History of the Kleeblattschädel deformity: origin of concepts and evolution of management in the past 50 years

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The history and evolution of surgical strategies for the treatment of Kleeblattschädel deformity are not well described in the medical literature. Kleeblattschädel anomaly is one of the most formidable of the craniosynostoses, requiring a multidisciplinary team for surgical treatment. The initial descriptions of this cloverleaf deformity and the evolution of surgical treatment are detailed in the present report. Two illustrative cases of Kleeblattschädel deformity, syndromic and nonsyndromic craniosynostoses treated by the senior authors, are also described along with insights into operative strategies. (DOI: 10.3171/2010.9.FOCUS10212)

KEY WORDS • Kleeblattschädel deformity • craniosynostosis • cloverleaf skull syndrome • chondrodystrophic hydrocephalus • hindbrain herniation

The cloverleaf skull, or Kleeblattschädel, is a rare skull deformity resulting from premature fusion of multiple cranial sutures and characterized by a trilobar skull with bossing of the forehead, temporal bulging, and a flat posterior skull.20,24,40 Inconsistent patterns of suture fusion have been reported, with the coronal and lambdoid sutures most often involved.1 The condition is further characterized by cosmetic facial deformity and micromyelia and can be further complicated by increased intracranial pressure, hydrocephalus, hindbrain herniation, skull base dysplasias, and impaired neurological function.2,10,28,38 The etiology of Kleeblattschädel syndrome is unknown; it has been attributed to abnormalities of both the calvaria and the skull base, making it one of the most complex craniosynostoses to treat. The Kleeblattschädel anomaly has been reported to occur in patients with both syndromic and nonsyndromic forms of craniosynostosis.39

Anatomical observations made in previous case studies involving the Kleeblattschädel anomaly have included inconsistent patterns of craniosynostosis, with the coronal and lambdoid sutures most frequently implicated.3,7 Other authors have also observed a shortened anteroposterior dimension of the cranial base, particularly affecting the anterior cranial fossa. The superior leaf of this deformity arises from a widely diastatic sagittal suture and/or metopic suture. If the sagittal suture is closed, a grossly expanded anterior fontanel is noted. The anterior cranial fossa has a shortened anteroposterior dimension and steep upward inclination, which extends to its posterior border at the sphenoid ridge. Correspondingly, the lesser wings of the sphenoid have been seen to have a steep upward inclination. It is suggested that these anomalies of the cranial base may transmit forces to the dura mater, which result in stenosis of the overlying cranial sutures.

Origin of Concepts: the Holtermüller-Wiedemann Collaboration

In 1849 Vrolik described a craniofacial malformation he called “dyscrania” that probably resembled a cloverleaf deformity. However, the name “Kleeblattschädel Syndrom” was given by Holtermüller and Wiedemann in their paper published in the journal Medicinische Bild in 1958 and subsequently included in the second edition (1959) of the Dictionary of Clinical Syndromes by Leiber. Karl Holtermüller, born in 1915, had practiced as a pediatrician in several cities in Germany, including Bonn, Berlin, and Hagen, prior to becoming head of the Children’s Clinic in Neunkirchen Kohlfhof (1953) and later Kinderklinik Saarbrücken, located at the Bürgerhospital, Saarbrücken. He consulted Hans-Rudolf Wiedemann (1915–2006; Fig. 1) regarding a newborn with an unusual head shape and circumference, which led to their 1960 article in Medizinische Monatsschrift.18,44 Wiedemann was at that time a well-
known scholar, teacher, and administrator in the Department of Pediatrics in Krefeld and later in Kiel, Germany. Having been trained in Jena with Jussuf Ibrahim, who influenced him to do neuropediatrics and clinical genetics, Wiedemann was first recognized for his documentation of a malformation epidemic in 1961, which was later understood to occur from thalidomide. Beyond the classic eponym Beckwith-Wiedemann syndrome (exomphalos-macroglossia-gigantism syndrome), Wiedemann was also known for phenotype descriptions in various lipidoses, mucopolysaccharidoses, hereditary skeletal dysplasias, and gonosomal aneuploidies. Furthermore, he harbored a keen interest in progeroid syndromes and defined a neonatal pseudohydrocephalic progeroid syndrome, referred to as “Wiedemann-Rautenstrauch syndrome.” In addition to receiving several national and international awards, he was the recipient of the Otto Heubner Prize awarded by the German Society of Pediatrics, the highest distinction and honor bestowed by that society. In the 1990s, Wiedemann suffered a major stroke that left him aphasic and hemiplegic for the last decade of his life; he died on August 8, 2006.

