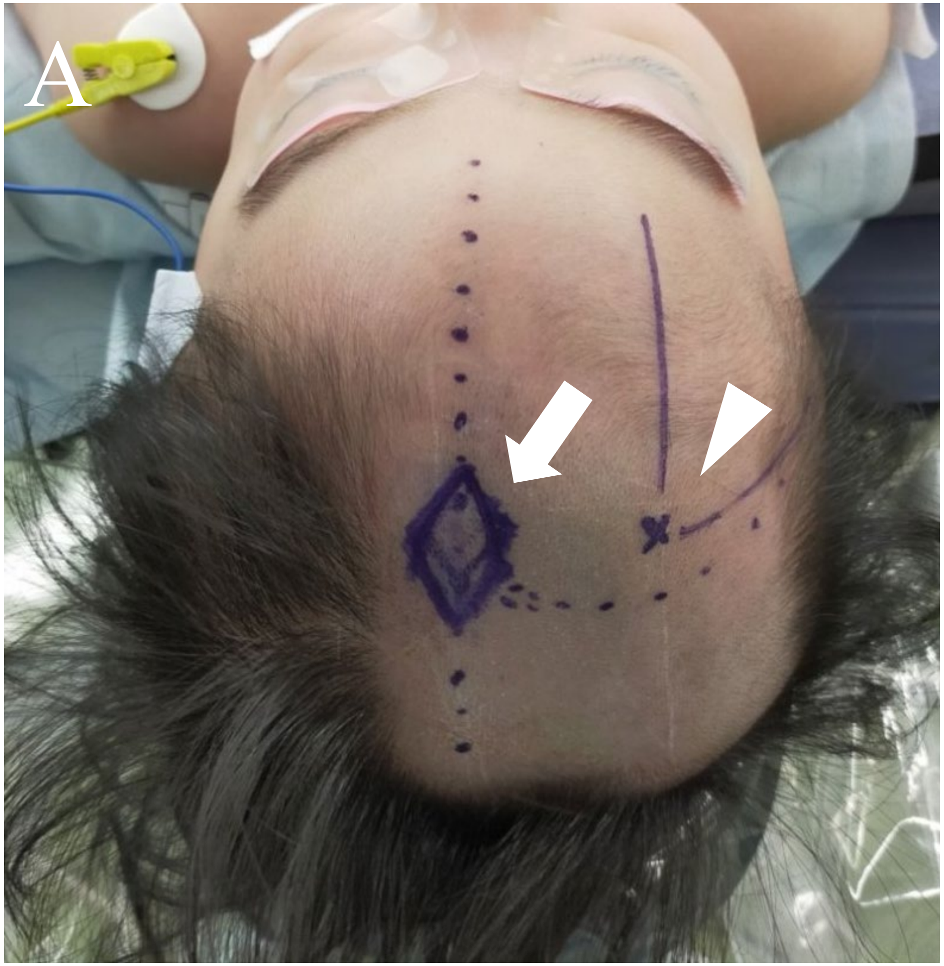
Raghuram Sampath [18]	2012	18	Frame-based stereotaxy	Impossible	NA	5.6%	5.6%

NA = not assessed; EM = electromagnetic

* Malposition includes placement of catheter tip into the contralateral ventricle, interhemispheric fissure, or brain parenchyma.

*[2] Complications include infection, hemorrhage, and revision.

