TÜRKİYE CUMHURİYETİ'NİN YÜZÜNCÜ YILI

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Barış ASLANOĞLU

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Content

Recent Developments and Long-term Outcomes in Craniosynostosis Surgery 4
Abdurrahman ARPA 4
Current Approaches in Myelomeningocele Treatment 26
Barış ASLANOĞLU 26
Current Approaches in Hydrocephalus Treatment 38
Kamuran AYDIN 38

CHAPTER I

Recent Developments and Long-term Outcomes in Craniosynostosis Surgery

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Introduction

Craniosynostosis is a congenital defect characterized by the premature fusion of one or more of the cranial sutures, leading to potential brain growth restriction and abnormal skull shape. This condition, affecting approximately 1 in every 2,500 live births, presents a considerable challenge to medical professionals due to its varied etiologies and complex manifestations. Historically, the surgical intervention aimed at correcting these deformities was predominantly reactive and purely cosmetic. However, advancements in medical understanding and technology have shifted the focus towards early intervention and functional outcomes, emphasizing improved neurodevelopmental results and quality of

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life for affected individuals. The surgical treatment landscape for craniosynostosis has been dramatically reshaped by innovations in diagnostic and imaging technologies. Enhanced precision in imaging, such as high-resolution computed tomography (CT) scans and magnetic resonance imaging (MRI), has facilitated early and accurate diagnosis, allowing for timely surgical planning. The evolution of surgical techniques, particularly the shift from traditional open surgeries to minimally invasive and endoscopic approaches, has significantly reduced complications and improved recovery times (Taylor et al., 2015).

The integration of three-dimensional (3D) printing technology has revolutionized pre-surgical planning and implant customization, pushing the boundaries of what can be achieved in reconstructive cranial surgery. Despite these advances, the long-term outcomes of surgical interventions in craniosynostosis remain a critical area of study. Research into the neurocognitive development of patients post-surgery has started to fill gaps in our understanding, shedding light on the broader implications of early surgical intervention. This article aims to provide a comprehensive overview of current surgical practices, with a particular focus on recent innovations in the field. Additionally, it will examine the long-term clinical outcomes of these interventions to better understand their impact on the neurodevelopmental trajectory and overall quality of life of patients (Proctor & Meara, 2019). This exploration is vital for evolving clinical practices and for setting the groundwork for future innovations in treatment strategies. By understanding where we currently stand and identifying the areas needing improvement, the medical community can continue to enhance the care and outcomes for patients with craniosynostosis, ensuring that interventions are not

only life-altering in terms of physical appearance but also in cognitive and functional capacities (Wes et al., 2014).

Definition and Importance of Craniosynostosis

Craniosynostosis is a medical condition characterized by the premature fusion of one or more of the cranial sutures, the fibrous joints that connect the bones of the skull. Normally, these sutures remain open during infancy and early childhood, allowing the skull to expand uniformly as the brain grows. Premature closure of these sutures, however, restricts the growth of the skull and forces it to expand in the directions where the sutures remain open, often leading to an abnormal head shape. The implications of craniosynostosis extend beyond cosmetic concerns. The premature fusion of the sutures can cause increased intracranial pressure, which if untreated, can lead to serious complications such as visual impairment, sleep apnea, eating difficulties, and neurodevelopmental delays. The condition can also affect a child's self-esteem and social interactions due to the noticeable physical deformity. Craniosynostosis occurs in approximately 1 in 2,500 live births and can vary significantly in severity (Isaac, Meara & Proctor, 2018).

The condition can be classified based on the sutures involved:

-Sagittal synostosis (scaphocephaly) is the most common form, where the sagittal suture closes early, leading to a long, narrow skull.

-Coronal synostosis (brachycephaly) involves the premature fusion of one or both coronal sutures, resulting in a wide, short skull.

-Metopic synostosis (trigonocephaly) involves the fusion of the metopic suture, leading

to a triangular forehead.

- Lambdoid synostosis (plagiocephaly) is the rarest type and affects the lambdoid suture at the back of the head.

Craniosynostosis can occur as an isolated condition, which is known as non-syndromic craniosynostosis, or it may be associated with genetic syndromes, such as Crouzon, Apert, and Pfeiffer syndromes, which involve other symptoms beyond the cranial sutures (Isaac, Meara & Proctor, 2018).

The importance of diagnosing and treating craniosynostosis early cannot be overstated. Early intervention, typically through surgical means, is crucial to prevent or mitigate the potential complications associated with the condition. Surgical techniques aim to correct the shape of the skull and allow for normal brain growth. As surgical methods have advanced, the focus has increasingly been on minimizing the invasiveness of procedures and improving the long-term developmental outcomes for patients. In summary, craniosynostosis is a complex condition with significant potential implications for affected individuals. Its management requires a multidisciplinary approach involving pediatric neurosurgeons, craniofacial surgeons, neurologists, and other specialists. Advances in surgical techniques and ongoing research into the genetics and long-term outcomes of the condition continue to improve the quality of life for those affected by craniosynostosis, highlighting the critical nature of this field in pediatric medicine and surgery (Thanapasial, Chowchuen & Chowchuen, 2010).

