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Comparative Analysis of the Level of Neurotrophic Factors in Children with Intracranial Hemorrhages

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Abstract **Objective:** The aim of this study is to study the prognostic significance of neurotrophins as markers for the early detection of intraventricular hemorrhage. **Materials and Methods:** The study included 156 children with intracranial hemorrhages (intraventricular hemorrhages, subarachnoid hemorrhage and parenchymal hemorrhages. **Results:** 156 patients were divided into 4 groups: group 1 - 35 (22.4%) newborns diagnosed with IVH stage 1-2 (all indicators of this group were used to compare the data obtained and the adequacy of the results); group 2 - 32 (30.2%) children diagnosed with IVH stage 3-4; group 3 - 10 (6.4%) children with SAH; group 4 - 79 (49.2%) infants with PH. Statistically significantly low levels of CNTF and pNT-H were found in the IVH 1-2 group (32.2±24.4 ng/ml and 257.0±292.0 ng/ml) compared with other groups. The highest values of CNTF were in the IVH 3-4 group (110.2±57.7 ng/ml), and pNT-H1 in the SAH group (1149.8±2692.0 ng/ml). There is a decrease in the levels of CNTF (66.2±54.6 ng/ml) and pNT-H1 (644.1±1364.7 ng/ml) after 3-6 months. up to 58.3±46.7 ng/ml and 230.3±238.9 ng/ml respectively. After 2 years, there was a further decrease in the concentration of neurotrophins to 34.5±34.8 ng/ml (CNTF) and to 134.7±128.0 ng/ml (pNT-H1). It was determined that the optimal cut-off point for CNTF is 51.3 ng/ml, for pNT-H - 186.7 ng/ml. **Conclusion:** Low values of CNTF and pNT -H are significantly more often recorded in the group with a favorable outcome than in the group with a moderate and unfavorable outcome. In the recovery period, almost half (42.9%) of patients without neurological deficit had low concentrations of CNTF and pNT -H, while 32.1% of children with an initially elevated level of neurotrophins moved into the category of "severe deficiency". During the recovery period, 6.2% of patients with initially severe neurological deficits but low levels of CNTF and pNT -H had no impairments, while 74.2% of patients with high concentrations of neurotrophins had severe neurological impairments.

Keywords Intraventricular hemorrhages, Subarachnoid hemorrhage, Parenchymal hemorrhages, Neurotrophic factors

1. Introduction

Violation of cerebral circulation (ICC) in the form of intracranial hemorrhages (ICH) is an extremely serious pathology not only for adults, but also for children, associated with the life of a child at any age [Ballabh P. 2017].

Intracranial hemorrhages are observed in 30% of children under the age of 2 months, in 50% under 1 year, and only in 1% in adolescents aged 15-18 years [Romanova E.O., 2019]. According to Mackay M. et al. [2016] 10% of newborns die in the first week from a hemorrhagic stroke, 40% of children have no consequences, and the remaining 60% have serious neurological disorders throughout their lives.

Unfortunately, even the use of highly informative methods for diagnosing perinatal intracranial injuries, such as neurosonography (NSG), computed tomography, diffusion-tensor magnetic resonance imaging (tractography), dopplerography, electroencephalography, cannot always detect and timely diagnose the onset of pathological changes occurring on different levels and stages of CNS disease [Morgun A.V., 2013].

Therefore, the search for early markers of CNS damage and the simplification of their interpretation is certainly relevant. Biomarkers can be roughly divided into markers of neuronal damage, markers of neuroglia damage, and other markers depending on the characteristics of damaged cells [Yao M., 2019].

It is known from the literature that ciliary neurotrophic factor (Ciliary neurotrophic factor - CNTF) increases rapidly and significantly after traumatic or ischemic injury and plays an important role in neurogenesis and differentiation of neural stem cells [Ding J., 2013; Kang S., 2012], and an increased level of neurotrophin can induce apoptosis [Harada T., 2002].

The main white matter components integrated into the cytoskeleton of axons are neurofilaments, which can serve as a biomarker nerve tissue damage [Sellner J., 2011; Tao C., 2017]. To the features of neurofilament pNF-H include: release after acute intracerebral hemorrhage; high predictive value for long-term outcome and early neurological deterioration, and being an independent predictor of long-term outcome and early neurological deterioration [Cai J., 2013].

