Lymphology 29 (1996) 10-14

LYMPHSPIRATION

THE BRAIN AND THE LYMPHATIC SYSTEM (II) *

M. Földi

Földiklinik, Hinterzarten, Germany

PART TWO: Morphologic Effects of Cervical Lymphatic Blockade

By careful experimental surgical blockage of the cervical lymphatics, one can bring about a subtotal obliteration of the "hemangiolymphatic" drainage pathway — the term subtotal is used because the intraadventitial spaces (channels) located in the wall of the vertebral and subclavian arteries remain intact. Moreover, although the intracranial portion of the "perineurolymphatic" drainage system is effectively blocked, the spinal component remains open. After cervical blockade, the following morphologic alterations occur (1-12). In the brain, there is overt edema (volume increase, herniation into the cisternae, dilatation of the ventricles). Microscopically there is intracellular edema of the astrocytes, nerve cells, pericytes and tanycytes (modified ependymal cells which function to transport molecules between the SAS and CIF). Myelin displays swelling and fragmentation. The leptomeninges demonstrate edema of the trabeculae while the chorioid plexus shows a decrease in the granular endoplasmic reticulum, the appearance of fat droplets and an increase in the electron density of epithelial cells. Blood vessels show lymphostatic hemangiopathy with OTAN positive granules (marker for cholesterol, cholesterol esters and phospholipids) in the adventitia and finally fibrosis. There is also exophthalmus, orbital, retinal and papillary edema, and swelling of the optic nerve whereas the cervical nerves demonstrate edema in the peri- and endoneurium as well as degeneration of myelin.

Our group also found a statistically significant increase in the total volume of the brain but without a percentage increase in its water content (8). Whereas Bradbury and Cserr (13) also failed to find a percentage increase in water content, they did not examine changes in brain volume or histopathology. Our findings, however, have been corroborated by Csanda et al (14) and Magari (11). Morphologic and clinical improvement in brain function after experimental cervical lymphatic blockage was seen in animals after treatment with benzopyrones, pantothenic acid and pyridoxine (15).

Functional Effects After Subtotal Obliteration of the Cervical Lymphatic System in Experimental Animals (Low Output Failure)

The outward manifestations include apathy, decreased spontaneous motor activity, slower orientation reaction, decreased learning ability, unimpaired memory, decreased reaction time to painful stimuli, lower convulsion threshold, and decreased tolerance to barbiturates and