*[3] This study included 50 patients, however 40 out of them underwent Ommaya reservoir placement into the lumen of the tumor.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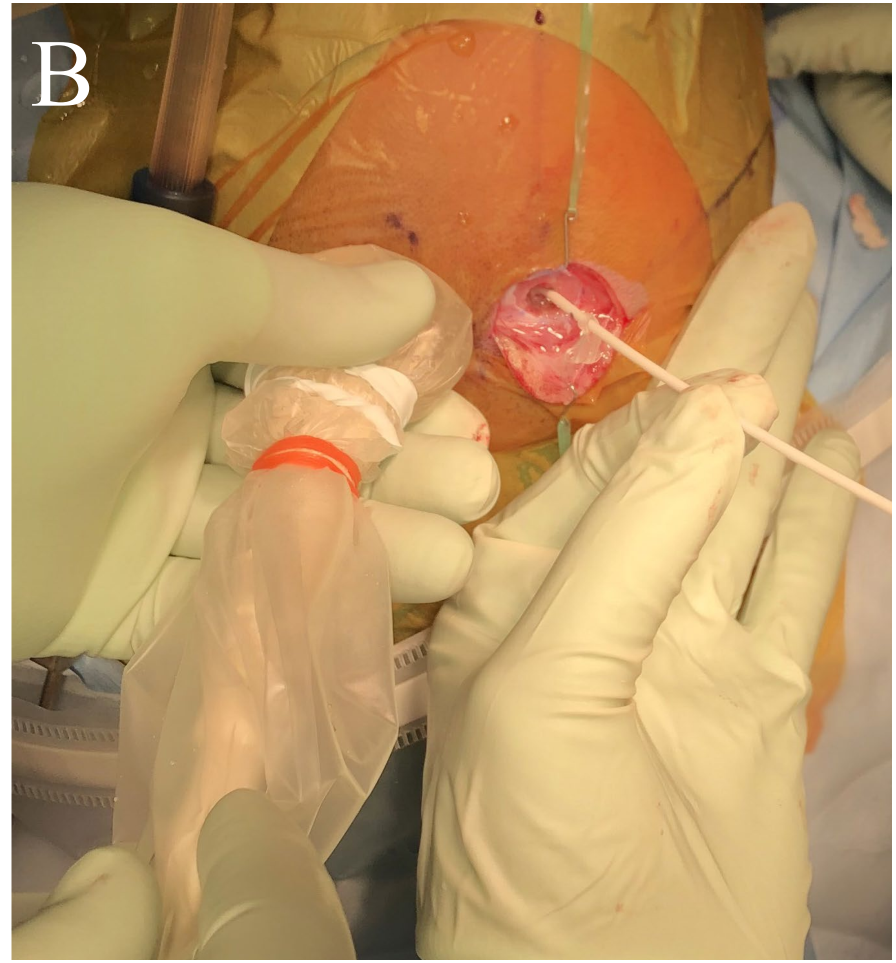
