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Investigation of the Effect of Cranial Vault Surgery On Parenchymal Perfusion Before and After Surgery in Craniosynostosis Patients

Kraniyosinostoz Hastalarinda Kubbe Cerrahisinin, Cerrahi Öncesi ve Sonrası Parankimal Perfüzyon Üzerine Etkisinin İncelenmesi

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ABSTRACT

Objective: In our study, it is aimed to examine the effect of surgery on brain perfusion with ASL sequence perfusion MRI taken before surgery and 12 weeks after surgery in cases of non-syndromic craniosynostosis treated in our clinic.

Material and Methods: The study was conducted between 28.12.2021-16.09.2022 with 10 patients who were evaluated preoperatively and treated surgically at the Neurosurgery Clinic of Ankara City Hospital. Perfusion MRI was performed preoperatively and 12 weeks postoperatively. The preoperative and postoperative images obtained were evaluated comparatively at the workstation.

Results: After the exclusion of patients who did not appropriate the study criteria, the results of 9 patients were examined. MRI scans were taken preoperatively and 87 days as average postoperatively. After surgery, there is perfusion enhancement in 7 patients and a perfusion impairment in 2 patients. Regarding the average perfusion rates, the results were found to be statistically significant in four of the seven patients in whom an increase was detected ($p \leq 0.050$), while the results were found to be statistically significant in one of the patients in whom a decrease was observed ($p \leq 0.050$).

Conclusion: Surgical treatment is effective on brain perfusion in patients with non-syndromic craniosynostosis. Perfusion alteration may be different according to surgical technique, patient age at the time of surgery, and type of craniosynostosis. In addition to cosmetic improvement, surgical treatment can also be effective in changing neurological functions. ASL sequence perfusion MRI, which doesn't require contrast and is non-invasive, is a successful method of demonstrating the quantitative effectiveness of surgery in patients with craniosynostosis.

Key Words: Cerebral Blood Flow, Craniosynostosis, Magnetic Resonance, Nonsyndromic, Perfusion Imaging

ÖZ

Amaç: Çalışmamızda kliniğimizde tedavi edilen non-sendromik kraniyosinostoz olgularında cerrahi öncesi ve cerrahiden 12 hafta sonra çekilen ASL sekans perfüzyon MRG ile cerrahinin beyin perfüzyonu üzerindeki etkisinin incelenmesi amaçlanmaktadır.

Gereç ve Yöntemler: Çalışma 28.12.2021-16.09.2022 tarihleri arasında Ankara Şehir Hastanesi Beyin ve Sinir Cerrahi kliniğinde cerrahi tedavileri, preoperatif ve postoperatif tetkikleri gerçekleştirilen 10 hasta ile yapıldı. Hastalara preoperatif

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara City Hospital, No. 2 Clinical Research Ethics Committee (E-21-1157/19.01.2021)

Contribution of the Authors / Yazarların katkısı*: *ASLAN ST: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***DEMIRCI H:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/ study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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ve postoperatif 12. haftada Perfüzyon MRG çekimleri yapıldı. Preoperatif ve postoperatif elde edilen görüntüler çalışma istasyonunda karşılaştırmalı değerlendirildi.

Bulgular: Çalışma kriterlerini karşılamayan hastaların çalışma dışında bırakılmasını takiben 9 hastanın sonuçları incelendi. Beş hastaya açık cerrahi rekonstrüksiyon dört hastaya endoskopik cerrahi uygulandı. Preoperatif ve postoperatif ortalama 87 gün sonra MRG çekimleri yapıldı. Cerrahi sonrası 7 hastada perfüzyon artışı ve 2 hastada perfüzyonda azalma oldu. Ortalama perfüzyon hızlarına bakıldığında artış saptanan yedi hastanın dördünde sonuçlar istatistiksel olarak anlamlıyken ($p \leq 0.050$) azalma görülen hastaların birinde sonuçlar istatistiksel olarak anlamlı bulundu ($p \leq 0.050$).

