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COMMENTARY

RELATIONSHIP BETWEEN CEREBROSPINAL FLUID AND EXTRACRANIAL LYMPH

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I read with great interest the *Commentary* by Földi (1) published in the June, 1999 issue of Lymphology about the anatomical relationships between brain parenchymal interstitial fluid, cerebrospinal fluid (CSF) and extracranial lymph. Much speculation dating back over 100 years has surrounded the relationships between these fluid compartments and yet the role of lymphatic vessels in CSF clearance has remained elusive and controversial. Since lymphatic vessels do not exist within the central nervous system (CNS), most neurophysiologists have assumed that the drainage of CSF occurs through specialized structures termed arachnoid villi and granulations.

It has always surprised me that, despite the considerable body of anatomical evidence referred to by Dr. Földi, most biomedical researchers remain unreceptive to the notion of CSF transport by extracranial lymphatics. This skepticism may be due to the paucity of convincing quantitative data. Bradbury's group (2) has made important contributions in this regard but several problems have hindered our understanding of the role of lymphatics in CSF clearance. First, the lymphatic vessels believed to drain CSF, collect lymph not only from the CNS but from many other tissues as well. This makes it difficult to obtain estimates of the total volumetric transport of CSF through these vessels. Second, the relative contribution of arachnoid villi and lymphatics to CSF absorption had never (until recently) been determined. Until this issue was resolved, it was difficult to put the role of lymphatics into perspective. Finally, the tracer recovery studies that have provided the best evidence for a CSF-lymph relationship have been problematic. A CSF protein tracer like albumin has at least 2 routes by which it can gain access to the plasma — arachnoid villi and extracranial lymphatics. This dual transport complicates tracer recovery data since the tracer that had transported into the plasma by the arachnoid villi route would filter back into the lymphatic compartment resulting in an overestimate of the lymphatic contribution to CSF clearance.

In the last few years, several new experimental strategies have been developed to address these issues. In sheep, it is possible to cannulate the lymphatic vessels that play a role in CSF transport (3). In order to determine the relative roles of arachnoid villi and lymphatics in the clearance of a CSF tracer (^{125}I or ^{131}I-human serum albumin), the CSF to plasma mass transport rate of the protein tracer was compared before and after lymph diversion/ligation in the same conscious sheep. With all lymphatic

pathways intact in the first phase of the experiment, the mass transport rate would represent total arachnoid villi plus lymphatic clearance. In the second phase of the experiment, the mass transport would represent only arachnoid villi drainage since lymph from the relevant lymphatics was not permitted to empty into the plasma. Before lymph diversion/ligation, the time averaged tracer transport into the plasma was 6.4 ± 1.0 %/hr with an average 6 hr plasma recovery of 38.2 ± 5.7% (percentage of injected dose). After lymph diversion/ligation, the values dropped to 2.9 ± 0.5 %/hr and 17.7 ± 2.7%, respectively. No significant differences were observed in sham-operated animals. From these experiments we concluded that extracranial lymphatic vessels in this species transported approximately one half of the protein tracer from the CSF compartment into plasma (4). A similar result in rats using essentially the same experimental protocol suggested that the important role for lymphatics in CSF transport we observed in sheep was not a species-specific phenomenon (5).

In collaboration with Dr. Flessner at the University of Rochester, a mathematical model was developed that permitted estimates of volumetric CSF absorption into lymphatics using tracer recovery data. An important element in the design of the model was the ability to correct the recovery data for errors introduced by filtration. To achieve this, mass balances were carried out around the plasma, the cervical lymph pathway and the thoracic duct and the resulting series of differential equations solved simultaneously to provide a method to calculate the rates of fluid transfer from experimental data. With the filtration factors accounted for, the data suggested that 40-48% of all CSF removed from the cranial compartment in adult sheep was cleared by lymphatics (6). Since we likely failed to identify some of the smaller cervical vessels, the proportional CSF clearance through lymphatics may be even higher.