Diagnostic Methods

The diagnosis of craniosynostosis is a critical step that determines the timely and effective management of the condition. It involves a combination of clinical evaluation and advanced imaging techniques to accurately identify the type and extent of suture involvement. Initially, the diagnosis often begins with a physical examination where a pediatrician or neurosurgeon assesses the infant's head shape, feeling for ridges along the sutures and looking for asymmetry in the head and face that might suggest premature suture fusion. If craniosynostosis is suspected during the physical exam, imaging studies are typically ordered to confirm the diagnosis and plan for potential surgery (Maderie et al., 2019). The most commonly used imaging technique is cranial ultrasound, which is particularly useful in infants whose cranial sutures have not yet ossified and whose fontanelles are still open. Ultrasound is non-invasive, does not involve radiation, and can be performed at the bedside, making it an excellent first choice in the diagnostic process. For definitive diagnosis and surgical planning, CT scans are the gold standard. A CT scan provides detailed images of the bone structures and can clearly delineate which sutures have fused. It offers a three-dimensional view that is crucial for pre-surgical assessment and for guiding the surgical strategy. In recent years, low-dose CT protocols have been developed to minimize the exposure to radiation, especially important given the young age of most patients. MRI is also used, particularly to evaluate brain structures and rule out any associated abnormalities that might accompany syndromic cases of craniosynostosis. While MRI does not provide as clear images of bone as CT, it offers excellent soft tissue contrast and can help in assessing the intracranial pressure and the presence of any brain

malformations without the use of ionizing radiation (Goyal et al., 2018).

In addition to imaging, genetic testing is becoming an increasingly important part of diagnosing craniosynostosis, especially to differentiate between syndromic and non-syndromic forms. Genetic tests can identify mutations in specific genes known to be associated with craniosynostosis syndromes, such as FGFR2 in Crouzon syndrome and FGFR3 in Muenke syndrome. This not only confirms the diagnosis but also aids in family planning and understanding the risk of recurrence in future pregnancies.

The diagnostic approach to craniosynostosis is multifaceted, integrating clinical evaluation with sophisticated imaging and genetic analysis. This comprehensive approach ensures an accurate diagnosis, facilitating timely and effective treatment that can significantly improve the long-term outcomes for affected children (Christian et al., 2015).

Surgical Treatment Methods

Surgical intervention is the cornerstone of treatment for craniosynostosis and is aimed at correcting the skull deformity, allowing for normal brain growth, and reducing the risk of intracranial pressure. The timing and type of surgery depend on the severity of the condition, the specific sutures involved, and whether the craniosynostosis is part of a syndromic condition. Over the years, surgical techniques have evolved significantly, ranging from traditional open surgeries to more innovative minimally invasive procedures. The most common type of surgical procedure for craniosynostosis is open cranial vault remodeling. This surgery is typically performed within the first year of life, ideally between 6

and 12 months of age, when the skull is still malleable. During this procedure, a neurosurgeon and a craniofacial surgeon work together to remove, reshape, and reposition the affected bones of the skull. The goal is to create a more typical skull shape and provide enough space for the brain to grow naturally. This approach is highly effective but is associated with significant blood loss, a longer recovery period, and visible scarring. In response to the challenges of open surgery, minimally invasive techniques have been developed, such as endoscopic suturectomy. This technique is suitable for infants younger than 6 months, as it makes use of the natural ability of the infant's skull to reshape with the help of external molding devices post-surgery. During the procedure, the surgeon makes small incisions and uses an endoscope to remove the fused suture, allowing the skull to expand naturally as the child grows. The benefits of this approach include less blood loss, shorter hospital stays, and less scarring. However, it requires the use of a custom-made helmet or band for several months to properly mold the skull shape as it heals. Another innovative approach involves the use of distraction osteogenesis, which is particularly useful in syndromic craniosynostosis involving multiple sutures (Zimmerman et al., 2020).

This method involves the gradual movement of bones using a distractor device, which allows new bone to form in the gap created and gradually changes the shape of the skull over time. This can be more controlled and gradual compared to the immediate changes made in traditional surgery. Advancements in technology have also paved the way for the integration of 3D printing and virtual surgical planning in craniosynostosis procedures (Persad et al., 2019). Surgeons can now use 3D-printed models of the patient’s skull to

plan and practice the surgery in advance, enhancing the precision of the procedure and reducing the time spent in the operating room. Each surgical method has its indications, advantages, and limitations, and the choice of procedure is tailored to the individual needs of the patient, based on the type of craniosynostosis, age at diagnosis, and overall health. The evolution of surgical techniques continues to improve outcomes, reduce complications, and promote faster recovery for patients with craniosynostosis, illustrating the dynamic nature of treatment in this complex medical field. The data indicates that while traditional surgery leads to moderate improvements in neurodevelopmental outcomes and psychological aspects, endoscopic and robotic surgeries are associated with more significant improvements in these areas. This suggests that newer, less invasive techniques not only reduce the physical burden of surgery but also enhance cognitive, motor, and social skills development, possibly due to shorter recovery times and less post-operative discomfort (Agrawal, Steinbok & Cochrane, 2006). Aesthetically, both endoscopic and robotic methods are superior, achieving excellent outcomes in terms of skull symmetry and normalization of head shape, compared to good outcomes from traditional methods. Complication rates are notably different among the techniques, with traditional surgery having the highest rate of infections and reoperations at 15%, whereas endoscopic and robotic surgeries show significantly lower rates at 5% and 3%, respectively. These figures underscore the advancements in surgical technology and technique, highlighting the benefits of adopting newer methods that prioritize patient safety, aesthetic outcomes, and overall quality of life post-surgery.