Sonuç: Non-sendromik kraniyosinostoz hastalarında cerrahi tedavi beyin perfüzyonu üzerinde etkilidir. Perfüzyon değişikliği cerrahi teknik, cerrahi sırasında hasta yaşı ve kraniyosinostoz çeşidine göre farklı olabilir. Cerrahi tedavi kozmetik düzelmenin yanında nörolojik fonksiyonların değişikliğinde de etkili olabilir. Kontrast gerektirmeyen ve non-invaziv olan ASL sekans perfüzyon MRG kraniyosinostoz hastalarında cerrahinin kantitatif etkinliğini göstermede başarılı bir yöntemdir.

Anahtar Sözcükler: Kraniyosinostoz, Manyetik Rezonans, Non-sendromik, Perfüzyon Görüntüleme, Serebral Kan Akımı

INTRODUCTION

Craniosynostosis, known as premature closure of the cranial sutures, is the second most prevalent craniofacial developmental disorder. According to the literature, it occurs 1 in every 2000-2500 live birth (1). There are many etiological factors. This suggests that there are multiple parameters for its occurrence (2). The vast majority of cases are sporadic cases with no accompanying medical problems or an identified mutation and genetic factor (3). Craniosynostosis can be classified in many different ways as simple or complex according to the type of occurrence, primary or secondary according to the reason of occurrence, and syndromic or non-syndromic according to its relationship with the syndromes.

It is thought that the morphological changes that occur in the cranium with craniosynostosis may cause functional impairments as well as cosmetic effects (4,5). The recent studies about intracranial pressure and cerebral perfusion changes in the cases of craniosynostosis supports that there may be functional disorders besides head deformities. However, the relationship between brain parenchymal perfusion change following intracranial pressure change and cortical dysfunctions continues to be discussed (6–8).

When we review the recent medical literature, it's shown that the disorders in neurocognitive functions such as speech, cognition, and behavior in cases of craniosynostosis are more frequent than normal population (9,10). It's thought that the intracranial pressure increment, the change of cerebral circulation dynamics, and the structural disorders of tissues embryologically interacted with sutures are effective in neurocognitive dysfunctions; but if we understand what the actual reason is, whether pressure or structural disorganization, will guide us developing existing surgical techniques (1,11–13).

In our study, we try to show the change in cerebral parenchymal perfusion with Arterial Spin Labeling (ASL) perfusion Magnetic Resonance Imaging (MRI) among the cases of non-syndromic craniosynostosis who had operated between December 2021 and July 2022 in our clinic and aged 0-18 months and ASL perfusion MRI images taken preoperatively and 12 weeks postoperatively. And we plan to determine surgical effectivity with the quantitative data.

MATERIALS and METHODS

We informed the patients, who were admitted pediatric neurosurgery outpatient clinic of Ankara Bilkent City Hospital between December 2021 and July 2022 and diagnosed with craniosynostosis, about surgical treatment techniques and all possible complications. The patients, who accepted the surgery, signed the written consent. Ten 0-18 months aged patients were selected then ASL perfusion MR images were taken with 1.5T Ge Signa Explorer MRI machine preoperatively and 12 weeks after surgery.

Compared to other imaging modalities, most MRI sequences need more time to acquire sufficient data to form an image. Motion artifacts are well-known problems of MRI for a long time. For young children, motion prevention with sedation is a successful technique during MRI according to the literature (14). In our study, all patients were sedated for imaging with the standard dose of sedation ketamine 1mg/kg IV and midazolam 0.1mg/kg IV. Sedation is a challenging factor for brain imaging. Two main mechanisms affect cerebral perfusion imaging. The first one is elevating intracranial pressure, and the second is hypotension after the cardiovascular effect. Theoretically, ketamine increases intracranial pressure and cerebral perfusion pressure, and midazolam depresses the cardiac and respiratory systems. According to the literature, the combination of these drugs in adequate doses ensures physiology and makes sedation safer and more effective (15).

Ten patients were included in the study, seven of them were diagnosed with sagittal synostosis, two of them were diagnosed with coronal synostosis, and one of them was diagnosed with metopic synostosis. A total of 20 MRI sessions were performed on each patient before and after surgery. Obtained images processed with GE Advantage Workstation Ready View software. We removed one patient from the study

due to inappropriate imaging techniques and technical issues with the workstation. We applied open cranial vault surgery for 5 patients and endoscopic surgery for 4 patients.