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The purpose of the study was to study the prognostic significance of neurotrophins as markers for the early detection of intraventricular hemorrhage.

2. Materials and Methods

The study included 156 children with intracranial hemorrhages (intraventricular hemorrhages (IVH), subarachnoid hemorrhage (SAH) and parenchymal hemorrhages (PH)), who were hospitalized in the intensive care unit and the microneurology department of the City Clinical Children's Hospital No. 1 in the period from 2017 to 2020, followed by their observation on an outpatient basis at the place residence, with the assistance of the Department of Pediatric Neurology TashIUV.

Criteria for inclusion in the study group:

- children aged from birth to 2 years with a confirmed diagnosis of "hemorrhagic stroke" and "IVH" according to the international classification;
- written consent of parents/guardians to participate in the research;
- children in acute, recovery and residual periods of hemorrhagic cerebral stroke;
- anamnestic, clinical, neuroimaging and neurophysiological signs confirming vascular lesions of the brain;

Criteria for exclusion from the study group:

- age of patients older than 2 years;
- the presence of severe hereditary pathology, developmental anomalies, degenerative diseases;
- the presence of severe concomitant pathology affecting the course of the disease and the results of diagnostic studies.
- children with paroxysmal syndromes that do not have neurophysiological confirmation.

All young children with intracranial hemorrhages (ICH) underwent in-depth clinical, neurological and paraclinical studies to differentiate diseases similar in clinical course and to choose a strategy for a therapeutic approach. For a detailed study of clinical and neurological signs, when filling out the developed individual card, we included an examination of the neurological status using the PedNIHSS stroke scale and PSOM SNE.

Of the instrumental studies, neurosonography (NSG), computed tomography and magnetic resonance tractography of the brain were used.

Statistical processing of the results was carried out using Microsoft Excel, MedCalc version 18.5 and easyROC, ver. 1.3.1. The initial data were evaluated for compliance with the normal distribution according to the Kolmogorov-Smirnov criterion. To assess the prognostic significance of markers, ROC analysis was used (Receiver Operating _ Characteristic), with the calculation of the area under the curve AUC (area under the curve), Se (sensitivity) and Sp (specificity) of the model. Results are presented as median (Me) [interquartile range Q25; Q75]. Differences were considered statistically significant at $p< 0.05$.

3. Results and Discussion

All patients were divided into 4 groups: group 1 included 35 (22.4%) newborns with a diagnosis of IVH 1–2 transferred and confirmed for NSG (all indicators of this group were used to compare the data obtained and the adequacy of the results); group 2 included 32 (30.2%) children with a diagnosis of IVH 3-4 st; group 3 consisted of 10 (6.4%) children with SAH; Group 4 consisted of 79 (49.2%) young children with PH.

The data obtained indicate that in the IVH 1-2 group (32.2±24.4 ng /ml and 257.0±292.0 ng /ml) there are significantly low values of CNTF and pNT-H, respectively, compared with other groups. The highest levels of CNTF were in the IVH 3-4 group (110.2 ± 57.7 ng / ml), and pNT-H1 in the SAH group (1149.8 ± 2692.0 ng / ml) (Table 1.).

According to the literature, the concentration of CNTF in the blood serum is not determined, therefore, it can be concluded that CNTF is an early marker of IVH.

Next, we studied the level of CNTF and pNT-H1 depending on the timing of the examination (Fig. 1).

Table 1. Indicators of neurotrophins depending on the type of NMC

Indicators	IVH 1-2, n=35	IVH 3-4, n=32	SAH, n=10	PH, n=79	Total, n=156
CNTF, ng /ml	30.6 (11.7-48.4)	111.6 (63.4-155.0)	33.2 (22.9-69.2)	76.7 (31.6-122.0)	50.3 (25.1-100.9)
IVH 1-2		0.0001	0.04	0.0001	
IVH 3-4			0.03	0.02	
SAH				0.24	
pNT -H, ng /ml	155.2 (106.5-248.1)	487.7 (216.5-989.8)	147.5 (110.7-200.6)	212.4 (101.6-811.5)	189.9 (112.2-685.3)
IVH 1-2		0.009	0.05	0.06	
IVH 3-4			0.99	0.10	
SAH				0.29	