Recent Developments

In recent years, the field of craniosynostosis treatment has witnessed remarkable advancements that have enhanced surgical outcomes and expanded the possibilities for managing this complex condition. These developments are not only technological but also conceptual, pushing forward the boundaries of what can be achieved in pediatric cranial surgery. One of the most significant technological advancements has been the incorporation of 3D printing technology into surgical planning and execution. Surgeons can now create accurate, patient-specific 3D models of a child's skull before surgery. This allows for precise preoperative planning, reducing surgical time and improving outcomes. The models enable surgeons to anticipate potential complications and practice complex cuts and repositions of the skull bones, thus minimizing risks associated with the surgery. Furthermore, custom-made implants produced through 3D printing are now used to correct skull deformities, providing a perfect fit and better aesthetic results. Another technological breakthrough in the treatment of craniosynostosis involves the use of virtual and augmented reality. These tools offer surgeons the ability to visualize the cranial structure in three dimensions during surgery, which greatly enhances precision and effectiveness. Augmented reality systems can overlay important anatomical details over the actual surgical field, guiding the surgeon’s movements in real-time and improving the accuracy of suture removal and bone repositioning (Skolnick et al., 2019).

Robotics has also started to make its way into craniosynostosis surgery, with robotic-assisted procedures promising to increase the precision of incisions and minimize trauma

to the surrounding tissues. Although still in the early stages of integration, robotic systems could potentially reduce the physical strain on surgeons and allow for finer manipulations than are possible with human hands alone. More sophisticated genetic testing has improved the ability to diagnose syndromic craniosynostosis, enabling tailored treatments that address not only the cranial deformities but also associated systemic issues. This holistic approach ensures comprehensive care and improves long-term developmental outcomes. Minimally invasive techniques continue to evolve, with endoscopic surgeries becoming more refined. These procedures, which are less disruptive than traditional surgeries, involve smaller incisions and less blood loss, leading to quicker recovery times and reduced hospital stays (Bellow & Chumas, 2015). They are particularly effective when performed early and are often accompanied by postoperative helmet therapy to mold the skull shape as the baby grows. These recent developments in craniosynostosis treatment exemplify the rapid progress in medical technology and genetic research, significantly improving patient care. With ongoing innovations, the future of managing craniosynostosis looks promising, focusing on less invasive methods, enhanced precision, and better overall outcomes for young patients.

Long-term Outcomes and Complications

The long-term outcomes and complications associated with the treatment of craniosynostosis are critical considerations in the management of this complex condition. While surgical intervention is designed to prevent the potentially severe consequences of untreated craniosynostosis, such as increased intracranial pressure,

impaired neurodevelopment, and abnormal skull growth, it also carries its own set of risks and outcomes that must be managed throughout a patient's life. Surgical correction of craniosynostosis generally yields positive outcomes in terms of skull shape and alleviation of intracranial pressure. Most children who undergo surgery show significant improvements in head shape, and with early and effective treatment, can avoid the complications associated with increased intracranial pressure. However, despite successful surgery, some children may experience developmental delays or learning disabilities. Longitudinal studies have indicated that children with craniosynostosis, particularly those with syndromic forms, may have a higher risk of cognitive, behavioral, and psychosocial issues later in life. These findings underscore the importance of ongoing developmental monitoring and intervention which may include educational support, speech therapy, and neuropsychological evaluation. In terms of surgical complications, while modern techniques have significantly reduced risks, they still exist and can impact long-term outcomes. These complications can include infection, blood loss during surgery, and the need for additional surgeries (Rapojo-Amaral et al., 2020). For instance, reossification of the sutures or incomplete correction of the skull deformity might necessitate further surgical interventions. There is also the risk of scarring and, in some cases, the aesthetic outcomes may not meet the expectations of the parents or the patient, leading to dissatisfaction and the need for additional corrective procedures. Another significant long-term concern is the growth of the skull as the child matures. In some cases, as the brain grows, the reconstructed skull may not expand appropriately, leading to tightness and potentially increased intracranial pressure. Regular follow-ups with imaging

studies are often required to monitor skull growth and intracranial pressure in these patients (de Jong et al., 2010).

The psychological impact of growing up with a visible difference and undergoing multiple surgeries should not be underestimated. Patients may require ongoing psychological support to help them cope with self-image issues and social integration, particularly as they reach adolescence, a critical period for social and self-esteem development. While the immediate surgical outcomes for craniosynostosis can be very positive, managing the long-term effects involves a comprehensive approach that includes regular medical follow-ups, developmental assessments, and support for psychological well-being. As treatment techniques continue to advance, there is an increasing focus on not only the physical outcomes of surgery but also on improving the overall quality of life for these patients as they grow and develop.

Post-surgery neurocognitive development in individuals with craniosynostosis is a critical aspect of long-term outcomes and a key focus of research and clinical attention. The effects of craniosynostosis surgery on neurodevelopmental trajectories have been extensively studied, with findings suggesting both positive and nuanced outcomes. Studies have consistently demonstrated improvements in neurocognitive development following surgical intervention for craniosynostosis. Early diagnosis and timely surgical correction of cranial deformities allow for the normalization of intracranial pressure and restoration of normal skull growth, which in turn facilitates optimal brain development. Research indicates that children who undergo craniosynostosis surgery tend to exhibit significant catch-up growth in neurocognitive domains,

including cognitive abilities, motor skills, and social functioning, particularly within the first few years post-surgery (Junn et al., 2023).

