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Correlation Between Findings of Cranial Tomography and the Levels of Cerebrospinal Fluid's Nerve Growth Factor in Hydrocephalic Infants

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ABSTRACT

Objective: To investigate the correlation between the NGF levels in the CSF and brain tomography indexes in preoperative and postoperative evaluations of hydrocephalic infants undergoing ventriculoperitoneal shunt.

Material and Method: A total of 27 patients were included. CSF samples were obtained in the during the operation and on the 3rd and 30th postoperative days, and CT evaluations were performed.

Results: No correlation was found between the NGF levels in CSF and CCT indexes using the Spearman correlation. The increases of NGF levels on the 3rd postoperative day were significantly higher than those of the peroperative levels ($p<0.05$). While the decrease was significant between the levels of NGF on the 30th and the 3rd postoperative days ($p<0.05$), the difference was not significant between the levels on the 30th postoperative day and the levels in the peroperative period ($p>0.05$),(0,023/0,015). The differences between the postoperative 3rd and 30th days were significant according to Evan's indexes, 3th ventricle indexes and ventricular scores ($p<0.05$). It was found that there was no significant difference between Sella media indexes in the preoperative period and on the postoperative 3rd day ($p>0.05$), (0,48/0,44), but that there was significant decrease on the 30th postoperative day ($p<0.05$).

Conclusion: Conclusions:There was no significant correlation between NGF levels of CSF and brain tomography indexes in the preoperative and postoperative evaluation of infants with hydrocephaly. However, significant relationship was seen within each parameter. The NGF levels of CSF and cranial tomography indexes can be helpful in the diagnosis, treatment and follow-up of hydrocephalus.

Key Words: *Cerebrospinal fluid, Computerized cranial tomography, Hydrocephalus, Nerve growth factor.*

ÖZET

Hidrosefalik İnfantlarda Kranial Tomografi Bulguları ve Beyin Omurilik Sıvısı Sinir Büyüme Faktörü Arasındaki İlişki

Amaç: Ventriküloperitoneal şant uygulanan hidrosefalili bebeklerin ameliyat öncesi ve sonrası değerlendirilmelerinde Beyin Omurilik Sıvısı Sinir Büyüme Faktörü (BOS NGF) düzeyleri ve beyin tomografisi endeksleri arasındaki ilişkiyi araştırmak.

Gereç ve Yöntem: Toplam 27 hasta dahil edildi. BT incelemeleri yapıldı ve BOS örnekleri ameliyat sırasında ve ameliyat sonrası 3. ve 30. günlerde alındı.

Bulgular: Spearman korelasyonu ile Bilgisayarlı beyin tomografisi (BBT) endekslerinde ve BOS NGF düzeyleri arasında korelasyon bulunamadı. Ameliyat sonrası 3. gün, NGF düzeyi ameliyat öncesi düzeylerine göre anlamlı olarak yüksek bulundu ($p<0.05$). NGF'nin ameliyat sonrası 3. günden 30. güne kadar azalması anlamlı iken ($p<0.05$), ameliyat öncesine göre, ameliyat sonrası 30. gün değerleri arasındaki fark anlamlı değildi ($p>0.05$), (0,023/0,015). Ameliyat sonrası 3. ve 30. gün arasındaki fark, Ewan's indeksi, 3. ventrikül indeksi ve ventriküler skorlara göre anlamlıydı ($p<0.05$) Ameliyat öncesi ve sonrası 3. günde sella media indeksinde anlamlı fark bulunamadı ($p<0.05$), (0,48/0,44), fakat ameliyat sonrası 30. günde anlamlı azalma vardı ($p<0.05$).

Sonuç: Hidrosefalisi olan bebeklerin ameliyat öncesi ve sonrası değerlendirilmesinde BOS NGF düzeyleri ve beyin tomografisi indeksleri arasında anlamlı bir ilişki saptanmadı. Bununla birlikte, her parametrenin kendi içinde anlamlı ilişkide olduğu görüldü. BOS NGF düzeyi ve BBT indeksleri hidrosefalinin tanı, tedavi ve takibinde yararlı olabilir.