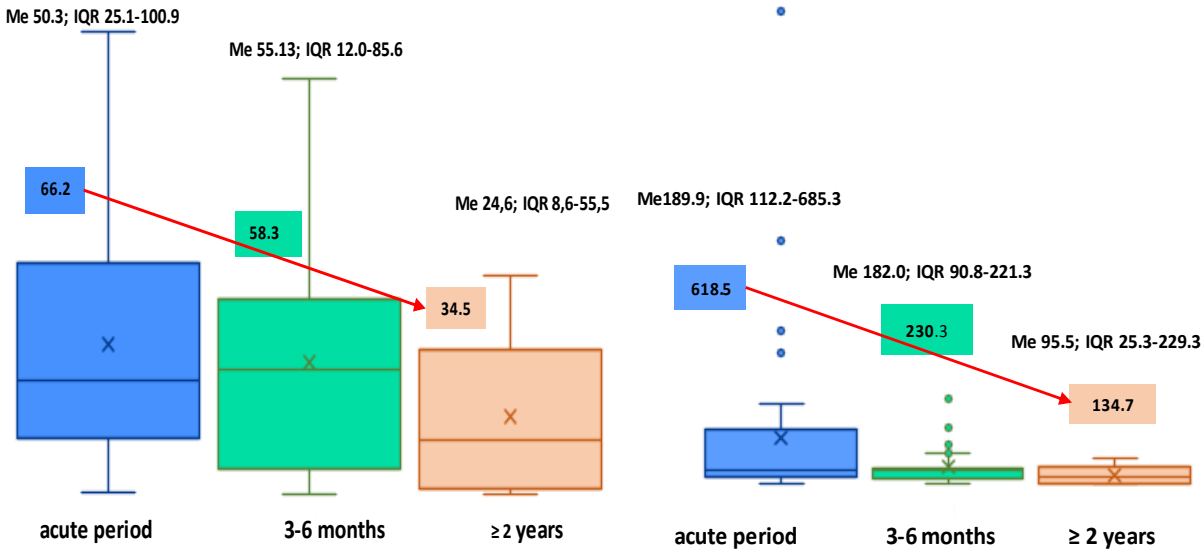


Figure 1. Dynamics of concentrations of CNTF and p NT -H1 according to the timing of the survey (the arrow indicates the direction of the dynamics), ng / ml