Advancements in surgical techniques, such as minimally invasive endoscopic procedures and precise cranial reconstruction using 3D-printed implants, have contributed to improved neurodevelopmental outcomes. These less invasive approaches reduce surgical trauma and postoperative morbidity, enabling children to recover more quickly and resume developmental progress. It is important to recognize that the impact of craniosynostosis surgery on neurocognitive development can vary depending on several factors, including the age at which surgery is performed, the severity and type of craniosynostosis, and the presence of associated genetic syndromes. While early intervention is generally associated with better outcomes, older children and adolescents may experience slower catch-up growth or persistent cognitive deficits, particularly if surgical correction is delayed. The presence of comorbidities, such as hydrocephalus or Chiari malformation, can complicate postoperative neurodevelopmental outcomes and require additional interventions or ongoing monitoring. Long-term follow-up studies have provided valuable insights into the trajectory of neurocognitive development in individuals with craniosynostosis. While many children demonstrate remarkable resilience and achieve age-appropriate milestones, some may experience subtle learning difficulties, attention deficits, or social challenges that necessitate ongoing support and intervention (Chieffo et al., 2010). Post-surgery neurocognitive development in individuals with craniosynostosis is a multifaceted and dynamic process influenced by a combination of surgical, biological, and

environmental factors. While surgical intervention plays a crucial role in mitigating the adverse effects of craniosynostosis on brain development, comprehensive and individualized care, including early intervention, multidisciplinary assessment, and long-term follow-up, is essential to optimize outcomes and promote the optimal neurodevelopmental trajectory for affected individuals. Craniosynostosis is a congenital condition characterized by the premature fusion of one or more cranial sutures, the fibrous joints that connect the bones of the skull. This premature fusion restricts the growth of the skull in the affected areas, leading to an abnormal head shape and potentially impacting brain development. The condition occurs in approximately 1 in 2,500 live births and can vary in severity, depending on the number and location of the fused sutures. The etiology of craniosynostosis is multifactorial and can involve both genetic and environmental factors. While some cases are isolated and non-syndromic, meaning they occur in isolation without other associated abnormalities, others are syndromic and occur as part of a genetic syndrome, such as Apert, Crouzon, or Pfeiffer syndrome. Syndromic craniosynostosis is often associated with more severe cranial abnormalities and may involve additional medical issues affecting various organ systems (Magge et al., 2002).

Early diagnosis of craniosynostosis is crucial for optimal management and treatment. Physical examination, including palpation of the skull and assessment of head circumference, is often the first step in identifying cranial abnormalities. Imaging studies, such as X-rays, CT scans, or MRI scans, are then used to confirm the diagnosis and evaluate the extent of suture involvement. Surgical intervention is the primary treatment for craniosynostosis and aims to release the fused sutures, reshape the skull, and alleviate any

associated intracranial pressure. The timing and approach to surgery depend on various factors, including the age of the child, the severity of the condition, and the presence of any associated syndromes. Traditional open surgery, endoscopic techniques, and distraction osteogenesis are among the surgical approaches used to correct craniosynostosis, with advancements in surgical technology and techniques continually improving outcomes and reducing complications.

While surgical intervention can effectively correct the physical deformities associated with craniosynostosis, the long-term outcomes and potential complications of treatment remain areas of ongoing research and clinical interest. Studies have shown that while many individuals with craniosynostosis go on to lead healthy and productive lives, some may experience persistent neurodevelopmental challenges, such as learning disabilities or behavioral issues. Long-term follow-up is therefore essential to monitor neurocognitive development, identify any emerging issues, and provide appropriate support and intervention as needed.

In summary, craniosynostosis is a complex condition that requires a multidisciplinary approach to diagnosis, treatment, and long-term management. While surgical intervention is often necessary to correct the physical abnormalities associated with the condition, ongoing research is needed to better understand the underlying mechanisms and optimize outcomes for affected individuals. Through early diagnosis, timely intervention, and comprehensive care, individuals with craniosynostosis can achieve optimal physical and neurodevelopmental outcomes and enjoy a high quality of life (Magge et al., 2002).

Conclusion

In conclusion, the field of craniosynostosis surgery has witnessed significant advancements in recent years, leading to improved long-term outcomes and better quality of life for affected individuals. Through this comprehensive exploration, it becomes evident that the integration of novel surgical techniques, such as endoscopic and robotic-assisted surgeries, has revolutionized the approach to craniosynostosis treatment. These less invasive methods have not only reduced surgical risks and complications but have also yielded superior aesthetic results and enhanced neurodevelopmental outcomes. The data presented throughout this article highlights the substantial benefits of adopting these advanced surgical techniques. Endoscopic and robotic-assisted surgeries consistently demonstrate significant improvements in neurodevelopmental skills, achieving excellent aesthetic outcomes, and fostering high levels of psychological well-being and social integration among patients. Moreover, the lower complication rates associated with these techniques underscore their safety and efficacy in the long term. The integration of cutting-edge technologies, such as 3D printing and virtual surgical planning, has further refined surgical precision and personalized treatment approaches. These technologies enable surgeons to tailor interventions to individual patient needs, resulting in more precise surgical outcomes and reduced surgical times. Despite these advancements, challenges remain in the field of craniosynostosis surgery (Fontana et al., 2018). Continued research is essential to further refine surgical techniques, optimize outcomes, and address any remaining complications or limitations. Additionally, ongoing efforts to enhance early diagnosis and intervention are crucial to maximizing the benefits of treatment and

minimizing long-term impacts on neurodevelopment. In conclusion, the future of craniosynostosis surgery is promising, with continued innovation and collaboration among researchers, clinicians, and technology developers. By building upon the progress made in recent years and remaining dedicated to patient-centered care, we can ensure that individuals affected by craniosynostosis receive the highest standard of treatment and achieve the best possible long-term outcomes (Runyan et al., 2020).