Anahtar Kelimeler: *Beyin omurilik sıvısı, Bilgisayarlı beyin tomografisi, Hidrosefali, Sinir büyüme faktörü.*

Hydrocephaly is a pathological condition in which the cerebrospinal fluid (CSF) accumulates in abnormal amounts in the ventricles and the subarachnoid spaces and results in ventricular dilatation. For the diagnosis, craniography, computerized cranial tomography (CCT), magnetic resonance imaging (MRI), ultrasonography are used as imaging methods. The most widely used method is the CCT. Depending on the

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CCT findings, measurements of the Evans indexes, 3rd ventricle indexes, sella media indexes, and ventricular scores, which have been defined by Mataro et al. are performed today (1).

Hydrocefalus is a troubled disease. Also it's effective treatment is very difficult. Therefore all of the entities, can be interrelated with it, have to be examined. Any discovered result may be used in its surgical or medical treatment in the future.

Nerve growth factor (NGF) which is a member of the neurotropin family and a molecule of polypeptide structure, was described in 1951. It has an important role in nerve cell development and regeneration (2). Recently, there have been several studies on NGF. The relation between the changes of blood, CSF NGF levels and several pathological situations and symptoms have been investigated. We could not find any study in the literature on the correlation between CCT findings and NGF levels in the peroperative and postoperative period of patients with hydrocephaly. In this study, we tried to shed light onto the prognosis and treatment of hydrocephaly with the help of findings regarding the relationship between peroperative and postoperative NGF levels and CCT findings.

MATERIAL AND METHOD

Selection of patients

A total of 27 patients composed of 16 females and 11 males with the diagnosis of congenital hydrocephaly were included in the study. The distribution of the patients according to the age was: 17 patients were 0-2 months of age, 6 patients were 2-4 months old, and 4 patients were 4-6 months old. Obstructive hydrocephaly was seen in 21 patients because of aquaduct stenosis while the remaining 6 patients had non-obstructive hydrocephalus. Furthermore, there were 6 lumbar and 1 thorasic meningomyelocele cases among the patients. Informed consent was obtained from all families after providing information about the study.The present study was carried out after the approval of the Ethics Board was obtained from our University Ethic Committee.

The groups were composed according to CT performed and CSF sampled times. We tried to evaluate the correlations between CCT findings and NGF levels in the 3 period; peroperative, postoperative 3rd day and postoperative 30th days.

Group 1: Preoperative CCT was performed. CSF was sampled for determining the level of NGF peroperatively.

Group 2: Control CCT was performed on the postoperative 3rd day. CSF was sampled from the shunt reservoir.

Group 3: Control CCT was performed on the postoperative 30th day. CSF was sampled from the shunt reservoir.

Evaluation by Tomography

Cranial computed tomography was performed in the preoperative period and on the postoperative 3rd and 30th days using a Hitachi 1000 tomography device in 5mm axial slices. Tomography findings were evaluated according to the indexes described by Mataro et al.(1):

Measures of sites of ventricular size:

(A) maximum width of thefrontal horns distance;

(B) distance between the caudate nuclei at the level of the foramen of Monro;

(C) maximum width of the third ventricle;

(D) minimum width of both sella media;

(E) maximum inner diameter of the skull at the level of the measurement of the maximum bifrontal distance; and

(F)maximal outer interparietal diameter at the level of the sella media measurement.

Evan's indexes: A/E

3rd Ventricular indexes: C/E

Sella media indexes: D/F

Ventricular scores: $\frac{A+B+C+D}{E} \times 100$

Biochemical Analyses

CSF was sampled from the patients during the operation or from the shunt reserviors in the postoperative period. Puncture of the reservior was performed using a sterile technique after preparing the scalp with antimicrobial solution. CSF was obtained by entering the needle of a scalp vein set that was lower than No. 25,in an oblique angle. Patients with additional pathologies like infection, traumatic birth, and cerebral atrophy were excluded from the study. The materials were stored at -20°C until the test.

