

EDITORIAL

MANUAL LYMPH DRAINAGE FOR ALZHEIMER'S DEMENTIA: A CLINICAL TRIAL WHOSE TIME HAS COME?

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ABSTRACT

Mounting evidence implicates brain lymphatic drainage in the pathogenesis of Alzheimer's disease and other dementias. Several recent basic and clinical science discoveries have suggested the impact of lymphatic therapy to stimulate lymph flow in the head and neck including improvement in cognition. Manual lymphatic drainage has potential as a simple inexpensive way to promote brain lymph drainage and is worthy of a well-designed clinical trial to evaluate its potential as a primary or adjunctive treatment of Alzheimer's disease at this time.

Keywords: Brain lymph, Alzheimer's dementia, treatment, manual lymphatic drainage, MLD, massage, lymphogenic encephalopathy

As long ago as 1790, Cruikshank observed the connection between cervical lymphatics and the brain in his early discovery of meningeal lymphatics (1). He stated: "The glands of the neck swell in some diseases of the brain" (2). Indeed, centuries later, mounting evidence indeed points to the importance of brain lymphatic drainage in Alzheimer's disease and other dementias (3-5). The degree to which this impairment is a contributory cause of progressive disease and beta-amyloid accumu-

lation remains unclear.

A potentially impactful approach to the frustration with current costly and effective medical treatments of Alzheimer's Disease (6) would be a low-cost, non-invasive approach to promote brain lymphatic drainage. This treatment approach may be Manual Lymph Drainage (MLD) and investigation could provide evidence to determine how crucial lymphatic drainage impairment is in the dementia and whether its use as an adjunct treatment could modify progression.

In a related setting, impaired head and neck lymphatic drainage, for example, after radical cervical lymph node dissection for cancer or in congenital generalized lymphedema, is often associated with a clinical syndrome of impaired cognition, somnolence, and other signs of brain dysfunction, which Földi termed 'lymphogenic encephalopathy' (7). He also reproduced this syndrome in experimental animals by ligating the cervical lymphatic system.

Clinically, the mainstay of treatment for head and neck lymphedema is MLD (8-10). This a light directed massage covering not only the site of the impaired lymphatics and nodes directly, but more generally the connected superficial lymphotomes (11). For head and neck lymphedema, this approach encompasses not just the entire head and neck, but the lymphotomes of the upper body and axilla.

Other forms of physical treatment for lymphedema, such as compression, is more challenging and less practical in the head and neck area (although there are devices designed to address this area). Therefore, MLD is a better option for lymph drainage above the neck, especially when considering it has been shown to be remarkably effective in reducing somnolence and headache. Also, MLD specifically for head and neck has instructions available on self-help websites as procedures which can be performed by patients or family caregivers (12). Finally, MLD can be effective alone in early limb lymphedema, which has also been seen in a rodent model of chronic hindlimb lymphedema (13).

Recently Jin, et al (14) have also used mechanical massage of facial and cervical lymphatics to increase lymph flow. They designed a special device with variable levels of mechanical force. Its use did not impair lymphatic vessel contractility which have vigorous activity in normal mice (15). When sessions of applied mechanical message were used on an anesthetized aged prox-1 reporter mice, lymphatic flow could be restored to levels found in younger mice (14). While a solid proof of the utility of facial and cervical massage for increasing lymphatic flow, it was performed on anesthetized mice and this would not likely be the same for use in clinical practice.

The publication by Bartlett, et al (16) brings a more practical approach and demonstrates its utility in an unanesthetized Alzheimer's disease mouse model. Using the 5XFAD mouse model, they demonstrated that two months of twice daily MLD of the head and neck resulted in improved cognitive and motor functions, as measured by spontaneous alternation in the Y-maze and nest building tests. In addition, MLD resulted in both decreased plasma levels of neurofilament light chain and a decrease in the A β 42/A β 40 ratio of hippocampal extracts. Moreover, anecdotal reports by physical therapists suggest that MLD alone has produced improvement in cognition, mood, appetite, and sleep in patients with Alzheimer's disease (17).

In this issue, Chen et al. (18) describe improvements in facial edema, relief of

oropharyngeal symptoms, and improvement in cognitive function in their patients who have been treated for lower-limb lymphedema. Whether this improvement is a direct result of the peripheral lymphaticovenular anastomosis alone or a result of the continued pre-operative conservative lymphedema therapy regimen or a combination of the two is an area for further study. It is intriguing to consider if lymphatic treatment (including with MLD) in one area of the body can stimulate lymphatic flow in other areas in a systemic effect and perhaps this effect produced the cognitive results seen in their two patients.

Fortunately, there is a good availability of MLD, and therapists trained in head and neck therapy. Although there are some reasonable precautions that have been cited for its use in the elderly head and neck, considering it is a very light technique that has not shown no complications may allow its further use in this area.

The limited evidence so far in experimental models, MLD trails improving cognition, mood, appetite, and sleep in patients with Alzheimer's, and the anecdotal potential systemic findings in the case report may indicate that it is appropriate to launch clinical trials in patients with Alzheimer's Disease at different stages of the dementia to follow behavioral tests and potential mechanisms (lymph flow, biomarker fibrillar protein, etc.) (19). Continued basic research should also look at the combined influence of lymphatic dysfunction on the Alzheimer's mice in an attempt to detail some potential mechanisms which may help explain these results as well as in animal models of other dementias such as Parkinson's Disease.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare no financial conflict of interest exist.

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