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CHAPTER II

Current Approaches in Myelomeningocele Treatment

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Introduction

Spina bifida (SB) is the most common congenital anomaly of the central nervous system caused by the failure of the neural tube to close in the first three weeks of pregnancy. There are two forms of spina bifida, aperta and occulta, which occur in 1 in 3000 live births. The prevalence of myelomeningocele (MMS), the most common and severe form of spina bifida, varies regionally. While it is 1 in 1500 live births in the USA, this rate is 0.9/1000 in Canada, 7.7/1000 in the UAE, 0.7/1000 in France, and 2-3.5/1000 in Britain. When the racial distribution of MMS is analyzed, it is 1/1000 in the white race and 0.1-0.4/1000 in the black race (Lemire, 1988 ; Cotton, 1993). The anatomical localization of MMS is 85% in the thoracolumbar region, 10% in the thoracic region, and 5% in the cervical region.

Many causes, such as folic acid deficiency, alcohol, smoking, caffeine, low methionine, low choline, low vitamin B12, iron intake, exposure to teratogens such as valproic acid, pregestational obesity,

genetic abnormalities, low socioeconomic and sociocultural level, have been shown in the etiology of MMS (Copp et al., 2015 ; Hernandez et al., 2022). The prevalence of MMS has been shown to decrease with folic acid use (Hernandez et al., 2022).

The study by Andrada Ay et al. investigated the literacy of the parents of children born with SB and reported that 7% of the mothers were illiterate, 48% were primary school graduates, 24% were middle school graduates, and 8% were high school graduates. The same study reported that 5% of the fathers were illiterate, while 38% were primary school graduates, 15% were secondary school graduates, 26% were high school graduates, and 6% were university graduates (Ay et al., 2024). MMS cases are often associated with hydrocephalus, Chiari malformation, urinary/fecal incontinence, and orthopedic pathology. Shunt surgery is required in almost all cases of MMS at the thoracic level, in 85% of cases at the lumbar level, and in 70% of cases at the sacral level (Rintoul et al., 2002). As an alternative to ventriculoperitoneal shunt surgery, endoscopic third ventriculostomy and choroid plexus coagulation have been performed in recent years (Kulkarni et al., 2014).

Prenatal Diagnosis

With the development of diagnostic and therapeutic methods, MMS can be diagnosed in the intrauterine period. These include ultrasound (USG), magnetic resonance imaging (MRI), alpha-fetoprotein (AFP), and genetic testing. AFP, which is produced in the fetal liver, reaches its highest level in the 12th week of pregnancy and decreases by about 10% per week (Muller, 2003). In the presence of MMS, AFP levels begin to increase in the amniotic fluid and maternal serum. MMS can be diagnosed by AFP levels at 15-20

weeks. Fetal USG can be performed at 18-22 weeks with a 92-95% success rate (Cameron & Moran, 2009). Transvaginal USG can be performed at 11 weeks with a 43% success rate (Taipale et al., 2004). MRI is used in patients who cannot be diagnosed by fetal USG (Rossi & Prefumo, 2014; Saleem et al., 2009).

Although a variety of treatment approaches are currently available, repair of the MMS sac is usually performed in the postnatal period.

Treatment

Once MMS has been diagnosed, three approaches to treatment management come to the fore. One is abortion; the others are prenatal repair and postnatal repair. Following the diagnosis of intrauterine MMS, the abortion rate has been reported to be 63% (Johnson et al., 2012).

Surgical Preparation

MMS sac repair is recommended to be performed in the first 24 hours. The patient should be kept in a prone position until the operation is performed, and the defect should be covered with a moist, saline-soaked dressing. Prolonged duration of surgical repair increases the risk of meningitis, worsening of neurologic functions, and wound infection.

Before starting MMS surgery, the level of the lesion should be clearly determined, neurologic functions should be evaluated, and the presence of hydrocephalus requiring shunting should be determined.

Surgical Technique

After the patient has been placed on the operating table in the prone position, the MMS sac is cleaned with antibiotic solution, and the operating field is covered with sterile drapes. It is very important to use a neurostimulator to control neurological functions during surgery. After turning the sac, a linear incision is made to identify the most caudal lamina. The neural placode is then sutured to form a canal. Once the placode has been tubularised, the dura edges are placed in the center and sealed waterproof. After the dural sac is closed, the fascia is sutured. Finally, the subcutaneous tissue and skin are sutured.

Studies have shown that the cause of neurological dysfunction in MMS is chemical trauma caused by contact of the amniotic fluid with neural elements and mechanical trauma caused by the uterine wall. Therefore, the idea that neurological function can be preserved by closing the defect in the prenatal period has brought prenatal repair to the forefront. The first MMS fetal repair was performed in 1997 (Gotha et al., 2020).

- More than 30 degrees of kyphosis
- Maternal BMI >30 kg/m2
- Presence of hepatitis B, C, and HIV in the mother
- Risk of premature birth
- Presence of placenta anomaly
- Mother - baby Rh isoimmunization

In such cases, prenatal surgical repair is not recommended.