**Presented in part at the Fourth International Symposium on Lymphedema. Buenos Aires, Argentina, September 1994.*

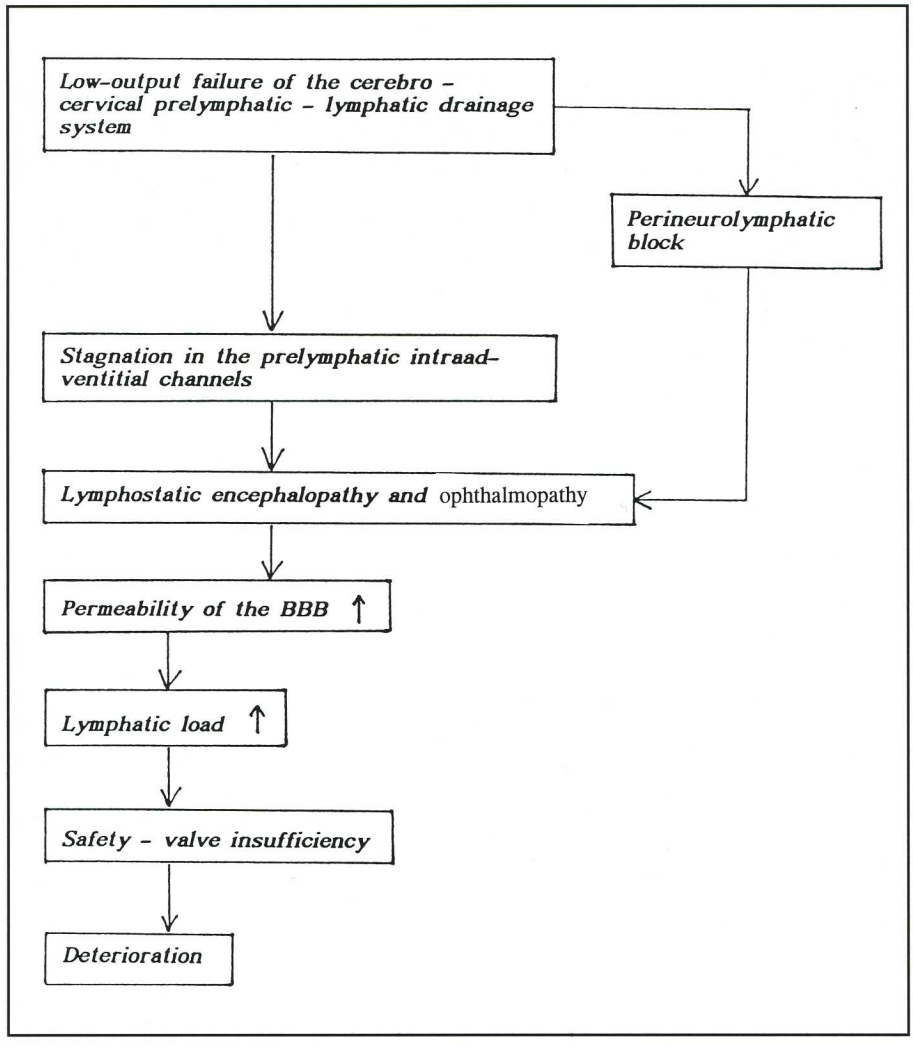

Fig. 1. Flow chart summarizing how mechanical insufficiency of the cerebro-cervical prelymphatic-lymphatic drainage system ultimately transforms into "safety-valve" insufficiency (see text).

harmine (an hallucinogenic alkaloid). There is also increased permeability of the blood brain barrier (BBB) while the electroencephalogram (EEG) demonstrates diffuse slowing or increased delta-theta wave activity.

The Cerebral Effects of "Safety Valve Insufficiency" of the Cervical Lymphatic System in Experimental Animals

Whereas low output failure of the lymphatics is characterized by a reduced lymphatic transport capacity and an inability to handle the normal lymphatic load, a much more severe form of lymphatic failure termed "safety valve insufficiency," arises when a decreased lymphatic transport capacity is combined with an increased blood capillary permeability or filtration rate; that is, an increased lymphatic load. Because low output failure of the cervical lymphatic system promotes a breakdown in the ability of the normally restrictive BBB, an increased number of plasma protein molecules pass into the cerebral interstitital space (CIS). With stagnation of these protein molecules, brain structure is altered with a gradual degradation of myelin (1). Myelin breakdown, in

turn, further produces a fat overload on the already compromised lymphatic transport capacity. Accordingly, reduction in the transport capacity of lymphatics draining the brain triggers a vicious circle with progressive cerebral deterioration *(Fig. 1)*.

Our group (16,17) and Csanda et al (18) have demonstrated that if one produces brain edema by combining an increased lymphatic load (uremia, cold injury, triethylene poisoning) with surgical blockage of the cervical lymphatics, a particularly severe form of brain edema and dysfunction ensues.

Similarly, with an experimental brain tumor, the hemangiolymphatic intraadventitial pathways are occluded and markers injected into the brain are no longer detectable either in these pathways or in the cervical lymph nodes (19). This dual effect of safety valve insufficiency occurs as the brain tumor with a breakdown in the BBB favors edema but concomitantly lymphatic drainage is compromised.