CSF beta NGF (catologue number: 900-K60) levels were measured using the PeproTech (PeproTech Elisa Development kit, USA) immunoassay kits. According to the guidelines of the kit procedure, the sandwich Elisa method was performed and the results were given as nanogram/millilitres.

It was investigated whether or not there was a significant correlation between CCT results and the CSF NGF levels in the peroperative period and on the postoperative 3rd and 30th days.

Statistical Analyses

The SPSS 8.0 programme was used (SPSS Inc. USA) for measuring the standard deviation and the mean values in the statistical analyses. Comparison of the patient groups was performed using the Wilcoxon rank test. A "p" value lower than 0.05 was accepted as significant. The Spearman correlation test was used for the correlation analyses (r,p).

RESULTS

Biochemical Findings

The NGF levels in group 2 (0.27±0.48) were statistically and significantly higher than the levels in group 1 and 3 (0.15±0.16, 0.13±0.13) ($p<0.05$).

There was no statistically significant difference between the NGF levels of group 3 and 1 (0.13±0.13, 0.15±0.16) ($p>0.05$). The levels of NGF have been displayed in Figure 1.

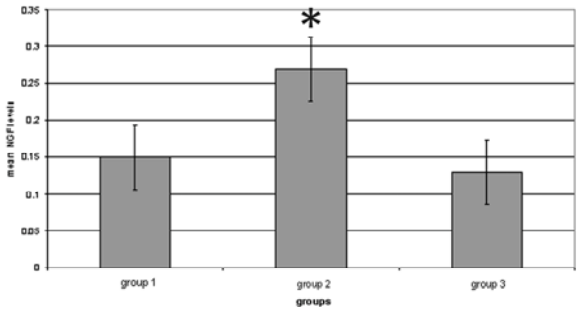

Figure 1: *Mean NGF levels of the groups.*
**p<0.05: mean NGF level of group 2 versus group 1.*

CCT Findings

*Evan's indexes: It was seen that the index of group 2 was lower than the index of group 1. Group 3 had a lower index than group 1 and group 2. The differences were statistically significant ($p<0.05$).

*3rd Ventricular indexes: The indexes were decreasing as group 1, group 2 and group 3, respectively. The differences between each other were statistically significant ($p<0.05$).

*Sella media indexes: The indexes of group 1 and group 2 were similar and the difference was statistically insignificant ($p>0.05$). The index of group 3 was lower than the index of group 1, and the difference was statistically insignificant ($p>0.05$). However the index of group 3 was much lower than the index of group 2, and the difference was statistically significant ($p<0.05$).

*Ventricular scores: The indexes were decreasing as group 1, group 2 and group 3, respectively. The differences between each other was statistically significant ($p<0.05$).
The mean ventricular scores according to the groups have been displayed in Figure 2. The mean Evan's indexes, 3rd ventricular indexes, and the Sella media indexes according to the groups have been displayed in Figure 3.

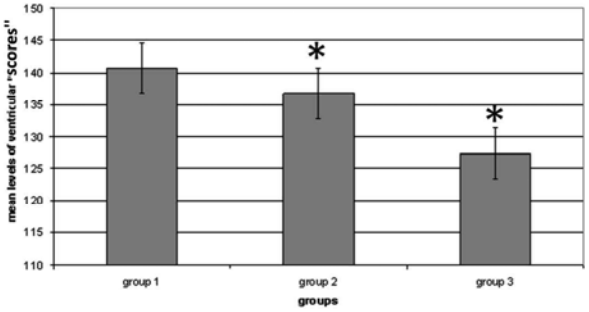

Figure 2: *Comparison of mean ventricular scores of the groups.*
**p<0.05: mean ventricular scores of group 2 and group 3 versus group 1.*