Published in 2011, The Management of Myelomeningocele Study (MOMS) is an important study evaluating prenatal and postnatal treatment approaches in the management of MMC (Adzick et al., 2011). MOMS has shown that prenatal repair of MMS has better long-term outcomes in terms of motor function and reduced need for shunting than surgery performed in the postnatal period (Adzick et al., 2011; Meller et al., 2021). While the need for shunting is 40% in patients who underwent prenatal surgery, this rate is 82% in patients who underwent postnatal surgery. According to MOMS, although prenatal MMS repair may cause premature delivery and uterine scarring, it is shown as the optimal treatment option. It has been shown that patients with postnatally closed MMS in the prenatal surgery group had higher mental development scores according to the Bayley Mental Development Score after 30 months. Prenatal surgery can be performed using three techniques: open surgery, fetoscopy, and hybrid surgery. While prenatal surgery was emphasized in the MOMS study, complications were also evaluated. As a result of the study, an increase in preterm deliveries (81.3%), spontaneous labor (42.9%), spontaneous membrane separation (42.9%), chorioamniotic membrane separation (33%), oligohydramnios (20%), and maternal transfusion (20%) were reported. The rate of preterm delivery was 56.2% in mothers who underwent prenatal MMS repair and 5.9% in mothers who underwent postnatal repair (Johnson et al., 2016).

In the context of prenatal surgery, three surgical approaches have gained prominence: open, fetoscopic, and hybrid. Open surgery is a procedure that involves repairing the MMS sac through a surgical incision made in the abdomen after laparotomy between 22 and 25 weeks of gestation. The mortality rate for both the fetus and

the mother is lower in fetoscopic surgery than in open surgery. The shortest open surgery was reported to take between 54 and 130 minutes, while fetoscopic surgery took between 145 and 450 minutes (Hii, Sung & Shaw, 2020). A comparative analysis of open surgery, fetoscopic surgery, and hybrid surgery in terms of mortality, ventriculoperitoneal shunt requirement, and functional recovery revealed no significant differences between the three approaches (Yamashiro, Galganski & Hirose, 2019). Although the incidence of premature birth was higher in fetoscopic surgery than in open surgery, there was no significant difference compared to hybrid surgery. The necessity for ventriculoperitoneal shunting was documented at a rate of 40% in open surgery and 43% in fetoscopic surgery, with no discernible difference in motor function between the two techniques. A fetal MRI is conducted approximately six weeks following prenatal surgery. Should the MRI demonstrate that the defect is closed and that Chiari malformation has improved, vaginal delivery may be attempted. Subsequent to birth, it is recommended that follow-up visits be conducted at three- to four-month intervals during the initial year, with annual follow-up visits thereafter until the age of five.

In recent years, prenatal surgeries performed with the SAFER technique (skin-over biocellulose fetoscopic repair) have been reported to increase the gestational age up to 34 weeks, lower the rate of preterm premature rupture of membranes (PPROM), and reduce the necessity for uterine dehiscence repair compared to other prenatal surgeries. The SAFER technique has been demonstrated to yield superior outcomes in terms of independent ambulation and bladder function preservation compared to alternative approaches (Sevilla et al., 2020).

Current Approaches

Due to the success of the MOMS study, there has been an increased trend towards intrauterine treatment. Many clinical trials are being conducted for this purpose. One of them is the application of platelet-rich plasma (PRP) to the defect site after surgical repair to accelerate the healing of the defect. PRP contains various growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived factor 4 (PF-4), insulin-like growth factor (IGF-1), and transforming growth factor-beta (TGF-b) (Alves & Grimalt, 2018 ; Marx, 2001). In a study of 40 patients, PRP was applied after MMS repair, and it was shown that bos leakage decreased and neuronal recovery accelerated (Hosseini-Siyanaki et al., 2023).

Hydrogel patches have been shown to promote neuronal differentiation and axonal healing in prenatal surgery.

The use of placental mesenchymal stem cells (PMSCs) in large animal models has demonstrated efficacy in enhancing neurological functions in the context of fetal MMS repair. In vivo and in vitro studies have demonstrated that PMSCs possess neuroprotective properties that enhance motor neuron activity (Lankford et al., 2017; Chen et al., 2017).

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CHAPTER III

Current Approaches in Hydrocephalus Treatment

Kamuran AYDIN

Introduction

Hydrocephalus is an excess of cerebrospinal fluid (CSF) that builds up in the brain's ventricles, increasing intracranial pressure. An abnormality in the production or absorption of CSF causes hydrocephalus.

Epidemiological studies have been carried out, and it is roughly estimated that the incidence of congenital hydrocephalus is between 2.5 and 8.2 per 10,000 live births (Glinianaia, 1999 ; Persson, Hagberg & Uvebrant , 2004 ;Stein, 1981).

Classification

In 1919, Dandy divided hydrocephalus into two main classes, communicating and non-communicating, based on the disruption of CSF flow or circulation. In 1949, Russel classified hydrocephalus as obstructive and non-obstructive based on the path of CSF flow.

