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Is Very Early Mobilization after Stroke Effective?

Although early mobilization after stroke is believed to be effective, there have been no controlled studies until now. Bernhardt et al. (1) tried to clarify this situation in their study published in Lancet Neurology in April 2005. Patients from 54 stroke centers in 5 countries were randomized into 2 groups; patients who took standard care, and patients who were mobilized very early after stroke. Of 2104 stroke patients, 1.054 were mobilized within 24 hours and 1.050 were given standard care. The primary end point was the number of patients whose modified Rankin scores at 3 months were 0-2. The mobilization procedure involved sitting, standing or walking activities at least 4 times within 24 hours after stroke. Dosages of activities were arranged according to the patients' clinical condition.

Interestingly, improvement rates were lower in the very early mobilized group compared with the standard care group (46% in very early mobilized group and 50% in standard care group; p=0.004.) Times to free walking were not different between the 2 groups. The mortality rate was 8% in the very early mobilized group, whereas it was 7% in the standard care group at 3 months after stroke.

This was the largest controlled study on acute stroke rehabilitation. Twenty-two of 30 stroke care guidelines recommend very early mobilization without describing specific protocols. This study showed intense mobilization in 24 hours after stroke did not have better results than standard care. However, standard care is complex and may sometimes be given very early; therefore, only recommending standard care to patients would be a simple approach. Although studies on rats showed that early and intense mobilization increased brain damage, new studies and meta-analyses suggested that earlier mobilization could result in better outcomes.

Two questions arise at this point; When do we have to start rehabilitation after acute stroke?, What is the extent of rehabilitation? Future studies can change the concept of stroke rehabilitation by answering these questions.

Reference

1. AVERT Trial Collaboration group, Bernhardt J, Langhorne P, Lindley RI, Thrift AG, Ellery F, Collier J, Churilov L, Moodie M, Dewey H, Donnan G. Efficacy and safety of very early mobilization within 24 h of stroke onset (AVERT): a randomized controlled trial. Lancet 2015;386:46-55.

Does Central Nervous System have a Lymphatic Circulation?

Weed (1) first showed in 1914 that cellular waste and metabolites leak from the interstitial space to cerebrospinal fluid (CSF) and are absorbed by arachnoid villi and enter the systemic blood circulation. This model attributes an "excretion system" feature to CSF and still stands today. In this model, CSF in the subarachnoid space is absorbed by arachnoid granulations and enters dural sinuses. Also, CSF enters peripheral lymphatic vessels of the nasal mucosa and cervical region via perineural spaces of cranial nerves (2).

However, according to recent findings, the central nervous system (CNS) may have an independent lymphatic circulation. In two studies, presence of vessels associated with dural sinuses were shown that did not take intravenous markers and had specific lymphatic endothelial markers LYVE1, PROX1, and VEGRF3. Moreover, markers applied to the CSF and interstitial space were shown to reach these vessels in these studies (3,4).

CSF enters the parenchyma from the subarachnoid space via the periarterial space, moves with arterial pulsation, enters the interstitial space via astroglial water channels called "aquaporin-4", diffuses and moves to the nearby perivenous space and lymphatic vessels related with dural sinuses, and finally drains to the cervical lymphatic nodes. This pathway is called the "glymphatic system"

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because it contains astroglial cells, which play important roles (2).

However, this model has a problem: If this pathway terminates in cervical lymphatic nodes, meningitis or other CNS infections should cause cervical lymphadenopathy, but they do not. Interestingly, when these cervical lymph node-draining lymphatic vessels are tightened, dural lymphatic vessels expand and T lymphocytes accumulate in these regions.

At this point, the major function of this alternative pathway is not clear. Antigens and immune cells of CNS, which were previously thought to be immune-privileged, are now thought to easily enter the systemic circulation. This situation might lead us to data that could change our understanding of the immunopathogenesis of chronic inflammatory diseases.

References

1. Weed LH. Studies on cerebro-spinal fluid. No. III: The pathways of escape from the subarachnoid spaces with particular reference to the arachnoid villi. J Med Res 1914;31:51-91.
2. Iliff JJ, Goldman SA, Nedergaard M. Implications of the discovery of brain lymphatic pathways. Lancet Neurol 2015;14:977-979.
3. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J. Structural and functional features of central nervous system lymphatic vessels. Nature 2015;523:337-341.
4. Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, Wiig H, Alitalo K. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med 2015;212:991-999.

Do Anti-Agrin Autoantibodies have a Role on Myasthenia Gravis?

Eighty percent of patients with myasthenia gravis (MG) have antibodies against acetylcholine receptors (anti-AChR). Furthermore, antibodies that do not directly target receptors but proteins (muscle-specific kinase; MuSK), which contribute to the aggregation of receptors on neuromuscular junctions also cause MG. Anti-MuSK antibodies are responsible for MG in half of all patients who are seronegative for anti-AChR antibodies. Also, lipoprotein receptor-related protein 4 (LRP4), which functions similar to MuSK, has recently been suggested as a potential target.