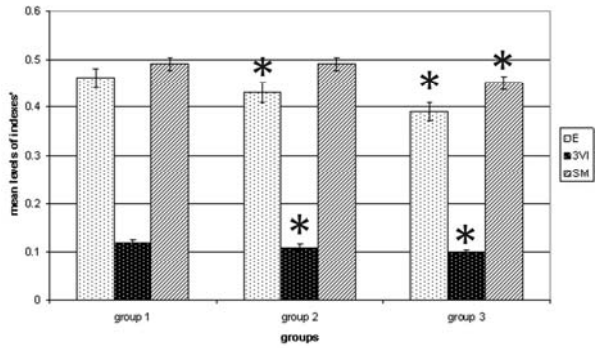

Figure 3: *Mean levels of indexes'of the groups. E: Evan's index, 3VI: 3rd ventricule index, SM: Cella media index.*
**p<0.05: E and 3VI of group 2 versus group 1. E, 3VI, SM of group 3 versus group 1.*

DISCUSSION

It is important for the prognosis of the patient to determine and treat the patients with hydrocephaly as early as we can. However, it is sometimes very difficult to decide whether surgical treatment or follow up is needed for ventriculomegaly. Every new study will provide benefits for the treatment of this disease, which occurs at a rate of nearly 100.000 new patients every year in the world.

CCT is still the most important tool for the diagnosis of hydrocephaly. Increase in ventricule size, subependymal passage (periventricular low dansity), ballooning of the frontal horns of the lateral ventricles (mickey mouse ventricle), compression-obliteration of basal cisternae, flocculation of contours, and thining of the parenchym are the findings of imaging (3). Furthermore, Evan's indexes, 3rd ventricular indexes, sella media indexes, and ventricular scores, which were defined by Mataro et al., could be measured depending on the CCT findings (1). The most important treatment protocol is ventriculoperitoneal shunting. However,

there may be some hesitations about the indications and the timing of shunts.

No biochemical markers for intracranial pressure have been put forth in recent years. NGF, which is a member of the neurotropin family and a molecule of polypeptide structure and described in 1951, has an important role in nerve cell development and regeneration. Its effects are produced via membrane receptors called TrkA and p75. Although several studies have shown that neurotropic factors have effects over controlling the cellular calcium hemostasis, regulating the cerebral blood flow, improving the results of cerebral ischemia, upregulating the enzymes in the antioxidation metabolism, and supression of free oxygen radicals, the mechanism in neuroprotection remains unclear. Increase in the NGF level following brain injury is the principle for neuronal healing (2). NGF levels in CSF and blood have been found to be increased in cerebral pathologies like hypoxia, ischemia, injury, senile atrophy, hydrocephaly, seizures, neuro-immunological diseases and increased intracranial pressure (2,4-7).

Recently, the relation between the changes in the blood and CSF NGF levels and several pathologic situations and symptoms have been investigated. However, we could not find any studies in literature on the correlation between the CCT findings and NGF levels in hydrocephaly.

When the literature was searched, it was found that NGF levels in the CSF were higher in children with hydrocephaly. Moreover, it was reported that NGF did not remain unchanged in the component of CSF, and that it played an important role in the pathogenesis of hydrocephaly (5).

It has been reported that CSF NGF levels of the patients whose ventricle size and symptoms had not changed following venticuloperitoneal shunting (arrest hydrocephaly) were higher than in patients whose ventricle size and symptoms had (high pressure hydrocephaly) decreased (2). Shunt application leads to an increase in NGF production in hydrocephaly patients. NGF levels in the CSF of patients who have undergone shunt application, transiently increases after 2-3 days. An increase in NGF after brain injury is crucial for neuronal healing. Despite the significant role of neurons in NGF synthesis under normal conditions, in brain injury, glial cells can produce NGF (8). The increase in the postoperative CSF NGF in the first 2-3 days after the shunt application in hydrocephaly patients depends on the increased glial cells after the brain injury. Arrest hydrocephaly occurs due to the primary cortical atrophy. As many neurons in the cerebral cortex become injured and reactive astrogliosis takes place, the increase in NGF in these patients becomes more prominent and the decrease of NGF concentration occurs slowly (7). The prognosis of the patients with arrest hydrocephaly after shunt operation is poor (2). In our study, the mean NGF levels on the 30th postoperative day is lower by approximately 14% of the peroperative NGF levels.