The classic paper by Holtermüller and Wiedemann compiled 13 cases; 12 were previously called “chondrodystrophic hydrocephalus” (Table 1). The original description of this new cloverleaf skull deformity included the following: a trilobar skull configuration with downward displacement of the ears, facial deformity with hypertelorism, nasal flattening, jaw abnormalities, micromelia and skeletal abnormalities, radiological documentation of cloverleaf skull, and hydrocephalus. An original published photograph and a radiograph featuring an infant with Kleeblattschädel deformity are shown in Fig. 2. Chondrodystrophy was implicated in several of the initial cases prior to the description of Kleeblattschädel anomaly; however, the Kleeblattschädel deformity lacked the genetic inheritance seen with the chondrodystrophies, and thus, patients with Kleeblattschädel often lacked the associated chondrodystrophic body habitus.

**Neurological Manifestations: Current Understanding**

Pathologically, the Kleeblattschädel specimen reveals patent sagittal and squamosal sutures with a circumferential ring of bone joined at the junction by the upper and lower leaves of the cloverleaf, dividing the upper part into 2 halves, with abundant endocranial molding (honeycomb pattern of the inner vault) and a small crowded posterior fossa often associated with tonsillar herniation. Bony deformities include a foreshortened anterior cranial fossa; flattened occiput; and thickened, sclerosed sphenoid wings. The neurological sequelae of the Kleeblattschädel deformity arise mainly from 1) hydrocephalus, 2) hindbrain herniation, and 3) venous hypertension.

**Hydrocephalus Association**

The origin of hydrocephalus in patients with Kleeblattschädel is often debated. All of the initial published reports on the deformity have cited hydrocephalus as an invariable association. Angle et al. reported basilar deformity causing fourth ventricular outflow obstruction, and Partington et al. suggested basilar impression documented at autopsy as a cause for hydrocephalus.

**Fig. 1.** Photograph of Hans-Rudolf Wiedemann, who collaborated with Holtermüller to describe the Kleeblattschädel deformity.

**Fig. 2.** Left: The Kleeblattschädel anomaly. Photograph demonstrating an infant with a cloverleaf skull, or trilobar cranial vault, frontal bossing, pronounced temporal bulging, and exophthalmos. Right: Anteroposterior radiograph demonstrating the constriction band believed to contribute to the formation of a trilobar skull. Both images reproduced with permission from Holtermüller K, Wiedemann HR: Kleeblattschädel-Syndrom. Med Monatschr 14:439–446, 1960.
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in cloverleaf skull deformities. Feingold et al.\textsuperscript{9} described a case of aqueductal stenosis with hydrocephalus in a case of Kleeblattschädel deformity. Shiroyama et al.\textsuperscript{37} documented 2 cases and reviewed 21 other cases of this deformity; communicating hydrocephalus was seen in 8 patients and noncommunicating hydrocephalus in 15 patients. The most common causes of noncommunicating hydrocephalus were basilar invagination, aqueductal stenosis, compression by a midline occipital bone crest, and posterior fossa deformities. Communicating hydrocephalus, when present, is thought to have resulted from venous hypertension and CSF flow obstruction at the constricting band of bone (Fig. 3).\textsuperscript{46} However, in 1980 Turner and Reynolds\textsuperscript{42} reported a case of cloverleaf skull without associated hydrocephalus, suggesting that hydrocephalus is not an invariable accompaniment to the Kleeblattschädel deformity.

Venous Hypertension

Intracranial obstruction can reroute venous drainage via the scalp veins, and such an interruption can lead to serious brain swelling and infarcts.\textsuperscript{25} Prominent veins in the scalp, sclera, and periorbital region are described in several reports on the Kleeblattschädel deformity, arguably a remnant of persistent embryonic cranial circulation. There are also case reports of severe proptosis leading to corneal ulcerations, often treated with tarsorrhaphies.\textsuperscript{12,35} Enlarged emissary veins, stenosis of the jugular foramina, and the presence of high-pressure, intraosseous, cranial venous sinuses communicating with a collateral scalp venous system lead to venous hypertension associated with the Kleeblattschädel deformity, according to Thompson et al.\textsuperscript{41} This observation was validated by the fact that their patient required shunt placement despite adequate release of the supratentorial constriction band of bone. Hence, the venous obstruction at the jugular foramen level was held at fault.