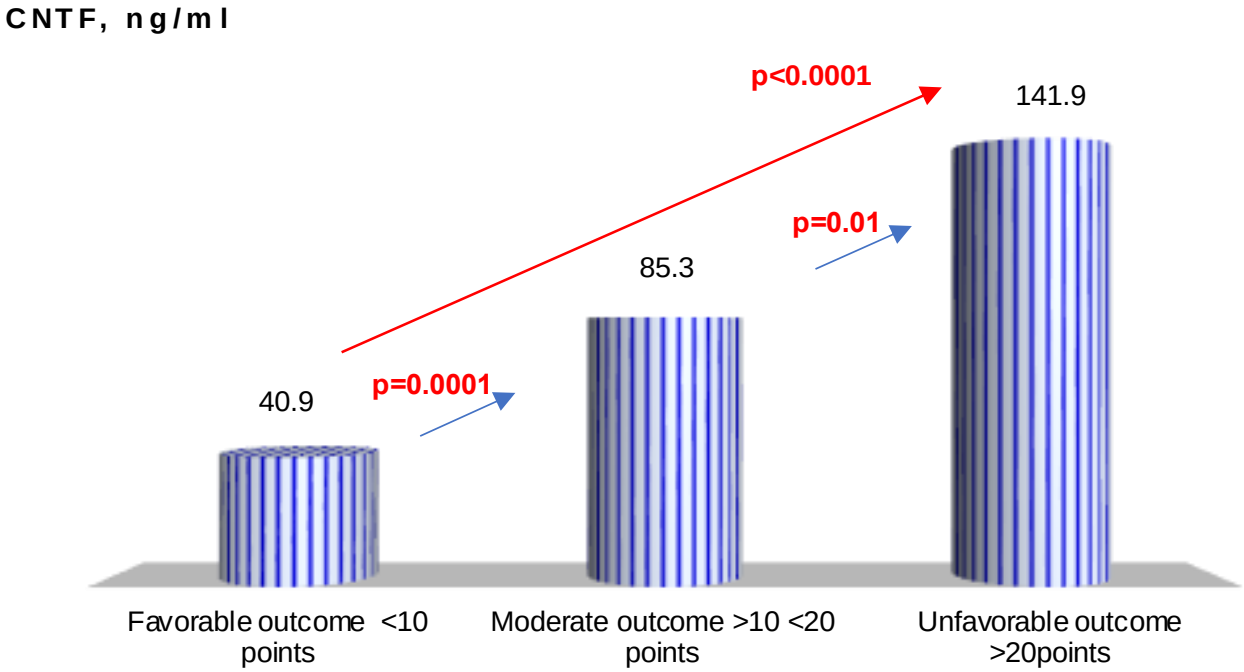


Figure 2. CNTF concentration relative to stroke severity

According to the received data of CNTF increased in the acute period - 66.2±54.6 ng / ml and p NT -H1 - 644.1 ± 1364.7 ng/ml, in dynamics after 3-6 months. brain damage decreased to 58.3±46.7 ng /ml and 230.3±238.9 ng /ml, respectively.

After 2 years, there was a further decrease in the concentration of neurotrophins to 34.5±34.8 ng /ml (CNTF) and to 134.7±128.0 ng /ml (pNT -H1).

Analysis of neurotrophin values depending on the outcome on the PedNIHSS scale showed that in the group with a favorable outcome, the levels of CNTF and pNT -H were significantly lower than in the groups with a moderate and unfavorable outcome (Fig. 2 and Fig. 3.).

Next, we studied the relationship between the level of neurotrophins and indicators of neurological deficit according to the PSOM S scale in dynamics.

Based on the studies, it was found that initially the average values of CNTF and pNT -H in groups of children who had no neurological deficit (37.7±26.3 ng /ml and 323.6±328.5 ng /ml, respectively) or insignificant (respectively 30.3±23.4 ng /ml and 199.7±248.6 ng /ml) is significantly lower than in patients with moderate (respectively 40.8±32.8 ng /ml and 309.1±364.8 ng /ml) and severe deficiency (87.1±58.6 ng /ml and 862.3±1656.9 ng /ml, respectively).

The study of the levels of CNTF and pNT -H depending on the degree of neurological disorders remaining in the

recovery period showed that in the category "without deficiency" 42.9% of patients had low concentrations of CNTF (mean - 35.7 ± 19.5 ng / ml) and pNT -H (363.2±377.5 ng /ml), while 32.1% of children with initially elevated levels of CNTF (mean - 152.2±37.3 ng /ml) and pNT - H (1279.6±652.9 ng /ml) moved into the category of "severe deficiency" (Fig. 4.).

