Ischemic Resistance of Motor Axons in Children with Viral Meningitis and Guillain–Barré Syndrome

Klimkin V. Andrey, MD, Voitenkov B. Vladislav, MD, PhD, Skripchenko V. Natalia, MD, DrSci, Professor

Scientific research institute of children's infections, Saint-Petersburg, Russia.

Abstract: Introduction: Nerve fibers in various pathological conditions are resistant to ischemia. In children, both in normal and in Guillain-Barre syndrome (GBS) effect of ischemia on neural conductivity is not investigated thoroughly. Methods: The effect of temporal local ischemia ofupper armon motor nerve conductionvelocity (MNCV) of the ulnar nerve in the healthy children (n=26), children with acute period viral meningitis (VM) (n=16), patients 14 days after the clinical manifestation of VM (n=11) and children with GBS in catamnesis (n=11) was evaluated. Results: Less pronounced decrease in MNCV on 10 minute of ischemia (by 50 % (p<0.00001)) was seen in children with GBS in catamnesis, comparing to the controls. In the acute period of the VM also less pronounced decrease in MNCV by 29%, than in the controls, was registered. Conclusions: Motor axons of the children in the acute period of VM and GBS are resistant to temporal limb ischemia.

Keywords: Local nerve ischemia, Guillain-Barre syndrome, inflammation, motor nerve conductionvelocity, children

1. Introduction

Among infectious diseases of the peripheral nervous system GBS has special severity andcharacterized by the destruction of myelin roots and peripheral nerves as a result of autoimmune inflammation. The degree and extent of demyelination determines the severity of paresis and sensitivity disorders, resulting in impairment of nerve conduction. [1].

However, an individual assessment of absolute parameters of neural conduction is not reliable enough due to the high interindividual variability of their values. [2] Using electromyography criteria of the violations only of nerve conduction is not always sufficient for the diagnosis of GBS. Often, in GBS, especially in the acute phase of the disease, changes of axonal excitability of peripheral nerves are seen, which complicates assessment of the conducting properties of nerves. [3] In the initial period of increasing symptoms (1-2 week of illness) indicators of nerve conduction, including terminal latency, duration of the compound muscle action potential (CMAP) amplitude, MNCV may not significantly differ from the normative data. [3]

Absence of changes of MNCV in the period of clinical manifestation and stabilization of symptoms in GBS and high interindividual variability parameters of MNCV requires a demand for new, additional electromyography (EMG) indicators for assessing the conducting properties of the peripheral nerves.

Corresponding author:

Klimkin V. Andrey, Federal State Budgetary Research Institute of children's infections of Federal Medical-Biological Agency of Russia, St. Petersburg, Russia. E-mail: emg.sonography@gmail.com.

It is known that the use of functional tests allows to normalize studied parameters. [2] Such effect may be seen in electroencephalographyrecording using tests with photostimulation, hyperventilation to detect epileptic activity.

As a functional test, temporal local ischemia of peripheral nerves by using a sphygmomanometer cuff is used in the recent studies of peripheral nerves. [4,5] Temporal local ischemia in the clinic is used as a provocative test in carpal tunnel syndrome [6], as well as to assess the impact of temporal ischemia on conduction and excitability of axons in polyneuropathy of dysmetabolic genesis [7,8,9], neurodegenerative diseases such as amyotrophic lateral sclerosis. [10]

Nerve fibers in various pathological conditions are resistant to ischemia. [8,9,10,11] So in patients with diabeteswithout clinical signs of polyneuropathy degree of decrease in MNCV of the ulnar nerve at 15 minutes of local forearm ischemia was significantly lower by 30% compared with the normative data. [7]

It is argued that during temporal local ischemia changes in neural conduction in adults may be an early sign of polyneuropathy. [7,10] In children, both in normal and in GBS effect of ischemia on neural conductivity is not investigated thoroughly. There is an assumption that the conductivity on the peripheral nerves may vary not only in autoimmune inflammation of nerves, but inflammation of other sites; possible reason may be the development of the cytokine-mediated channelopathy. [12,13] It can be assumed that the changes of neural conduction may be an early marker of inflammation. This assumption led to the setting of objectives of this study.