The role of venous hypertension and the development of hydrocephalus seem to be linked.\textsuperscript{12,23} Portnoy et al.\textsuperscript{32} postulated that the venous hypertension is dependent on the status of cranial sutures (open or closed) and the re-

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Cited Diagnosis</th>
<th>Brief Patient History</th>
<th>Additional Cranial Pathology</th>
<th>Systemic Malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vrolik, 1849\textsuperscript{†}</td>
<td>hydrocephalus chondro-dystrophicus</td>
<td>1 infant: 17-wk-old M, footling breech birth</td>
<td>downslanting palpebral fissure; occipital encephalocele (vs biparietal bone)</td>
<td>foreshortened extremities; possible abdominal hernia</td>
</tr>
<tr>
<td>Mayer, 1912 &amp; 1924</td>
<td>hydrocephalus chondro-dystrophicus</td>
<td>2 infants: 1 M, 40 cm; 1 F, 36 cm</td>
<td>occipital encephalocele versus biparietal bone; cleft palate; downslanting palpebral fissure; tribasilar bone (chondrodystrophic shortening of the chondrocranium)</td>
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<tr>
<td>Gruber, 1926</td>
<td>hydrocephalus chondro-dystrophicus</td>
<td>5 infants: 1, 36 cm; 2, F, 45 cm; 3, referenced from Gottingen; 4, originally described by Rudolphia, 1824; 5, originally described by physician at University of Vienna</td>
<td>biparietal bone; downslanting palpebral fissure; tribasilar bone shortening</td>
<td>consistent w/ chondrodys-trophy (chondrodystrophia fetalis)</td>
</tr>
<tr>
<td>Dietrich-Weinnoldt, 1926</td>
<td>hydrocephalus chondro-dystrophicus</td>
<td>1 infant, stillbirth</td>
<td>biparietal bone; coronal synostosis; constriction of the foramen magnum</td>
<td>consistent w/ chondrodys-trophy</td>
</tr>
<tr>
<td>Welter, 1936</td>
<td>hydrocephalus chondro-dystrophicus</td>
<td>1 infant, F, 46 cm</td>
<td>biparietal bone w/ osseous propulsion along posterior fontanelle w/ tumorous rim; tribasilar bone; coronal &amp; lambdoid synostosis; abnormal CSF flow; jugular foramen constriction</td>
<td>pathological confirmation of chondrodystrophia fetalis; hepatomegaly</td>
</tr>
<tr>
<td>Krauspe, 1958</td>
<td>hydrocephalus chondro-dystrophicus</td>
<td>2 infants, unknown birth length</td>
<td>skull base narrowing; multiple craniosynostoses</td>
<td>consistent w/ chondrodys-trophy</td>
</tr>
<tr>
<td>Holtermüller &amp; Wiedemann, 1960\textsuperscript{‡}</td>
<td>hydrocephalus chondro-dystrophicus</td>
<td>1 infant, M; ultimately died due to hydrocephalus</td>
<td>occipital &quot;buckelschadel&quot; (tuberous skull); extreme exophthalmos; elevated palate; rudimentary parietal bones merging into osseous formation w/in fontanel; underlying parenchymal maldevelopment</td>
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sultant ICP that acts over the sagittal venous sinus pressure, the rate-limiting factor in CSF absorption. With the multiple cranial synostoses that occur in the Kleeblattschädel deformity, the chances of venous hypertension developing are high. The presence of venous collaterals were documented by Pierre-Kahn et al.,31 which eventually led to an extracranial-intracranial bypass in a patient with Crouzon syndrome, whose hydrocephalus resolved postoperatively. We believe that a shunt surgery or vault expansion surgery could be a less invasive initial approach in treating these patients.