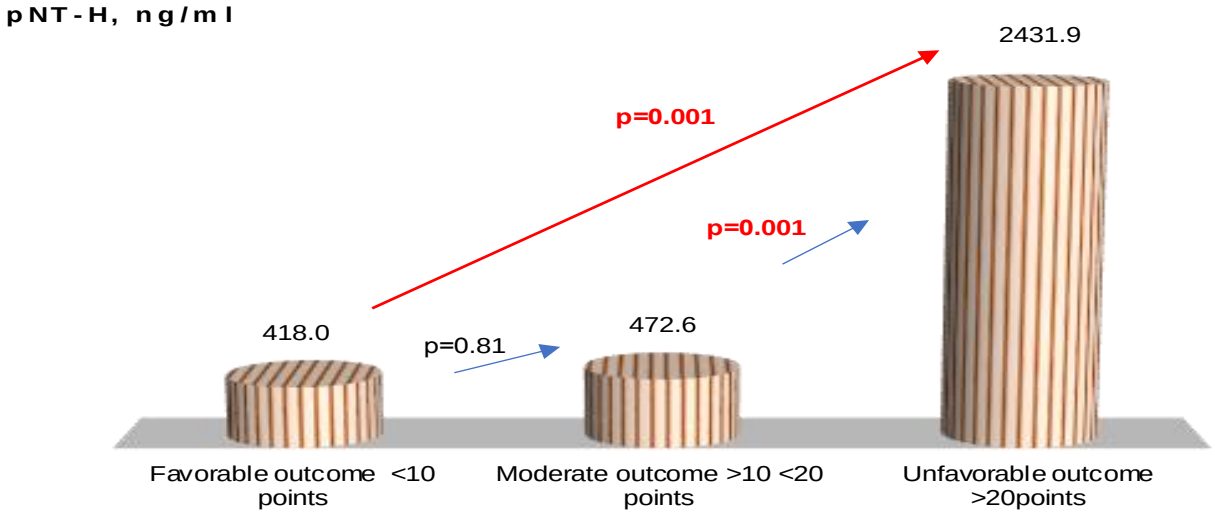


Figure 3. pNF -H concentrations relative to stroke severity

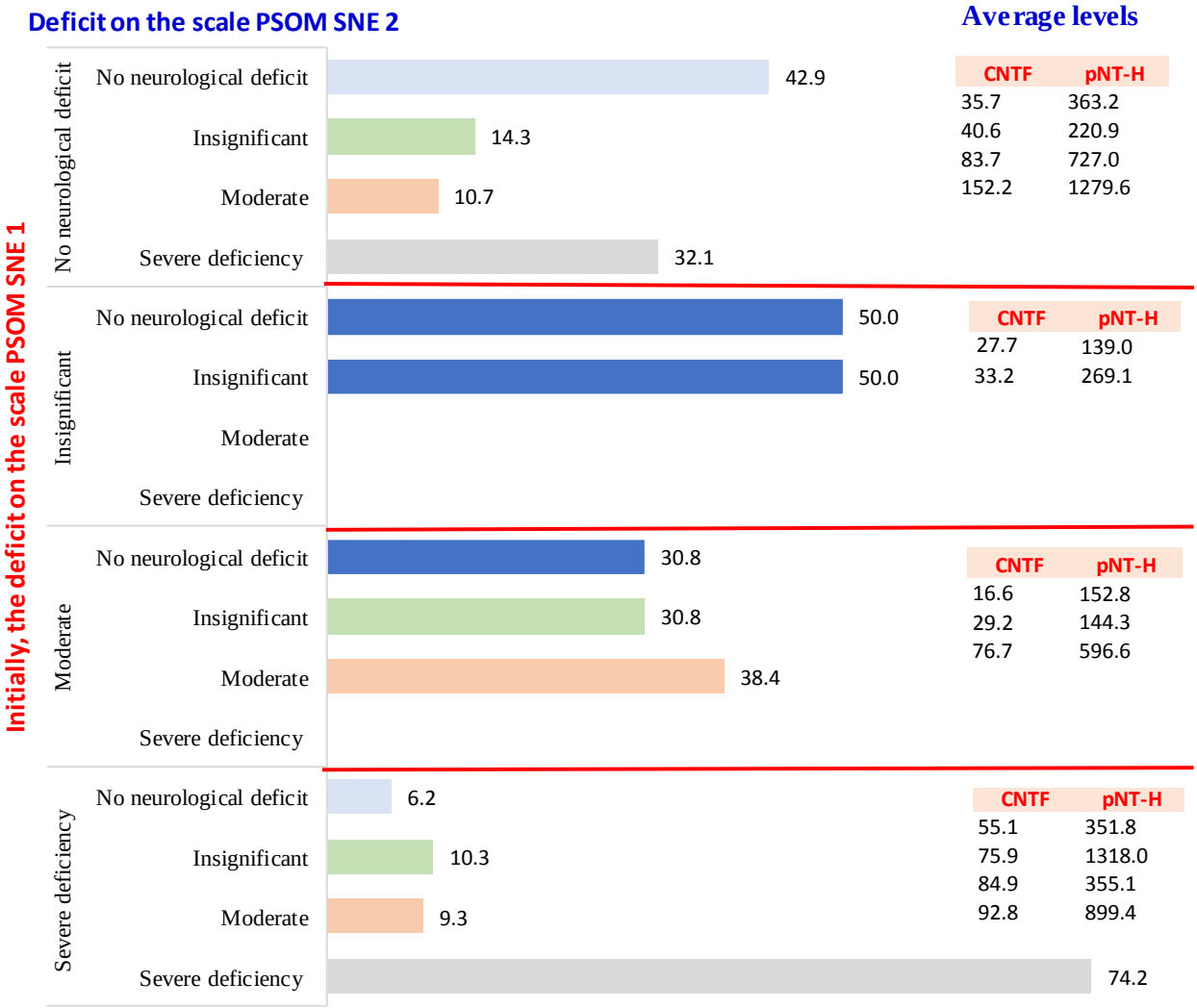


Figure 4. Level of neurotrophins (CNTF and pNT -H) depending on the degree of neurological deficit

In the group with initially severe neurological deficit, the re-examination revealed that 6.2% of children with low levels of CNTF and pNT -H (mean - 55.1±28.6 ng /ml and pNT -H - 351.8± 394.5 ng /ml) there were no disorders, while 74.2% of patients with high concentrations of neurotrophins (mean - 92.8±60.7 ng /ml and pNT -H - 899.4±1586.8 ng /ml) had severe neurological impairment.