ASL Perfusion MRI

ASL perfusion MRI is an imaging technique that can show parenchymal blood supply quantitatively with the use of water molecules in the blood, which penetrates the brain parenchyma freely, marked with radiofrequency inversion pulses. The main advantages, compared with other imaging techniques that show blood perfusion, are showing regional blood perfusion rate and being a non-invasive imaging method. The main disadvantage of ASL perfusion MRI is low Signal to Noise Ratio (SNR). However, with comparing adults, higher cerebral blood flow and faster flow rate at carotid arteries and higher cerebral water content of pediatric patients are parameters for better SNR physiologically. Because of that ASL imaging is effective and featured for the pediatric population (16,17).

There is no standard for processing ASL perfusion MRI images in literature. In this study, we used brain segmentation that was used frequently previous some other studies and described by Limperopoulos et al.(18) At first, with a plane that passes from Anterior Commissure (AC) and Posterior Commissure (PC) each hemisphere is divided into two segments craniocaudally. After that with 3 coronal planes, each hemisphere is divided into 8 segments named Dorsolateral Prefrontal (DLPF), Premotor (PM), Sensorimotor (SM), Parieto-occipital (PO), Orbitofrontal (OF), Subgenual (SG), Midtemporal (MT), Inferior occipital (IO) (18). OF and IO segments weren't used, because of the measurement artifact due to anatomical neighborhoods (Figure 1).

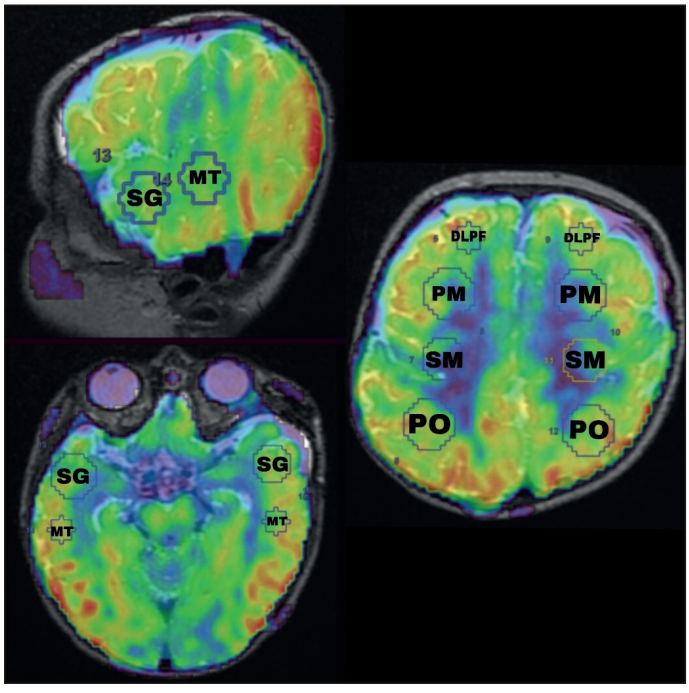

Figure 1: Brain segmentation described by Limperopoulos et al (18).