**Hindbrain Herniation**

The hindbrain herniation in syndromic craniosynostosis was first reported by Saldino et al.30 Venes43 also described hindbrain herniation in a case of cloverleaf skull deformity and advanced the concept of an acquired Chiari malformation. It has been postulated that the venous hypertension, small posterior fossa, and hydrocephalus would be contributing variables in the development of hindbrain deformation/herniation. Cinalli and colleagues3,6 posit that the chronic tonsillar herniation in craniosynostosis is a result of venous hypertension and cephalocranial disproportion (brain growth and small posterior fossa). This theory applies to all the complex craniofacial craniosenotic states, such as cloverleaf skull deformity.

**Associated Conditions**

There are reports of an association between the Kleeblattschädel deformity and achondroplasia, Crouzon craniofacial dysostosis, and Apert syndrome (acrocephalosyndactyly). Available reports reveal that 20% of cloverleaf malformations are associated with Pfeiffer syndrome (acrocephalosyndactyly Type V).22 Cohen8 has proposed 3 clinical subtypes of Pfeiffer syndrome and has attributed a poor prognosis to those associated with Kleeblattschädel deformity. It has been noted that an isolated Kleeblattschädel deformity without an associated craniofacial syndrome is relatively rare.

Several postulates are available for the pathogenesis of the Kleeblattschädel: abnormal membranous bone ossification,1 abnormal enchondral ossification,4 and generalized chondro dysplastic process.4 The first classification of Kleeblattschädel deformity was proposed by Partington et al.30 in the following 3 groups: Type I, cloverleaf skull associated with generalized chondrodysplasia and thanatophoric dwarfism; Type II, cloverleaf skull with localized skeletal lesions such as bony ankylosis of elbows and subluxation of radial heads or hips; and Type III, cloverleaf skull deformity without any skeletal deformity.30

The current neurogenetic grouping of the Kleeblattschädel deformity is under thanatophoric dysplasia Type II—whereas Type I is more common and patients classically present with curved femur bones that look like telephone receivers and a flattened spine (platyspondyly). The term “thanatophoric” is Greek for “death bearing,” and infants with thanatophoric dysplasia are usually stillborn or die of respiratory failure shortly after birth.17,33,48 This type of dysplasia arises from mutations in the FGFR3 gene, which has been mapped to chromosome band 4p16.3 and is involved in the development and maintenance of bone and brain tissue. Note that FGFR3 is part of the tyrosine kinase receptor family and that mutations in this gene cause the FGFR3 protein to be overly active, which leads to the severe disturbances in bone growth that are characteristic of thanatophoric dysplasia, which often shows an autosomal dominant pattern of inheritance. Germline mosaicism has not been clearly documented but remains a theoretical possibility. In the existing medical literature, all patients with thanatophoric dysplasia Type II (Kleeblattschädel deformity) have a single point mutation, p.Lys650Glu, with an A→G nucleotide transition in the tyrosine kinase domain of FGFR3, also known as K650E. This occurs in 99% of patients with Type II dysplasia and remains the only reported gene mutation in Kleeblattschädel deformity. Thanatophoric dysplasias Type I and II may both carry a cloverleaf skull deformity, although it is extremely rare in Type I. However, they do not share common FGFR3 gene mutations.99 Sequence and targeted mutation analysis of FGFR3 is currently available to assist with diagnosis when clinical concerns are high.27

**Surgical Strategies in Kleeblattschädel: Evolution in the Past 5 Decades**

Early reports documented death of the affected infant soon after birth,1,2 with an overall poor prognosis. In 1972 Arseni et al.2 first described surgical treatment in the form of linear craniotomies along the coronal, lambdoid, and temporoparietal sutures in 2 stages at intervals of 4 and 7 weeks. These patients had survived to 6 years and 3 months of age because of a milder form of hydrocephalus. In both patients, the authors described improvement in symptoms such as headaches and agitation; however, the trilobar cranial deformity was not corrected in either patient.

In 1975 Muller and Hoffman35 described the use of a 2-stage craniectomy in a 4-month-old child to correct a cranial deformity. A preoperative lumboperitoneal shunt was inserted to achieve decompression of the hydrocephalus. In the first stage, the bony constricting band separating the cephalic and lateral leaves of the skull was removed and cut back to the transverse sinuses. In a second stage 3 weeks later, an occipital craniectomy was performed, resulting in a circumferential bony decompression. The patient was alive and well at 9.5 years of age; however, there was significant intellectual and growth retardation.