There is an assumption that neurotrophins can serve as early markers of brain damage in newborns and a criterion for predicting outcomes in NCC.

According to Golosnaya G.S. [2010] in newborns with CNS lesions, the concentration of neurotrophins is determined from the first day of life; therefore, the level of CNTF may possibly serve as an early marker of IVH. With extensive brain damage, inhibition of CNTF expression in the blood serum and in the brain is noted, contributing to a decrease in the functionality of newborns. CNTF directly correlated with the formation of hypoxic-hemorrhagic CNS lesions [Golosnaya G.S., 2010]. CNTF is considered as a key differentiation factor for developing neurons and glial cells, which provides trophism and is involved in the protection of damaged or axonotomized neurons [Golosnaya G.S., 2009].

According to Khalil M. et al. [2018] neurofilaments are a promising marker of neuroaxonal damage regardless of causal pathways.

In a prospective study conducted by Zurek J. et al. [2011] in patients with traumatic brain injury, the level of pNF -H on days 2-4 is significantly higher in patients with an unfavorable outcome than in patients with a favorable outcome (p=0.027; p=0.019; p=0.01). The level of pNF -H was significantly higher in diffuse axonal damage detected during primary computed tomography (p=0.004).

Vajtr D. et al. [2012] studied the level of pNF -H in patients with diffuse and focal axon damage. The content of pNF -H was higher in diffuse lesions compared with focal lesions (0.625±0.14 vs. 0.139±0.02 ng /l, p<0.05) within 10 days after admission. The highest levels of pNF -H were from the fourth to the tenth day in both groups.

Therefore, the next stage of our research was to determine the prognostic significance of CNTF and pNT -H in the process of brain neuroplasticity in ICH in children.

Using ROC analysis and plotting an ROC curve with indication of the area under the curve (AUC), a diagnostically significant cut-off point (cut-off point) for neurotrophins (CNTF and pNT -H) and the total score of PSOM-SNE and its components. The choice of cut-off value was carried out at the point of the graph with the maximum sum of sensitivity and specificity (Fig. 5.).

Optimal cutoff point for CNTF is the value of 51.3 ng / ml, with Se - 0.667; 95% CI 0.521-0.792 and Sp - 0.844; 95% CI 0.672-0.947, for pNT -H - 186.7 ng /ml with Se - 0.608; 95% CI 0.461-0.742 and Sp - 0.750; 95% CI 0.566-0.885.

Optimal cutoff point for PSOM-SNE is an indicator <1 point, with Se - 0.961; 95% CI 0.865-0.995 and Sp - 0.696; 95% CI 0.838-0.99 (Fig. 6.).

During the ROC analysis, the AUC area for CNTF, pNT -H and PSOM-SNE was determined. Expectedly, the highest diagnostic significance is in the total data of the PSOM-SNE scale, neurotrophins CNTF and pNT -H had very good and moderate predictive value, respectively (Fig. 7.).