2. Purpose

1. To studyinfluence and diagnostic possibilities of using the tourniqueton theupper armon MNCV of the ulnar nervein children with GBS;

2. This study is an attempt to shed some light on the electrophysiological changes in the motor axons of theulnar nerve with the tourniquetattached on theupper armduring acute phase of infection.

3. Materials and Methods

The experimental protocol was reviewed and approved by the local ethical committee. Nerve conduction studies were performed on 26 controls (14 girls, 12 boys, mean age 11.1 ± 2.3 years), 16 children in acutephase VM (all cases were of enterovirus etiology, 6 girls, 10 boys, mean age 11.7 ± 2.9 years), 11 children 14 days after the clinical manifestation of VM (7 boys, 4 girls, mean age 11.6 ± 3.1 years) and 11 children with demyelinating form of GBS (5 boys, 6 girls, mean age 14.4 ± 3.1 years) in seven temporary cuts: before ischemic test, on 2, 5, 10 minutes of test and on 1, 5, 10 minutes after it. Study was carried out in shielded cabinet with a constant controlled temperature (average 24 °C).

Children with GBS in catamnesis had reduced MNCV owing to thetransferred inflammatory polyneuropathy in terms of 6 to 720 days after onset of paresis.

Stimulating and recording electrodes were placed on the right upper extremity of each subject to stimulate the ulnar nerve.Before placement, the skin below the electrodeswas slightly abraded to reduce impedance. A ground electrode was fastened to a convenient site between the stimulating and recording electrode. The recording site wasabductor digiti minimi muscle. R1 and R2 electrodes wereplaced in such a way that R1 is placed over the musclebelly of abductor digiti minimimuscle and R2 over the fifth metacarpophalngeal joint. Stimulation sites were elbow (S2) and wrist (S1). The resting MNCV, CMAP and latency measurements of the ulnar nerve for each

subject were carried out. Stimuli were single, supra-maximal 0.2 ms duration pulses and MNCV were obtained before ischemic test, on 2, 5, 10 minutes of test and on 1, 5, 10 minutes after test.

Sphygmomanometer cuff of 14 cm width was used as tourniquet in the study. [10,14] The cuff was inflated around upper arm to 20–30 mm Hg above its respective systolic blood pressure ranging from 143 to 162 mm Hg and was kept inflated for 10 minutes (Fig. 1).We held control of skin temperature using an infrared thermometer, skin temperature was maintained above 30 °C using a warmer.

The MNCV before and following the application of the cuff was calculated by dividing the distance between the two stimulation sites by the difference in the onset latency proximal and distal to the cuff i.e.

MNCV (m/s) = Distance (mm)/Latency(msec.) prox.tocuff – Latency(msec.) distaltocuff

The percentage of MNCV was calculated using the formula i.e.value of each MNCV atdifferent time durations/baseline value MNCV*100 (%).

Statistical analysis and processing of received data were performed using the software IBM SPSS Statistics, version 22. Initially 2-way ANOVA with post-hocMultiple Comparison test was applied to theobtained data. No statistically significant difference wasobtained between the parameters compared for the twogroups, so a more sensitive Paired t-test was applied.

4. Results

Within 10 minutes of ischemia there was a gradual decrease of MNCV in all groups. Already at 2 minutes of ischemia in all groups was a significant decrease of MNCV, which grew and became maximal on 10 minute of ischemia. After ischemia in all groups significant increase MNCV was seen already on 1 minute, except for children with GBS (Table 1).

Percentage MNCVon 10 minute of ischemia in children with GBS was by50% significantly less ($p<0.00001$)and in children with acute VM by 29% significantly less ($p<0.05$), than in controls. Children with VM 14 days after the clinical manifestation and complete sanation of cerebrospinal fluid had no differences with controls (Table 2).