In the study of Mataro et al. the effects of shunt operation on the cognitive functions in young patients with hydrocephaly were investigated. In addition, the Evan's indexes, 3. ventricle indexes, sella media indexes and ventricular indexes in the preoperative and postoperative CCT findings were measured and the correlation between them were evaluated (1). It was found that ventricular sizes were decreased dramatically, and that large ventricles may be related with bad performance in verbal and visual tests. A study can be performed that would investigate the relation between the ventricular indexes and motor and cognitive functions after the shunt operation. In most of our patients, the CCT indexes decreased after the shunt operation. On the postoperative 3rd day, Evan's indexes decreased in 18 of 27 patients; the index increased in 6 of 27 patients, and in 3 patients, it remained unchanged. The third venticle index decreased, did not change, and increased in 21, 3, and 3 patients, respectively. The Sella media index decreased in 18 of 27 patients, it increased in 8 of 27 patients, and it remained unchanged in 1 patient. The ventricular score decreased in 21 patients, and increased in 6 patients. As a result, in the tomographic evaluation, a prominent decrease in the 3rd ventricular index and ventricular score can be expected. It was seen that the increase in Evan's index was parallel to the increase in ventricule score. Increased and unchanged indexes may be caused by shunt dysfunction or ventricular wall weakening due to excessive CSF or non-collapsing ventricles after the shunt operation.

Many researchers have investigated the changes in ventricular size after surgical treatment of patients with hydrocephaly. There will not be prominent changes in ventricular size in the early postoperative period in patients undergoing endoscopic third ventriculostomy, which is performed for the treatment of hydrocephaly with good results (9, 10). Similarly, it has been found that there will not be a correlation between the decrease of ventricular size and clinical improvements in normal pressure hydrocephaly patients who have undergone the operation in the same fashion (11).

Several studies have shown that clinical symptoms are not trustworthy for predicting the intracranial pressure (12, 13). NGF levels were found to be increased in both blood and CSF during increased intracranial pressure. For this reason, in patients with hydrocephaly, shunt insufficiency, and craniosynostosis, tomography will not provide information about the intracranial pressure by looking at the ventricle sizes. Blood and CSF NGF levels, which can be used for the follow-up treatment of patients, can be helpful in this matter.

Infants who have had a moderate level of ventriculomegaly, will not develop hydrocephaly, because the majority stabilize spontaneously and regress. Beside these, there is a significant tendency towards cognitive and psychomotor underdevelopment, parallel to the ventricle size (14, 15). These children can be followed up by measurement of the NGF levels.

In our study, NGF levels and also ventricle sizes decrease in the postoperative 30th day. These parameters are meaningful in the follow up of hydrocephalus independently, because no significant correlation has been found between the CSF NGF levels and CCT indexes according to the Spearman correlation analyses. We can't say ventricule size indicates NGF level with these statistical results. As in previous studies, NGF levels on the postoperative 3rd day were significatnly higher than the levels in the preoperative period. The levels on the 30th postoperative day had not been investigated in previous studies. It was found that the decrease in NGF levels were statistically significant when compared with the level on the 3rd postoperative day, but insignificant when compared with the level in the preoperative period.

In the evaluation by tomography, it can be expected that Evan's indexes, 3rd ventricule indexes and ventricular indexes can decrease progressively. It was seen that the difference between the levels of sella media indexes on the 3rd postoperative day and that of the preoperative period were not significant, but the difference between the postoperative 3rd and 30th day was significant. Although the ventricular index was the mostly correlated index with other indexes, each of the 3rd ventricular indexes was only correlated with one index.