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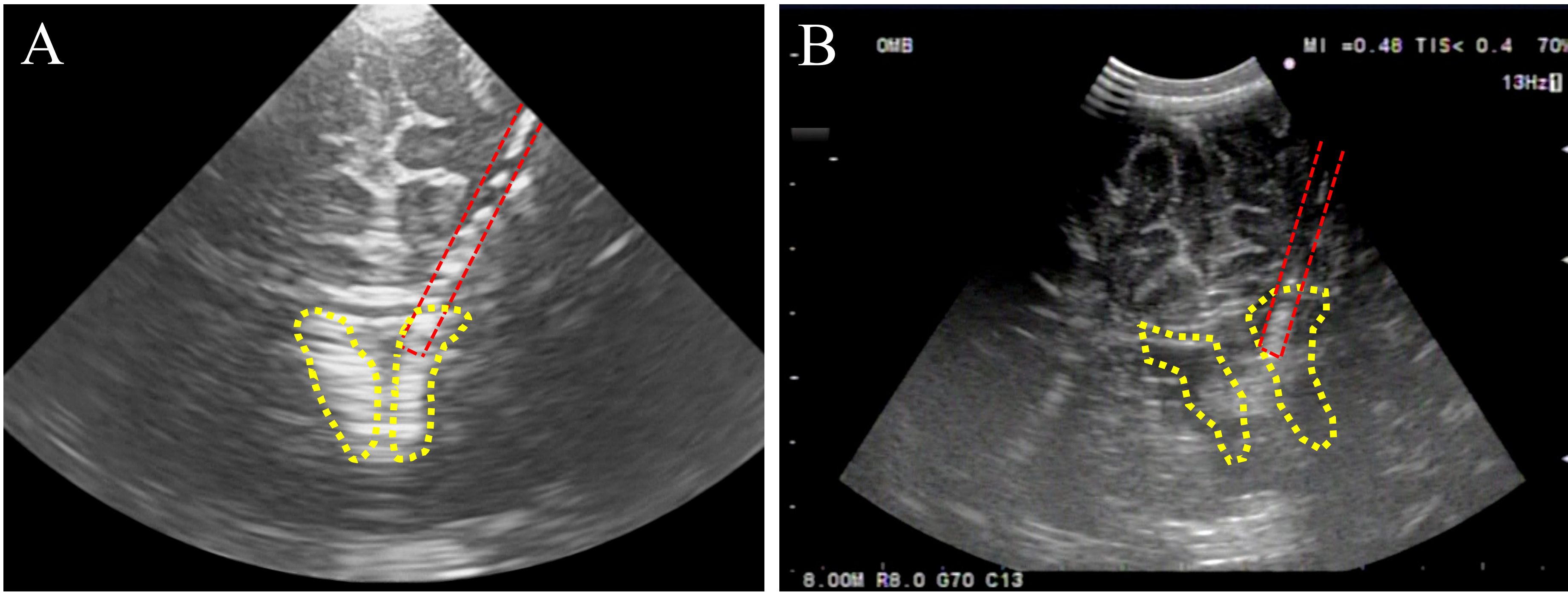
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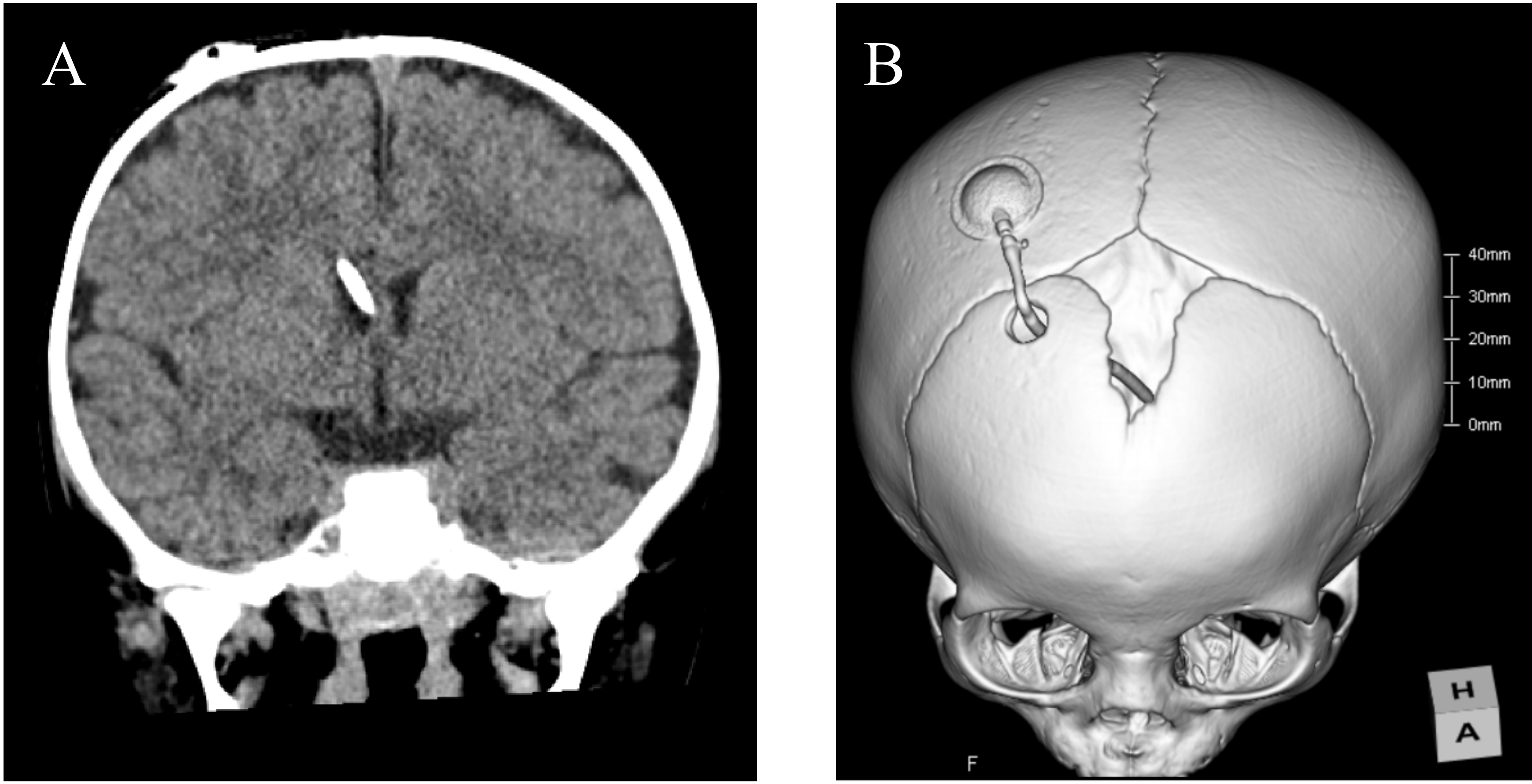
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