Graphics of reduction MNCV are U-shaped in all groups. However, in healthy children waveform has a greater reduction than in the other groups (Fig. 2).

Children in the acute and subacute period of GBS (up to 2 months) had a significantly lower values of the percentage MNCV 3.8 ± 0.5%, than children with GBS after 6 months of clinical manifestation, which were 5.5 ± 0.4% ($p <0.05$).

5. Discussion

On 10 minute of ischemiaofupper arm in healthy children reduction in MNCV of the ulnar nerve similarwith one registered in healthy adults: for children it is - 8.5 ± 1.9%, for adults - 8.7%. [7]

Significant resistance of motor axons to local ischemia in children with GBS, which we obtained in this study, is similar to that in adults detected by other authors in dysmetabolic polyneuropathy. [9,15] It`s worth to underline

significant, although less strong resistance of the axons in children with VM - a condition in which peripheral nerve lesion is usually not considered as part of the pathogenesis.

Possible cause of axonal resistance to local ischemia in diabetes may be chronic ischemia of the nerve fibers due to microangiopathy *vasa nervorum*, which provides the effect of preconditioning in acute ischemia. [7] In studies of patients with amyotrophic lateral sclerosis resistance of peripheral axons to ischemia may be due to reduction in K+ transport from the cell and constant Na+transport across the membrane that in turn supports axon excitability. [10]

Ischemic resistance of motor axons in children with GBS and in acute period of VM may be caused by a new type of acquired channelopathy affecting the inactivation properties of Na+ channels. [12,13,16] It is shown that the thick myelinated fibers are more sensitive to damaging factors, including ischemia than unmyelinated fibers. [17,18] Due to demyelination, channelopathy, MNCV reflect conduction by more sensitivity myelinated fibers. In normal conditions MNCV reflect conduction by myelinated fibers and in ischemia observed greater reduction MNCV, due to sensitivity of these fibers to ischemia.

In the acute period of VM ischemic resistance of motor axons can be explained by the influence of pH extracellular space on the axon excitability as a result of fluid and electrolyte imbalance during infection process. [19]

Significant less pronounced decrease of MNCV on 10 minute of local ischemia in children with VM may be related to the fact that changes and the focus of inflammation are localized in the meninges of the brain. Severity of channelopathy in VM is lower than in GBS, which is characterized by inflammation lesions of peripheral nerves.

6. Conclusions

Reduction of MNCV of the ulnar nerve in response to local ischemia of upper arm in healthy children and adults does not differ.

Motor axons of the children in the acute period of VM and GBS are resistant to temporal limb ischemia.

Reduction of MNCV on local ischemia in children in the acute periodof GBS matters less than $3.8 \pm 0.5\%$ and during the sanogenesis tends to normalize ($p<0.05$). Influence of ischemia on conductionof motor axons in children with GBS needs further study, including the development of additional diagnostic criterion of GBS.

Abbreviations

CMAP –compound muscle action potential;

EMG –electromyography;

GBS–Guillain-Barre syndrome;

MNCV –motor nerve conductionvelocity;

VM–viral meningitis.

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Table 1. MNCV (m/s) in controls, withVM in the acute period, 14 days after the acute period and children with GBS before, during and after ischemia (M ± σ)

Stages test	Controls (n=26)	VM acute period (n=16)	VM 14 days after the acute period (n=11)	GBS (n=11)
Before ischemia	59.9±3.7	57.9±3.9	59.3±2.7	47.5±6.9
2 minute of ischemia	58.5±4.0*	56.3±3.8*	57.9±2.4*	46.9±6.4*
5 minute of ischemia	56.9±3.7*	55.8±3.4*	56.9±1.9*	46.7±6.6*
10 minute of ischemia	54.8±3.2*	54.4±3.9*	54.1±2.1*	45.4±6.7*
1 minute after ischemia	57.3±3.5†	56.4±3.4†	57.7±2.2†	45.6±7.5
5 minute after ischemia	58.4±3.4†	57.2±3.8†	58.0±1.8†	46.5±7.1
10 minute after ischemia	58.7±3.6†	57.7±4.5†	58.5±2.0†	46.9±7.5†

*Significant decrease MNCV in relation to baseline values (p<0.05).