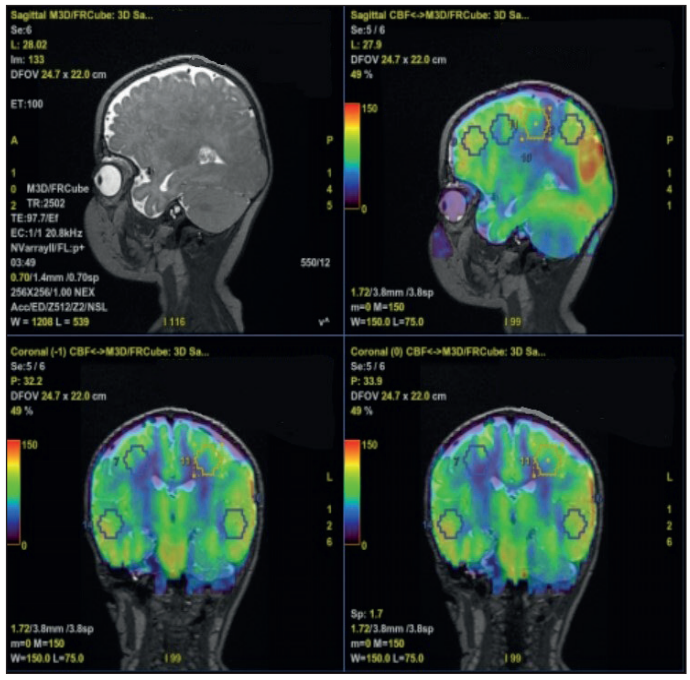

Figure 2: ROI placement at workstation

During the measurement of processed images, we used 3-Dimensional (3D) Region Of İnterest (ROI). We chose the biggest ROI volume for each imaging session after brain segmentation. In this study, the biggest ROI was 3.28 cm^3 and the smallest ROI was 3.96 cm^3. Cerebral Blood Flow (CBF) rate unit was "ml/100gr/min". We placed the ROI's subcortical levels, due to measurement artifacts that extremely high CBF caused by cortical vessels and extremely low CBF caused by ventricles and cisterns. All ROIs were controlled in axial, coronal, and sagittal planes and then confirmed as the proper position for segmentation.

The study was approved by Ankara City Hospital, No. 2 Clinical Research Ethics Committee (E-21-1157/19.01.2021)

Statistics

In this study, the patient's age at MRI session and the time between surgery and postoperative MRI session for each patient were analyzed statistically within the "day" unit. After excluding the patient, for the remaining 9 patients, a total of 12 segments were placed in each hemisphere symmetrically (Figure 2). Then with the measurement of 3D ROIs, for each segment we obtained minimum, maximum, and average CBF values after that we compare preoperative and postoperative results with Wilcoxon Analysis.

RESULTS

The 9 patients included in the study operated at the mean age of 160 days (SD: ± 135). Postoperative imaging was done

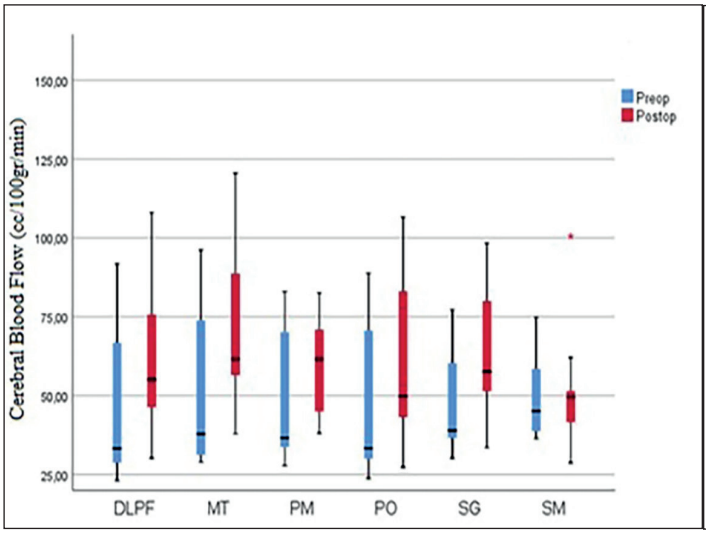

Figure 3: Average perfusion rate of right hemisphere.