Gasperi et al. (1) studied the role of antibodies against extracellular matrix protein called "agrin" in MG, which is the ligand of LPR4 and plays an important role in aggregation of AChR by activating MuSK, in their study published in Neurology in June 2014. Mutations in the ARGN gene, which encodes agrin in humans and rats, cause congenital myasthenic syndrome by impairing neuromuscular transmission.

Investigators used serum samples of 15 anti-MuSK and 9 anti-AChR antibody-positive patients and 30 patients with seronegative generalized MG. The authors investigated mini-agrin antibodies using enzyme-linked immunosorbent assay (ELISA) and staining of neuromuscular junctions of HEK293 and mature mice cells transfected with human mini-agrin with immunohistochemistry. Findings were compared with serum samples of 16 healthy subjects. They found anti-LPR4 antibodies in 14 and anti-agrin antibodies in 5 patients' serum samples. Four of these 5 patients also had antibodies against MuSK and 2 of were also mildly seropositive for anti-LPR-4 antibodies. When the two groups were compared, seropositivity for anti-agrin antibodies reached a statistically significant value ($p<0.05$). There were no differences in levels of serum anti-agrin antibodies between the controls and seronegative patients.

Anti-agrin antibodies and serum samples from 3 patients, who were seropositive for anti-agrin antibodies, stained neuromuscular junctions of mice with different degrees and caused a cross reaction. The authors concluded that a small number of patients with MG had autoantibodies against natural agrin and these antibodies could have an important role in impairment of neuromuscular transmission in MG.

Anti-agrin used with ELISA is functional but it does not contain some epitopes of natural agrin; because of this, some anti-agrin positive serum samples can be missed. Five samples that were seropositive for anti-agrin antibodies also had antibodies against other neuromuscular junction proteins. The authors suggested that the togetherness of the antibodies could play an important role in explaining the clinical heterogeneity and severity of disease.

The pathogenetic effects of anti-agrin antibodies on muscle weakness in MG is not known. Nevertheless, these antibodies can occur against neoantigenic epitopes, which split from the neuromuscular junction instead of being de novo. Moreover, being measured at low titers and coexistence with other antibodies suggest that anti-agrin antibodies may not contribute to MG; however; agrin's important role in nerve transmission and in vitro effects demand larger case studies.

Reference

1. Gasperi C, Melms A, Schoser B, Zhang Y, Meltoranta J, Risson V, Schaeffer L, Schalke B, Kröger S. Anti-agrin autoantibodies in myasthenia gravis. Neurology 2014;82:1976-1983.

A New Treatment in Multiple Sclerosis: Daclizumab High Yield Process

Daclizumab, a humanized monoclonal antibody, binds to the alpha subunit (CD25) of the high-affinity receptor of interleukin 2 (IL-2) and cause IL-2 mediated transmission via moderate affinity receptors. The hypothesis that daclizumab can be effective in multiple sclerosis (MS) comes from studies that showed that CD25+ effector T cells played a key role in the pathogenesis of MS. These cells also showed immunologic effects by increasing the number of natural killer CD56+ cells and decreasing the number of lymphoid tissue-inducing cells. Daclizumab' s high yield process (HYP) causes less antibody-associated cytotoxicity than its first produced forms.

Kappos et al. (1) compared efficacies of daclizumab HYP and interferon beta-1a in the DECIDE study, which was published in the New England Journal of Medicine in 2015. One thousand eight hundred forty-one patients from 144 centers in 28 countries were included in the study. Patients were randomized into two groups. One group was given 150 mg Daclizumab HYP every 4 weeks subcutaneously and the other group was given 30 µg interferon beta-1a once per week intramuscularly.

The primary end point of the study was annualized relapse rates. The secondary end points were enlarged or newly occurring T2 lesions, increase in persistent disability rates, and Expanded Disability Status Scale (EDSS) points.

The patients included in the study were aged between 18-55 years, matched with McDonald 2005 criteria, had EDSS scores between 0-5,0, had 2 or more attacks during last 3 years, and had at least one of these attacks during last year.

Annualized relapse rates and enlarged or newly occurring T2 lesions significantly decreased in the daclizumab HYP group (0.22 vs. 0.39; 45% lower rate with daclizumab HYP; $p<0.001$ and 4.3 vs. 9.4; 54% lower number of lesions with daclizumab HYP; $p<0.001$). The number of contrast-enhancing lesions, T1 lesions, and percentage of annual brain parenchyma loss did not differ between the 2 groups. Infections, cutaneous events, and elevations in liver enzymes were more common in the daclizumab HYP group than in the interferon beta-1a group.

In summary, daclizumab HYP showed efficacy superior to that of interferon beta-1a administered intramuscularly at low dose, but adverse effects were more common. These should be considered before giving this treatment, which is expected to be licensed next year.

Reference

1. Kappos L, Wiendl H, Selmaj K, Arnold DL, Havrdova E, Boyko A, Kaufman M, Rose J, Greenberg S, Sweetser M, Riester K, O'Neill G, Elkins J. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med 2015;373:1418-1428.