Lymphostatic Encephalopathy and Ophthalmopathy

Lymphostatic encephalopathy and ophthalmopathy in patients arises in combination with either primary or secondary lymphedema of the head and neck. For example, Vaillant et al (20) reported a case history of a ten year old boy with primary lymphedema of the arms, legs, genitalia, and head and neck. An EEG showed paroxysmal, hypersynchronous activity characterized by 2-4 sec intervals and sporadic generalized bilateral, symmetrical, high amplitude (100-200 mV) delta-theta waves. Secondary lymphedema also occurs after bilateral radical neck dissection or by malignant blockage of the cervical lymphatics. As Taillens points out (21) *"Whereas blockage of cervical venous circulation develops without complication, lymphatic blockage is not tolerated. A widespread carcinomatous lymphangitis which has caused blockage of the lymphatic outflow [leads] to progressive edema of the face, the orbit, the eyelid, the neck, the tongue, the brain and exophthalmus."* Similarly, Hollo reported severe lymphedema of the head and neck after bilateral neck dissection. The intraocular pressure rose to 35 mmHg and aqueous humor outflow became markedly restricted (22). Coexistent lymphatic blockade probably also explains why superior vena caval obstruction (but not isolated inferior vena caval ligation where lymphatic drainage is uninterrupted) with both cervical venous and lymphatic inflow blockage promotes severe facial suffusion and orbital edema (hyphema).

Another form of lymphostatic encephalopathy and ophthalmopathy is described in children in whom chronic intercurrent inflammation of the upper respiratory tract leads to chronic cervical lymphadenitis. The term "aprosexia nasalis" has been applied to explain the inattention, hearing deficit and chronic catarrh of the nose characteristic of these children.

Symptoms of lymphostatic encephalopathy and ophthalmopathy in patients are similar to those described in experimental animals with cervical lymphatic blockade. Indeed, we have provided evidence that breathing exercises in conjunction with manual lymphedema treatment of the head and neck alleviates retinal edema in this condition (23). Pseudotumor cerebri and communicating hydrocephalus are other poorly understood phenomena, which may be linked to an impaired lymphatic drainage system in the brain (24). Of related interest, acute whiplash injuries may be associated with disruption of the BBB and the symptoms and EEG changes that ensue bear a striking similarity to those of lymphostatic encephalopathy (25-27).

CONCLUSION AND OUTLOOK:

Eighteen years ago in examining these issues, I wrote the following (28) which is as valid today as it was then. "Our papers on the prelymphatic-lymphatic drainage of the

brain and on lymphostatic encephalopathy have only found a minimal resonance until now. According to Stent (29), data that cannot be transformed into a structure congruent with canonical knowledge are a dead end. That is, they remain meaningless until a way be shown to transform them into a structure that is congruent with the canon." Perhaps this annotation [discourse] will help to give the necessary insight into the viewpoints of lymphology and convince both physiologists and clinicians that the time is ripe to dispose of some cherished dogmata and accept the reality that without taking lymphatic drainage of the brain into consideration, understanding and analysis which concern both normal function and states of disease must remain incomplete.