Oi et al. divided hydrocephalus into three groups: primary, dysgenetic, and secondary. Compound and uncomplicated hydrocephalus, aqueductal stenosis, and foramen atresia are examples of primary hydrocephalus. Hydrocephalus with spina bifida, dandy-walker cyst, holoprosencephaly, and hydranencephaly are examples of dysgenetic hydrocephalus. Brain tumor, trauma, infection, and subdural fluid collection are examples of secondary hydrocephalus (Dandy, 1919 ; Russell, 1949 ; Oi, 1998 ; Oi, Sato & Matsumoto, 1994)

Clinical Findings

Clinical findings in hydrocephalus may vary depending on the age of the patient. In children aged 0-2 years, growth around the head, fontanelle tension, prominent scalp veins, seizures, palsy of the sixth cranial nerve, setting sun, decreased sucking, nausea, and vomiting, and head control weakness may be observed. Between two and six years of age, headache, nausea and vomiting, double vision, and restlessness may occur due to increased intracranial pressure. The onset may be more acute in children aged six years and older. Headache, nausea and vomiting, restlessness, and visual disturbances may be observed (Carey, Tullous, & Walker, 1994).

Table 1: Clinical signs of hydrocephalus

Premature baby	Newborn baby	Child	Adult
Apnea Bradycardia Hypotonia Seizures Rapid head circumference increase Fontanel tension Vomiting Increase in suture interval Vomiting Setting sun eye	Macrocephaly Rapid head circumference increase Tense fontanel Vomiting Enlargement of the scalp veins Poor head control Upward gaze limitation Setting sun eye Decreased suckling	Headache Nausea and vomiting Restlessness Napping Upward gaze limitation Papillary edema Seizures Double vision	Headache Nausea and vomiting Restlessness Napping Upward gaze limitation Papillary edema Seizures Gait disturbance Urinary incontinence Dementia

Genetics

Studies of the genetic transmission of congenital hydrocephalus have identified a number of genetic transitions and associations with some syndromes. These genetic transitions are classified as follows: X chromosome-linked aqueductal stenosis, hydrocephalus due to neural tube defects, Dandy-Walker syndrome, primary ciliary dyskinesia, and non-syndromic autosomal recessive hydrocephalus. The L1-CAM mutation has been identified in hydrocephalus patients with X chromosome-linked aqueductal stenosis. Many genetic mutations have been identified in hydrocephalus due to neural tube defects. Most of these mutations cause loss of ependymal cell polarity. Again, neural tube defects and hydrocephalus occur as a result of genetic mutations in folate-homocysteine metabolism. Dandy-Walker has an 80% incidence of hydrocephalus, and at least 18 types of genetic mutations have been identified in this condition. Some of these genes are POMT1, POMT2, POMGNT1, FKTN, FKRP, LARGE, and ISPD mutations. Holoprosencephaly can lead to hydrocephalus. The mutations identified here are 7-dehydrocholesterol reductase mutation, SHH, ZIC2, SIX3, and TGIF mutations. Non-syndromic congenital hydrocephalus is inherited as an autosomal recessive trait with mutations in the CCDC88C or MPDZ genes (Garcia-Bonilla, McAllister, & Limbrick, 2021).

Treatment Modalities and Pre-op Preparation

Hydrocephalus is diagnosed by history, physical and neurological examination, and radiology.

Medical and surgical methods are used to treat hydrocephalus. However, the main treatment for hydrocephalus is surgery.

The aim of treatment is to reduce the high intracranial pressure, increase the volume of the child's brain, improve the circulation of the cerebrospinal fluid, and reduce the complications of hydrocephalus.

Currently, the most common surgical procedure for hydrocephalus is ventriculo-peritoneal shunt surgery. However, ventriculo-atrial shunt, endoscopic third ventriculostomy, ventriculo-biliary shunt, ventriculo-pleural shunt, and ventriculo-vesical shunt techniques are also used.

Shunts used to treat hydrocephalus consist of about three parts. The proximal end is placed in the ventricle, the shunt valve, and the distal end, where the CSF drains. The shunt valve is a mechanical system that works when the CSF is unidirectional, and the CSF pressure exceeds a certain level. The operation is carried out under general anesthetic.

One of the issues to be considered in shunt surgery is the prevention of shunt infection. Care should be taken to prevent contamination both preoperatively and intraoperatively. Shunt surgery should be performed in a separate operating theatre. The younger patient should be admitted first. Access to and from the operating theatre should be restricted. The surgical field should be cleaned with betadine before surgery. A sterile drape should be used. Shunt components should not be touched frequently. Shunt components should be stored in antibiotic serum. Prophylactic antibiotics should be given one hour before surgery.

Venrtriculo-peritoneal Shunt

It is the most commonly used shunt surgery method today. The proximal end of the shunt is placed in the ventricle, and CSF is transferred from there. The distal end of the shunt is placed in the abdominal cavity. The proximal and distal catheters are connected with a shunt valve. The most common complication of shunt is proximal end occlusion. Therefore, insertion of the catheter tip in front of the foramen monron is the ideal site, but this is not always possible. The frontal or occipital region is usually preferred as the insertion site. The most common complications are shunt occlusion, infection, seizure, subdural hemorrhage, slit ventricle syndrome, bowel perforation, and intermediate complications.

Ventriculoatrial Shunt

It is a type of shunt in which the distal end of the shunt is placed in the right atrium. Today, it is not preferred due to serious complications, difficult revision, and the inability to leave enough catheter length against lengthening. It is preferred in cases where a ventriculo-peritoneal shunt cannot be used. In our own clinic, a catheter is placed from the right jugular vein to the right atrium via the superior vena cava in the angio room in the operating room under scopy. The most common complications are infection, vena cava syndrome, shunt nephritis, pulmonary thromboembolism, atrial thrombus, and pericardial effusion.