Subsequent authors in larger series advocated early subtotal craniectomy with preoperative shunting of hydrocephalus to achieve internal decompression. Hecck et al.16 described early subtotal craniectomy combined with frontoorbital advancement to decrease intracranial pressure, preserve vision, and increase patency of the upper airway. Because of the high mortality rate (3 of 11 patients) following early radical surgery, however, the authors suggested that early total craniofacial mobilization before 3 months of age should be reserved for severe cases in which the natural history of the disease would result in death without immediate intervention.

In their series, Resnick et al.34 described a similar high morbidity with the use of initial radical decompres-
sive craniectomy. In their experience with 4 patients, at least 50% of the cranial vault was removed in early infancy to relieve high intracranial pressures. Of these 4 children, however, only 1 child had a neurologically normal outcome. These authors reported better results utilizing a staged approach with anterior and posterior craniectomies and bone morcellation and replacement.

Because of the uniformly poor outcomes achieved with early subtotal craniectomy, staged release of the involved sutures has evolved to become the surgical technique of choice. Lodge et al. described initial excision of the coronal ring of sutures before 6 months of age, followed by staged combinations of frontoorbital advancement and lambdoid craniectomies in a series of 10 patients. Staged surgery allows calvarial remodeling, expansion of the brain, and orbital decompression between surgeries. Crouzon syndrome (6 patients) followed by Pfeiffer syndrome (4 patients) was diagnosed in the majority of patients in their series. Nine of the 10 patients in the study required ventriculoperitoneal shunting for the treatment of hydrocephalus following initial calvarial decompressive procedures. These authors also emphasized the importance of managing the airway due to midfacial retrusion restricting patency of the upper airway.

Gosain et al. reported a similar approach in a 2-month-old patient, with the initial decompressive craniectomy involving both coronal sutures and the right lambdoid suture to release the constricting calvarial ring, followed by subsequent frontoorbital advancement and cranial vault remodeling at 8 months and 2 years of age to correct the anterior cranial deformity, respectively. The patient eventually required a ventriculoperitoneal shunt at 9 months of age for decompression of the hydrocephalus. The authors noted the presence of progressive turricephaly after the initial decompressive craniectomy and early frontoorbital advancement due to continued growth of the brain in the presence of a shortened anterior cranial fossa, but they asserted that there was no solution for the problem at that time.

Jarrah et al. analyzed a series of 14 patients who had staged correction with a ventriculoperitoneal shunt in early infancy, frontoorbital advancement between 3 and 6 months of age, and posterior vault expansion at 1 year of age. They, like other authors, concluded that patients who underwent early cranial vault remodeling experienced more complications such as pneumonia, meningitis, bleeding, and seizures and required longer stays in the intensive care unit. Patients who underwent early cranial vault remodeling also had delays in intellectual development and performed worse on preschool tests. In contrast, in the group that underwent staged surgical correction, 85% of the patients had normal IQ scores at 4 years of age. Based on their experience, the authors advocate staged correction with initial placement of a ventriculoperitoneal shunt in the neonatal period, followed by frontoorbital advancement between 3 and 6 months of age and posterior vault remodeling at around 1 year of age. Frontoorbital advancement both corrects the trilobar head shape and reduces the development of turricephaly while providing intracranial space for the growing brain, whereas posterior vault remodeling corrects the occipital flattening, reduces turricephaly, and provides additional space for the brain in the posterior cranial vault. Good aesthetic results were achieved using their technique, with the restoration of a normal cranial shape. A substantial number of these patients did subsequently require monobloc or midfacial advancement in later childhood; however, this result concurs with findings in other patients with craniosynostosis and is not unusual.

### Illustrative Cases

#### Case 1: Kleeblattschädel Anomaly With Syndromic Craniosynostosis

**History and Examination.** This 1-month-old boy with Apert syndrome presented with bitemporal and frontal bossing resulting in a trilobed skull. He also had a palpable bicornal ridge and profound exorbitism. Closed bilateral coronal and right lambdoid sutures were noted on CT.

**Operation.** The child subsequently underwent craniectomy of the stenotic coronal sutures bilaterally and the right lambdoid suture at 2 months of age, releasing the point of fusion of the cephalically displaced sphenoid ridge with the bicornal synostosis. Multiple bone spicules extending from the region of the bicornal synostosis pushed the dura mater inward to cause impressions on the underlying brain (Fig. 3).