†Significant increase MNCV in relation to 10 minute of ischemia (p<0.05).

Table 2. Percentage MNCV in controls, with VM in the acute period, 14 days after the acute period and children with GBS before, during and after ischemia (M ± σ)

| Stages test	Controls (n=26)	VM acute period (n=16)	VM 14 days after the acute period (n=11)	GBS (n=11)	VM acute period vs controls	VM 14 days after the acute period vs controls	GBS vs controls
2 minute of ischemia	2.4±1.9	2.8±2.6	2.4±2.4	1.0±1.6	NS*	NS	NS
5 minute of ischemia	5.0±1.9	3.6±2.8	3.9±2.5	1.6±1.4	NS	NS	p<0.0001
10 minute of ischemia	8.5±1.9	6.1±3.2	8.7±3.2	4.3±0.9	p<0.05	NS	p<0.00001
1 minute after ischemia	4.3±2.4	2.5±3.4	2.7±2.4	4.0±5.1	p<0.05	NS	NS
5 minute after ischemia	2.6±2.3	1.3±3.7	2.2±2.2	2.1±4.4	NS	NS	NS
10 minute after ischemia	1.9±2.2	0.4±2.9	1.3±3.1	1.3±4.4	NS	NS	NS

*NS – not significant
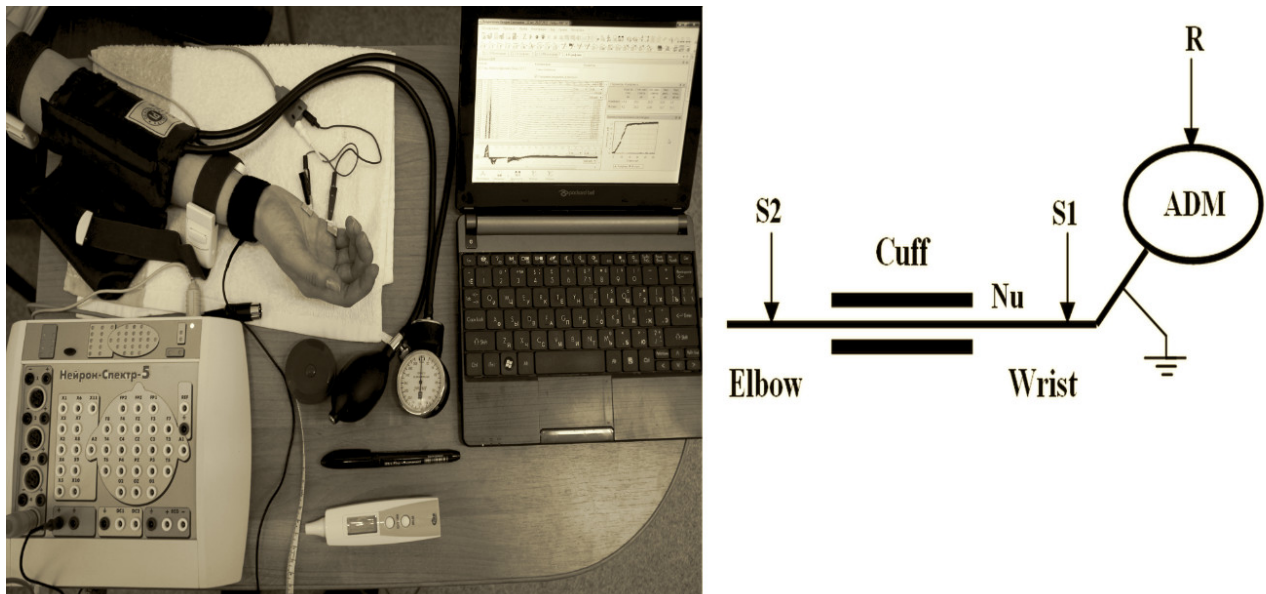
Fig. 1. Left: the location of the electrodes and the sphygmomanometer cuff on the forearm. Right: schematic position stimulating electrodes and a pneumatic cuff. S - stimulating electrode, R - recording electrodes, Nu - ulnar nerve, ADM - m. abductor digiti minimi.
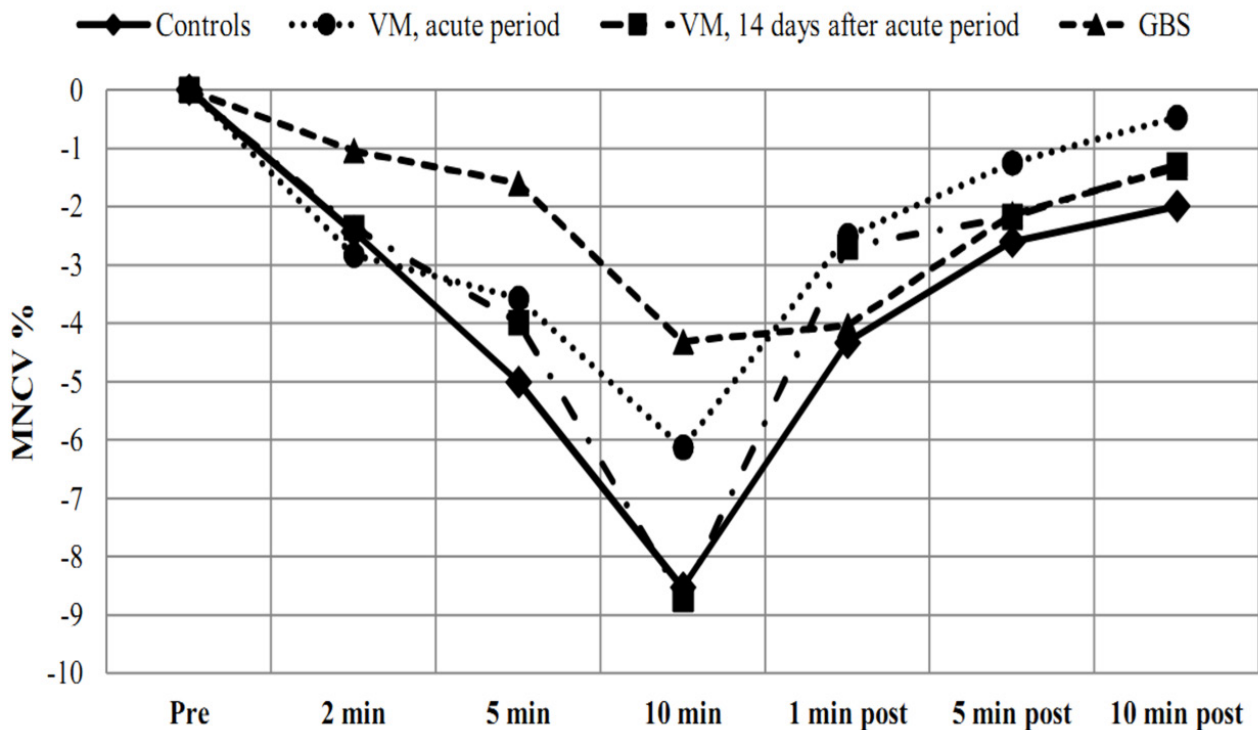

Fig. 2. Mean values of the percentage MNCV in controls children (n = 26), in children with GBS catamnesis (n = 11), in children in the acute period VM (n = 16) and in children 14 days after the acute period of VM during and after ischemia.