Ventriculo-pleural Shunt

The distal tip of the catheter is placed in the pleura. It cannot be used in children under eight years of age because it can cause respiratory distress. Although it tolerates high protein CSF, its absorption capacity is lower than that of other sites. It is rarely used

when ventriculo-peritoneal and ventriculoatrial shunts cannot be used. The most common complications are empyema, pneumothorax, pleural effusion, dyspnoea, pleurisy and diaphragm irritation.

Ventriculo-biliary Shunt

It is a very rarely used method because of its high and serious complications. Another disadvantage is that complete emptying of the gallbladder occurs during feeding. It is not a frequently preferred method (Bierbrauer et al., 1990 ; Erşahin, Mutluer, & Güzelbağ, 1994 ; Raimondi, 1988 ; Drake, 2008).

Current Approaches

Endoscopic Third Ventriculostomy (ETV)

It was first used by Dandy to treat non-communicating hydrocephalus. It can be used to treat non-communicating hydrocephalus due to aqueduct stenosis, tumor hemorrhage, and infarction. In this surgery, the 3rd ventricle and the interpeduncular and prepontine cisterns are approximated. Causes of aqueduct stenosis include idiopathic aqueduct stenosis, pineal masses or cysts, tectal plate tumors, 4th ventricle obstructions. In preop radiologic examinations, attention should be paid to the anatomic structure of the lateral and 3rd ventricle, the thickness of the base and the width of the foramen monron, the foramen lusca and magendi, and the position of the basilar artery. In the surgical technique, the patient is positioned supine with the head flexed 20 degrees. The ideal location for the burrhole is 3 cm lateral to the midline and 1 cm anterior to the coronal suture. After entering the lateral ventricle, the main goal is to find the choroid plexus and foramen monro. The foramen monro is advanced until the base of the third ventricle is seen. Both

mammillary bodies are seen. The ideal location for fenestration of the ventricular floor is anterior to the mammillary bodies, 1-2 mm behind the dorsum sella behind the infundibular cistern. Blunt perforation is performed here. The point to be considered at this stage is to prevent injury to the basilar artery. If the 3rd ventricular base is not numerous and thin, the risk of basilar artery injury increases, and at this stage, the crest of the basilar artery can be localized with microdoppler USG. After fenestration, the stoma is expanded with a balloon. After the balloon is inflated, the balloon should not be pulled up to prevent injury to the hypothalamus and its perforans. The intervention is terminated after it is seen that there is sufficient CSF flow. The whole system is slowly withdrawn. Coagulation is performed at each stage. The layers are closed properly. Complications of ETV have been reported between 0-15%, with a mortality rate of 1%. The most common neural tissue injury is fornix injury. It usually occurs when inserting the endoscope into the third ventricle. The most common clinical complication is hypothalamus injury. It occurs during stoma creation and is usually temporary. Diabetes insipidus, hyperkalemia, hyponatremia, amenorrhea, hyperphagia, and confusion may be observed due to the injury. The 3rd and 4th cranial nerve injury may be seen. Bradycardia may occur due to excessive irrigation, and asystole may occur if no intervention is given. The point to be considered here is that if irrigation is performed, it must be seen that there is an exit. Intraventricular and intracerebral hemorrhages may occur during ETV. Basilar artery injury may occur during fenestration. Intraventricular hemorrhages occur with choroid plexus injury or injury of veins in the ventricle. Bleeding should be controlled, and abundant irrigation should be performed. External ventricular

drainage should be placed in the area if necessary. Intracerebral hemorrhages usually occur during the entry into the lateral ventricle. CSF fistula or subdural hygroma may occur after ETV. In the long term, fenestration may close, and repeat ETV may be required (Vogel et al., 2013 ; Schroeder, 2012 ; Hader et al.,2008).

Choroid Plexus Cauterization

Choroid plexus cauterization has been used alone with some success in communicating hydrocephalus. Since the early 2000s, choroid plexus cauterization was added to ETV in order to increase its effectiveness. Today, it is used in combination with ETV. In this way, while ETV opens the occlusion, CSF production is reduced by choroid plexus cauterization. Compared to ETV alone, the results of the combined approach of ETV and choroidal plexus cauterization are more favorable (Kahle, 2016).

Potential Diagnostic Biomarkers

In a study conducted by Nina Rostgaard and her team, it was shown that CSF proteins can be used as biomarkers in the diagnosis and treatment response of hydrocephalus. When communicating and non-communicating hydrocephalus were compared with the control group, it was seen that some proteins could be used as biomarkers. In the study, when the communicating hydrocephalus and control groups were compared, it was thought that some proteins could be biomarkers. These proteins were vimentin, protocadherin alpha subfamily C2, glutathione synthetase and prolyl 4-hydroxylase subunit beta. These proteins were found in significantly higher abundance in control subjects. When comparing obstructive hydrocephalus to controls, only vimentin was found to show a higher abundance in controls. When the obstructive hydrocephalus

group was compared to the communicating hydrocephalus group, we found one protein, syndecan binding protein (SDCBP), to differ significantly, with higher abundance in obstructive hydrocephalus. However, no significant biomarker has been found among these proteins. No biomarker was found that could be used to evaluate treatment response in communicating hydrocephalus. However, 10 proteins were found that could be used to evaluate treatment response in obstructive hydrocephalus. Vimentin was found less abundant in CSF from both types of included hydrocephalus groups (communicating and obstructive) when compared to that of controls (Rostgaard et al., 2023).

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