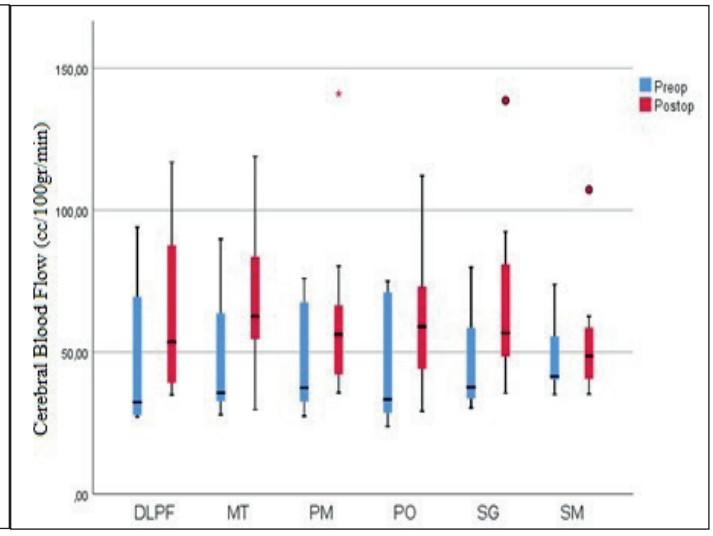

Figure 4: Average perfusion rate of left hemisphere.

mean 87 days (SD: ± 6) after surgery. Average ROI volumes were 3.78 cm^3 (SD: ±0.211) at preoperative measurement and 3.72 cm^3 (SD: ±0.176) at postoperative measurement.

In this study, there were seven sagittal synostoses, one unilateral coronal synostosis, and one metopic synostosis. About unilateral coronal synostosis; there were increased CBF on both hemispheres, but statistically insignificant (p>0.050). According to measurements of metopic synostosis, both hemispheres had increased cerebral perfusion and all changes were statistically significant except the change of left hemisphere minimum CBF (p≤0.050). About sagittal synostosis; 5 patients had increased CBF in all measurements, one patient had decreased CBF in all measurements; one patient had increased maximum CBF, decreased minimum and average CBF on both hemispheres. Two of the patients, whose results were all increased, data were found statistically significant and the patient's data, whose all CBF results decreased, was found statistically significant (p≤0.050).

With the comparison of all segment minimum, maximum, and average CBF values we found that cerebral perfusion rates of all segments raised after surgery, except the left SM minimum value. According to statistics; right DLPF maximum, right SG minimum and average, left SG average, right MT maximum, and left MT maximum CBF changes were found statistically significant (p≤0.050). Other than that, found statistically insignificant (p>0.050). Postoperative results showed that minimum perfusion rate enhanced 26.40%, maximum perfusion rate enhanced 36.94%, average perfusion rate enhanced 28.32% at right hemisphere and minimum perfusion rate enhanced 42.76%, maximum perfusion rate enhanced 26.73%, average perfusion rate enhanced 34.98% at left hemisphere (Figure 3,4).

DISCUSSION

Craniosynostosis affects cranial development with premature suture fusion and disarranges cerebral parenchyma with the change of intracranial volume (19,20). Regardless of shape and volume change, there is also neuronal disorganization. Theoretically, with surgical reconstruction, the aim is to make room for cerebral growth and restore the physiological position of the brain parenchyma. But the neurodevelopmental effects are not limited to sutures and their surroundings according to recent MRI studies (4).

In recent studies, this is told that there are two main mechanisms described in neurodevelopmental disorders of craniosynostosis patients. One of them is intracranial pressure rise and hypovascularity, the other one is cerebral extraordinary development (19). The goal of treatment was primarily craniofacial cosmetic appearance previously but, with recent studies, neurological improvement is also as important as cosmetic results. Because of that, new researchers try to find the relationship between neurodevelopment, intracranial pressure and surgical timing, and surgical technique (8,9,21,22). So, we could choose the optimal technique and optimal timing for the treatment of craniosynostosis.

According to the age of the patients on the operation day, 7 of them were younger than 180 days, and 2 of them were older than 180 days. And aside from that, with postoperative results, the most improved cerebral perfusion was found in the second youngest patient and the two oldest patients (older than 180 days) were the only patients whose cerebral perfusion decreased. The surgical treatment is recommended for non-syndromic craniosynostosis as soon as possible due to prevent deformity complicated with time and reduce the probability of neurological disorders. By the delay of surgery, experts worry about decreasing cosmetic and functional cosmetic results in recent literature (4,9). Our data shows us the operated patients'

results differ, between the age younger and older than 180 days, which supports the literature about surgical timing. When we tried to connect postoperative perfusion results and surgical technique, we couldn't establish a significant relationship between them.