**Postoperative Course.** Following the craniectomy, there was gradual resolution of the bitemporal bossing. A repeat CT scan 3 months after the craniectomy demonstrated release of the fusion between the sphenoid ridge and the stenotic coronal sutures. Releasing these constricting elements led to a more rounded contour of the superior...
portion of the skull. Four months after craniectomy, the trilobed skull began to show correction in shape, with persistent deformity observed in the forehead contour.

At the age of 8 months, the patient underwent frontoorbital advancement and cranial vault remodeling to correct the anterior cranial deformity. Follow-up examination 1 month postoperatively demonstrated resolution of the trilobed skull configuration. A ventriculoperitoneal shunt was placed for the postoperative worsening of hydrocephalus.

By 2 years of age, however, the patient’s calvarial growth demonstrated progressive turriccephaly with exorbitism. Therefore, repeat frontoorbital advancement and cranial vault remodeling were performed. Although correction of the frontofacial deformity remained good, with improvement in exorbitism 16 months after surgery (age 40 months), the patient demonstrated gradual progression of anterior turriccephaly characteristic of patients with Apert syndrome (Fig. 4).

**Case 2: Kleeblattschädel Anomaly Without Syndromic Craniosynostosis**

**History and Examination.** This 1-year-old boy with a trilobed skull and prominent frontal bossing was referred for evaluation because of an abnormal head shape, a developmental delay, and multiple medical problems. The child was the second born to a gravida 2 para 2 healthy mother and was delivered via Cesarean section at 38 weeks gestation due to polyhydramnios. He had medical comorbidities including pulmonary artery stenosis, hypertension, hepatomegaly, chylothorax, and mitral valve regurgitation. He had undergone Nissen fundoplication for gastroesophageal reflux disease and suffered cardiopulmonary arrest at 8 months of age. On examination, he had an occipitofrontal circumference of 41 cm (< 3rd percentile) with brachyturriccephaly and prominent scalp veins. Additionally, bilateral exophthalmos, a bifid uvula, and diffuse hypotonia were noted. Three-dimensional CT revealed the absence of bilateral coronal sutures and the right lambdoid suture (Fig. 5).

**Operation and Postoperative Course.** The patient underwent bifrontal cranioplasty with bilateral coronal synostectomy and flattening of the parietal bones superiorly (Fig. 6). This procedure led to significant aesthetic improvement, although the patient remained seriously debilitated from his multiple medical comorbidities.

**Conclusions**

Advances in surgical technique, anesthesia, and intensive care management have rendered a previously untreatable craniofacial condition, the cloverleaf skull syndrome, treatable, with the potential for decent neurological and aesthetic outcomes. Historically, surgical treatment involved simple decompression in the form of craniotomy or craniectomy or early radical subtotal calvariectomy, with uniformly poor results. Treatment has evolved over the past 5 decades toward the performance of staged surgeries, with much better outcomes. An initial ventriculoperitoneal shunt or simple craniectomy of the coronal sutures allows decompression of the hydrocephalus or release of the constriction ring around the skull, respectively. These temporizing measures allow the delay
of definitive surgical intervention until the child is older and better able to tolerate the stresses of surgery and anesthesia.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Manjila. Acquisition of data: Manjila, Chim, Eisele. Analysis and interpretation of data: all authors. Drafting the article: Manjila, Eisele, Chowdhry. Critically revising the article: Cohen, Chim, Chowdhry, Gosain. Reviewed final version of the manuscript and approved it for submission: Cohen. Administrative/technical/material support: all authors. Study supervision: Cohen, Gosain.

Acknowledgments

The authors acknowledge Ms. Marianne Gruner, who typed the original manuscript of the Kleeblattschädel deformation in 1960 for Dr. Weidemann; Dr. Peter Thomas, retired attending physician in Krefeld; and Prof. Jens Möller, current chief pediatrician in Saarbrücken.

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Fig. 6. Case 2. A: Intraoperative photograph revealing bony abnormalities in cloverleaf skull deformity. B: Photograph of excised frontal and temporal bone demonstrating irregularities of the inner table and changes in the cranial sutures. C: Intraoperative photograph taken following bony remodeling and replacement of skull bones.


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