As a result, CCT has an important role in making a decision on the treatment and follow-up of infants with hydrocephaly. Indexes defined in tomography are also helpful. As NGF, which has important role in neuron development and regeneration, is increased in the preoperative period in patients with hydrocephaly and shows changes in the postoperative period, it can be used in neuron healing directly or used for deciding on the surgical decision, and be helpful in the follow-up. There was no significant correlation between CSF NGF levels and CCT indexes using the Spearman correlation, but it was found that each has some significant relations within each other. Measured NGF levels after shunt surgery can be helpful in the follow up of hydrocephalus. When it is not possible to decide on surgery with the CCT findings, measurement of the CSF NGF level can provide an idea. Especially if there is a risk of cognitive and psychomotor development in patients with moderate ventriculomegaly, patients can be followed up by measurement of NGF levels. Future studies on NGF, which produces effects on several systems in the organism, will be very helpful for the diagnosis and treatment of several diseases.

REFERENCES

1. Mataro M, Poca MA, Sahuquillo J, et al. Cognitive changes after cerebrospinal fluid shunting in young adults with spina bifida and assumed arrested hydrocephalus. J Neurol Neurosurg Psychiatry 2000; 68: 615-21.
2. Yang JT, Chang C, Hsu H, et al. Increase in CSF NGF concentration is positively correlated with poor prognosis of postoperative hydrocephalic patients. Clin Biochem 1999; 32: 673-75.
3. LeMay M, Hochberg FH. Ventricular differences between hydrostatic hydrocephalus and hydrocephalus ex vacuo by CT. Neuroradiol 1979; 17: 191-95.
4. Erol FS, Yakar H, Artas H, et al. Investigating a correlation between the results of transcranial Doppler and the level of nerve growth factor in cerebrospinal fluid of hydrocephalic infants: clinical study. Pediatr Neurosurg 2009; 45: 192-7.
5. Mashayekhi F, Salehi Z. Expression of nerve growth factor in cerebrospinal fluid of congenital hydrocephalic and normal children. Eur J Neurol 2005; 12: 632-37.
6. Sofroniew MV, Howe CL, Mobley WC. Nerve growth factors signalling, neuroprotection and neural repair. An Rev Neurosci 2001; 24: 1217-81.
7. Suzaki I, Hara T, Tanaka C, et al. Elevated nerve growth factor levels in cerebrospinal fluid associated with progressive cortical atrophy. Neuropediatr 1997; 28: 268-71.
8. Lu B, Yokoyama M, Dreyfus CF, et al. NGF gene expression in actively growing brain glia. J Neurosci 1991; 11: 318-26.
9. Kulkarni AV, Drake JM, Armstrong DC, et al. Imaging correlates of successful endoscopic third ventriculostomy. J Neurosurg 2000; 92: 915-19.
10. Schwartz TH, Ho B, Prestigiacomo CJ, et al. Ventricular volume following third ventriculostomy. J Neurosurg 1999; 91: 20-5.
11. Meier U, Mutze S. Does the ventricle size change after shunt operation of normal–pressure hydrocephalus? Acta Neurochir Suppl 2005; 95: 257-59.
12. Eide PK. Quantitative analysis of continuous intracranial pressure recordings in symptomatic patients with extracranial shunts. J Neurol Neurosurg Psychiatry 2003; 74: 231-37.
13. Fouyas IP, Casey AT, Thompson D, et al. Use of intracranial pressure monitoring in the management of childhood hydrocephalus and shunt-related problems. Neurosurg 1996; 38: 726-32.
14. Liechty EA, Gilmor RL, Bryson CQ, et al. Outcome of high-risk neonates with ventriculomegaly. Dev Med Child Neurol 1983; 252: 162-68.
15. Low JA, Galbraith RS, Sauerbrei EE, et al. Motor and cognitive development of infants with intraventricular hemorrhage, ventriculomegaly or periventricular parenchimal lesions. Am J Obstet Gynecol 1986; 155: 750-56.