REFERENCES

1. Földi, M: Lymphostatic ophthalmopathy. Lymphol 3 (1970), 135-139.
2. Varkonyi, T, J Polgar, ÖT Zoltan, et al: Lymphostatic retinal hemangiopathy. Exper. 26 (1970), 67-68.
3. Földi, M, E Csanda, ÖT Zoltan, et al: Oedema of the optic nerve and the retina as a consequence of experimental cervical lymphatic blockage. Angiol. 4 (1967), 341-347.
4. Csanda, E, M Földi, F Obal, et al: Cerebral oedema as a consequence of experimental cervical lymphatic blockage. Angiol. 5 (1968), 55-63.
5. Földi, M: Prelymphatic-lymphatic drainage of the brain. Am. Heart J. 93 (1977), 121-124.
6. Casley-Smith, JR, L Clodius, E Földi, et al: The effects of chronic cervical lymphostasis on regions drained by lymphatics and by prelymphatics. J. Pathol. 124 (1978), 13-17.
7. Földi, M, B Csillik, ÖT Zoltan: Lymphatic drainage of the brain. Experientia 24 (1968), 1283-1287.
8. Deak, I, S Sonkodi, E Börcsök, et al: Volumen und Wasseraviditätsbestimmungen im Gehirn bei der lymphogenen Enzephalopathie. Angio. 7 (1970), 117-126.
9. Magari, S: The effect of cervical lymph blockage in the central and peripheral nervous system. In: *Ergebnisse der Angiologie, Band 12*, F.K. Schattauer-Verlag, Stuttgart-New York, 1976.
10. Magari, S, Y Akashi, S Asano: Über die feinstruktuellen Veränderungen im Ependym des III. Ventrikels des Kaninchens bei experimenteller Blockade des zervikalen Lymphsystems. Acta. Anat. 85 (1973), 232-247.
11. Magari, S: The spinal cord and the lymphatic system. In: *Lymphangiology*. Földi, M, JR Casley-Smith (Eds.), Schattauer-Verlag, Stuttgart-New York, 1983.
12. Chengming, X, L Xingming, S Wki, et al: The effect of blocking the cervical lympha-tic drainage. In: *Progress in Lymphology XIV*, Witte, MH, CL Witte (Eds.), Lymphology 27(suppl) (1994), 742-746.
13. Bradbury, MWB, HF Cserr: Drainage of cerebral interstitial fluid and of cerebrospinal fluid into lymphatics. In: *Exper. Biol. of the Lymphatic Circulation*. Johnston, M (Ed.), Elsevier, Amsterdam, 1985.
14. Csanda, E, F Obal, F Obal, Jr: Central nervous system and lymphatic system. In: *Lymphangiology*. Földi, M, JR Casley-Smith (Eds.), Schattauer-Verlag, Stuttgart-New York, 1983.
15. Casley-Smith, JR, E Földi-Börcsök, M Földi: A fine structural demonstration that some benzopyrones act as vitamin P in the rat. Amer. J. Clin. Nutr. 28 (1975), 1242-1254.
16. Casley-Smith, JR, E Földi-Börcsök, M Földi: Fine structural aspects of the influence of lymphatic blockage on cold injury of the brain and skin, and the effects of Benzo-pyrones. Arzneim.-Forsch. 27 (1977), 367-378.
17. Casley-Smith, JR, E Földi-Börcsök, M Földi: Electron microscopy of the aggravating effect of vitamin B complex deficiency and of vitamin (factor) P deficiency on the conse-quences of lymphatic blockage: Benzo-pyrone therapy. Folia Angiol. 24 (1976), 248-254.
18. Csanda, E, S Komoly, O Major: The effect of lymphatic blockage of resolution of vasogenic brain edema. In: *Brain Edema*. Imaba, Y (Ed.), Springer, Berlin-Heidelberg, 1985.
19. Dubois-Ferriere, H: Les voies d'écoulement des liquides intracraniens. Ann. d'Anat. Path. 16 (1939-1940), 1081-1114.
20. Vaillant, L, F Baulien, E Gaisne, et al: Generalized primary lymphedema in a 10 year old boy with behavioured and sleep disturbances: A lymphostatic encephalo-pathy? In: *Progr. in Lymphol. 13, Excerpta. Med. Intern. Congr. Ser.* 994 (1912), 507-518.
21. Taillens, JP: Considerations sur les evide-ments jugulaires bilateraux. Acta. Oto-rhino-laryng. Belg. 12 (1958), 435-450.
22. Hollo, G: Bilateral intraocular pressure elevation and decrease of facility of aqueous hunor outflow as a consequence of regional lymphedema of head and neck. Acta.

Ophthalm. 71 (1993), 415-418.
23. Földi, E, M Földi, H Van Husen: Retinal edema in patients with generalized primary lymphedema. Lymphology 18 (1985), 82-83.
24. Földi, M: Pseudotumor cerebri. In: *Progress in Lymphology*, Thieme, Stuttgart, 1966, 266-268.
25. Domer, FR, YK Lin, KB Chandran, et al: Effect of hyperextension-hyperflexion (whiplash) on the function of the BBB. Exper. Neurol. 63 (1979), 304-310.
26. Fischer, O, H Palleske: Das EEG nach sog. Schleuderverletzung der Halswirbelsäule. Zbl. Neurochir. 37 (1976), 25-35.
27. Bühring, M: Reflexdystrophie nach sog. Schleudertrauma. Z. Orthop. 122 (1984), 281-286.
28. Földi, M: Prelymphatic-lymphatic drainage of the brain. Am. Heart J. 93 (1977), 121-124.
29. Stent, GH: Prematurity and uniqueness in scientific discovery. Sc. Am. 227 (1972), 84.

Prof. Prof. h.c. Michael Földi, M.D.
Földiklinik GmbH & Co. KG
Rößlehofweg 2-6
79856 Hinterzarten, GERMANY