Additionally, using a ventriculo-cisternal perfusion system to control CSF pressure in anesthetized sheep, we observed that elevations of intracranial pressure resulted in enhanced CSF clearance from the cranial vault not only through arachnoid villi but also through cervical lymphatic vessels (7). Cervical lymphatic pressure and the lymph flow rate increased as intracranial pressure was elevated with flows at 70 cm H2O intracranial pressure observed to be 4 fold higher than those at 10 cm H2O intracranial pressure (8). It was remarkable that ~77% of the total lymph in cervical vessels had its origins from CSF at the highest intracranial pressure tested.

The physiological and anatomical evidence suggests that the major route by which CSF gains access to extracranial lymph is by passage through the subarachnoid space through the cribriform plate into the nasal submucosa (2). Both Földi and Weller have suggested that CSF in humans may also transport through the adventitia of cerebral blood vessels leading ultimately to the internal carotid arteries with final absorption into the cervical lymphatics in the neck (discussed in 1). This is an interesting concept but it is necessary to design appropriate experiments to test the functional significance of this pathway.

In summary, it is evident that in some species at least, about one-half of volumetric CSF transport occurs through extracranial lymphatic vessels and that cervical lymphatics play an important role in venting CSF as intracranial pressures are elevated. Where do we go from here? The anatomical relationship between CSF and extracranial lymph continues to be an important issue. However, while anatomy can point the way, quantitative studies with functional outcomes will be required to convince the skeptical biomedical audience that lymphatics have a role in CSF transport. In this regard, it will be especially important to design experimental approaches that can be applied to humans. The circumstantial evidence seems to support a role for lymphatics in CSF clearance in man but clearly, much more

work has to be done to clarify the lymphatic contribution. One intriguing possibility arises from a consideration of prenatal CSF mechanics. There is some suggestion in humans that arachnoid villi may not exist or exist in small numbers in the fetus. Perhaps extracranial lymphatic vessels provide the dominant pathway for CSF clearance before birth, an hypothesis we are investigating currently (9). If this is the case, we would have to rethink the concept of pediatric hydrocephalus with the lymphatic circulatory system assuming an important position in the conceptual framework that drives research in this area.

It seems a lesson in irony that lymphatic vessels may turn out to be extremely important in defining CSF dynamics in health and disease even in an organ system in which these vessels do not exist. The confluence of anatomical studies and physiological experimentation would seem to have provided us with an intriguing and fruitful area for future investigation.

REFERENCES

1. Földi, M: The brain and the lymphatic system revisited. Lymphology 32 (1999), 40-44.
2. Bradbury, MWB, HF Cserr: Drainage of cerebral interstitial fluid and of cerebrospinal fluid into lymphatics. In: *Experimental Biology of the Lymphatic Circulation 9.* Johnston, MG (Ed.), Elsevier, Amsterdam, 1985, pp. 355-394.
3. Boulton, M, A Young, JB Hay, et al: Drainage of CSF through lymphatic pathways and arachnoid villi in sheep: Measurement of ^{125}I-albumin clearance. Neuropathol. Appl. Neurobiol. 22 (1996), 325-333.
4. Boulton, M, M Flessner, P Armstrong, et al: Lymphatic drainage of the CNS: Effects of lymphatic diversion/ligation on CSF protein transport to plasma. Am. J. Physiol. 272 (1997), R1613-R1619.
5. Boulton, M, M Flessner, D Armstrong, et al: Relative contribution of arachnoid villi and extracranial lymphatics to the clearance of a CSF tracer in the rat. Am. J. Physiol. 276 (1999), R818-R823.
6. Boulton, M, M Flessner, D Armstrong, et al: Determination of volumetric cerebrospinal fluid absorption into extracranial lymphatics in sheep. Am. J. Physiol. 274 (1998), R88-R96.
7. Boulton, M, D Armstrong, MF Flessner, et al: Raised intracranial pressure increases CSF drainage through arachnoid villi and extracranial lymphatics. Am. J. Physiol. 275 (1998), R889-R896.
8. Silver, I, B Li, JP Szalai, et al: Relationship between intracranial pressure and cervical lymphatic pressure and flow in sheep. Am. J. Physiol. 277 (1999) (in press).
9. Johnston, M, M Boulton, M Flessner: Absorption of CSF from the cranial vault revisited: Do extracranial lymphatics play a role? Neuroscientist (In Press).

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