By reviewing the literature, a few studies could be found about the neurocognitive effects of craniosynostosis. For example, in a review conducted by Speltz et al. (23) examining 17 studies that contain the cases followed between 1972 and 2003, there were decays of 35-40 % of patients in advanced neurological functions such as language, cognition, and behavioral development, although patients IQ was mostly within the normal range. According to the estimation made with the results of this study, independent from the suture type, craniosynostosis cases have 3-5 times higher risk of developing neurological disorder than normal population (4). Becker et al. (9) composed a study with 214 cases of craniosynostosis and found there was 23 % speech disorder that require speech therapy, there were 45 % psychological disorders. Then Becker et al. (9) tried to compare their results with recent studies about neurological disorders found in normal population. The results were found as speech disorders were 23 % in cases of craniosynostosis and 5.5 % in normal population, problems with school success were found as 16 % in cases of craniosynostosis and 5 % in normal population, behavioral disorders were found as 35 % in cases of craniosynostosis and 16% in normal population. As a result, Becker et al. (9) found similar results with Speltz et al. (23) and proved the previous estimation. Besides, the results of operated and unoperated patients couldn't be compared, due to the very low number of unoperated patients, according to Becker et al.(9). In addition to this, they commented that surgery stops the p rogression of neurological problems, but can't correct the effects of primary brain deformation caused by disruption of the structural organization of the brain (9). There is also increasing evidence of disorders in neuropsychological functions such as planning, spelling, reading, language development, and attention in studies conducted with older children diagnosed with craniosynostosis. In summary, the evidence shows us that craniosynostosis may be related to mental retardation and loss of neurological function, regardless of age (24). However, the number of studies that compare cognitive functions and anatomical changes, which use neuropsychological data and imaging modalities, are insufficient.

In this study, we realized that with surgical reconstruction, because of decreased intracranial pressure, postoperative cerebral blood flow increased. As stated in the literature, with increased CBF we try to reassure the homeostasis of brain parenchyma affected premature suture fusion and we plan to enable the recovery of neurological functions, theoretically (6,9). At the same time, we revealed the effectivity of applied surgical technique with perfusion measurement, quantitively.

Considering the functions of the brain regions, complex neurological functions such as memory, impulse control, and planning are managed by the dorsolateral frontal region (25,26). When we paraphrase the data of this study with literature, it may suggest that surgical treatment of craniosynostosis paves the way for the development of advanced neurological functions such as memory, impulse control, attention, and planning. Regarding social attention deficits and visual motor problems of pediatric autism spectrum disorders and schizophrenia cases, in the literature authors thought that may be related to functional and structural anomalies of the premotor and prefrontal regions (4). In light of the literature, it may be thought that parenchymal deformation of the brain in craniosynostosis cases gives rise to neuropsychological pathologies. The postoperative changes of CBF in premotor and prefrontal regions show us surgical treatment may be protective against developing neuropsychological pathologies of craniosynostosis cases.

According to Becker et al. (9), in craniosynostosis cases, speech disorders and problems with school success are more frequent than normal population. Becker and other researchers thought that the problems with school success were the result of visual and reading disturbances (9,27). In consideration of Broadmann's areas; on the occasion of increasing CBF of parietooccipital (PO), subgenual (SG), and midtemporal (MT) segments with surgery; theoretically, it is thought that the frequency of speech and school success disorders in craniosynostosis cases decrease with treatment.

In this study, with increasing the number of patients and varying the types of craniosynostosis included, the surgical numeric results guide us to create new treatment techniques or find new treatment algorithms or build new ideas. Besides, the statistical significance will be steadier with an increasing number of studied patients.

CONCLUSION

In the end, until the last two decades, craniosynostosis was only known as the deformed head shape and used to be operated on for appearance. Nowadays, with scientific advancements, the effects of craniosynostosis on neurological development have also gained importance. The literature and this study show that craniosynostosis should be treated at the most appropriate time and with the most appropriate technique to maintain or develop complex neurological functions in addition to their external appearance for patients.

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