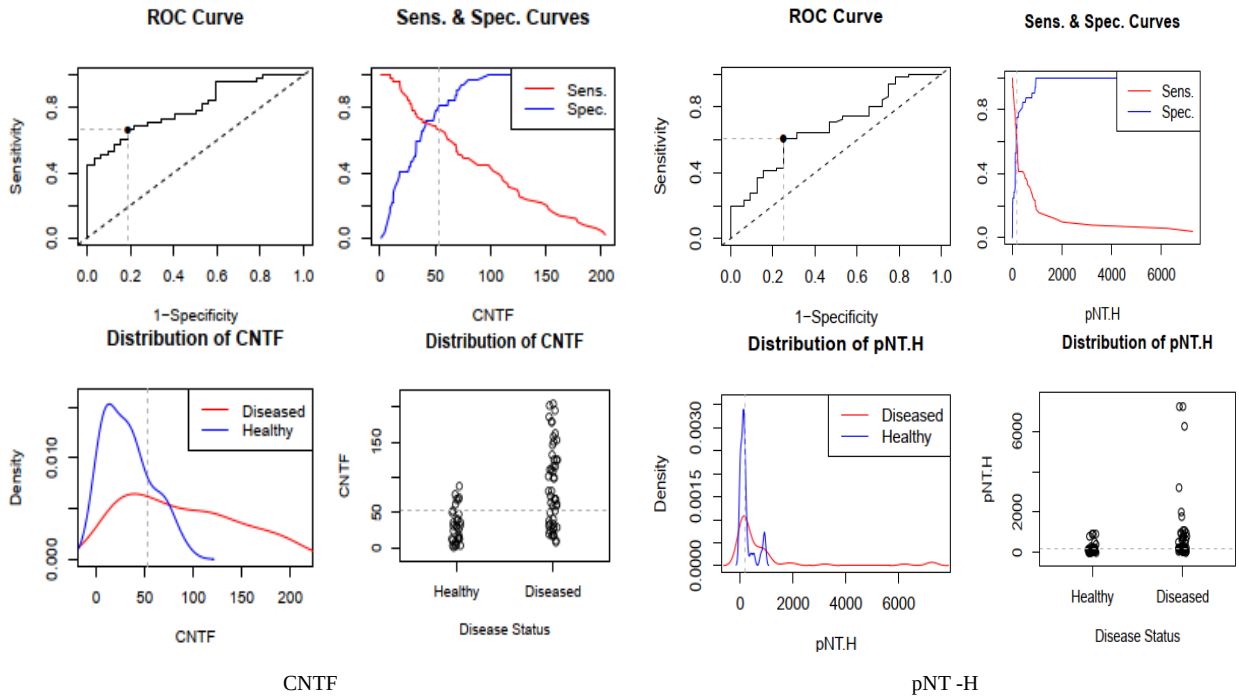


Figure 5. cut - off point for neurotrophin levels

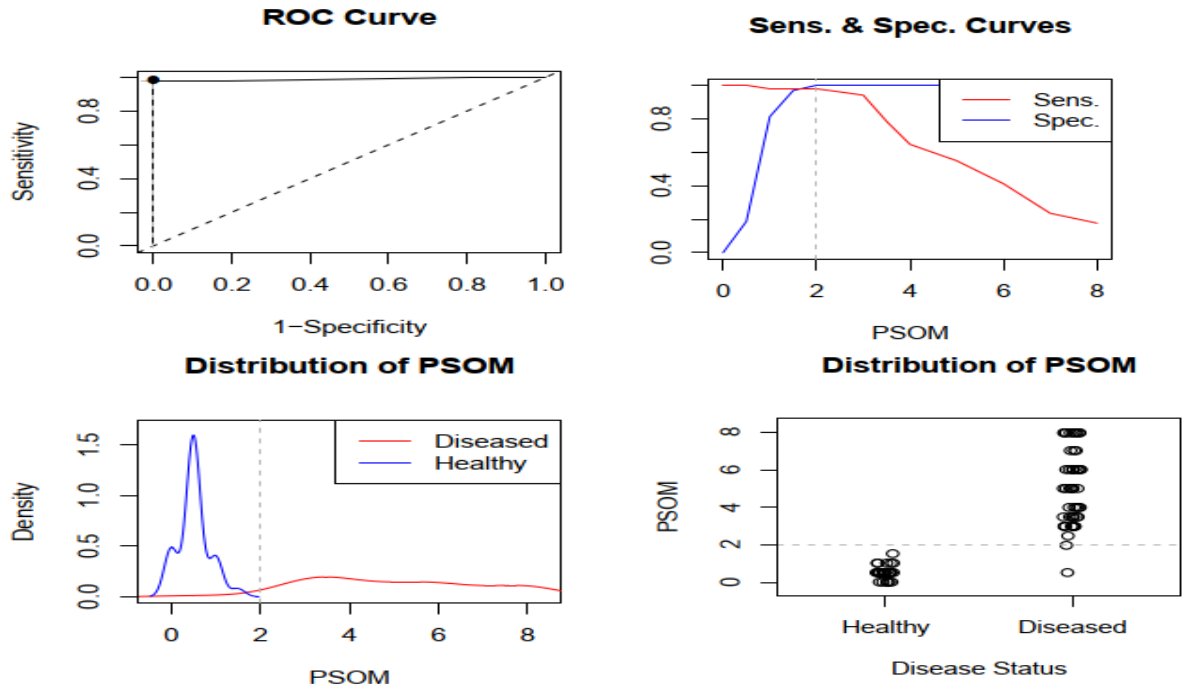
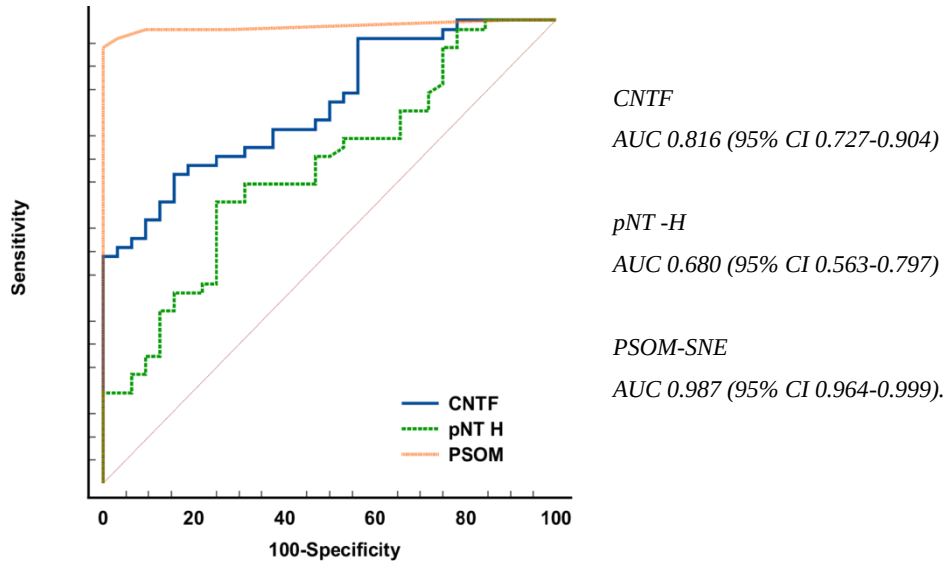


Figure 6. cut - off point for PSOM-SNE summary



CNTF

AUC 0.816 (95% CI 0.727-0.904)

pNT -H

AUC 0.680 (95% CI 0.563-0.797)

PSOM-SNE

AUC 0.987 (95% CI 0.964-0.999).

Figure 7. ROC curve of the prediction model

We also determined the significance for predicting the outcomes of childhood stroke of such neurological status indicators as: ensomotor deficit (AUC 0.980; 95% CI 0.953-0.999) - gradation " excellent" value, cognitive impairment (AUC 0.811; 95% CI 0.690-0.932) - gradation " very good", impaired speech reproduction (AUC 0.743; 95% CI 0.591-0.894) - - gradation " good" significance and impaired speech comprehension (AUC 0.580; 95% CI 0.413–0.748) had a low grade.

4. Conclusions

Thus, we have established that:

the highest levels of CNTF and p NT -H1 are detected in the acute period of stroke, with a significant decrease during the recovery period (after 2 years);

low values of CNTF and pNT -H are significantly more often recorded in the group with a favorable outcome than in the group with a moderate and unfavorable outcome ;

Initially, the content of CNTF and pNT -H in children without neurological deficit was significantly lower than in patients with moderate and severe deficiency;

in the recovery period, almost half (42.9%) of patients without neurological deficit had low concentrations of CNTF and pNT -H, while 32.1% of children with an initially elevated level of neurotrophins moved into the category of

"severe deficiency";

during the recovery period, 6.2% of patients with initially severe neurological deficits but low levels of CNTF and pNT -H had no impairments, while 74.2% of patients with high concentrations of neurotrophins had severe neurological impairments;

the optimal cut-off point for CNTF and pNT -H is 51.3 ng /ml and 186.7 ng /ml, respectively, cut - off point for PSOM-SNE indicator <1 point;

neurotrophins CNTF and pNT -H were respectively very good (AUC 0.816) and average (AUC 0.680) predictive value.

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