

MATTERS ARISING

Lymphatic vessels of the dura mater: a new discovery?Fabio Bucchieri,^{1,2} Felicia Farina,¹ Giovanni Zummo¹ and Francesco Cappello^{1,2}¹Human Anatomy Section, Department of Experimental Biomedicine and Clinical Neuroscience, University of Palermo, Palermo, Italy²Euro-Mediterranean Institute of Science and Technology, Palermo, Italy

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Dear Editor,

Two recent papers (Aspelund et al. 2015; Louveau et al. 2015) reported the presence in mice of lymphatics in the cerebral dura mater, the most external of the meningeal layers covering the brain. This datum was reported as a novel discovery in the fields of neuroanatomy and neuroimmunology. However, for the sake of clarity, we would like to highlight the following issues:

1. The presence of lymphatics in human dura mater has already been described by other authors: the first, to our knowledge, was Mascagni (1787) in his 'Vasorum lymphaticorum corporis humani historia et ichonographia' (Fig. 1). More recent reports (Lecco, 1953; Li et al. 1996) have also confirmed this historic observation.
2. The most recent studies (Aspelund et al. 2015; Louveau et al. 2015) did not confute the dogma that lymphatics in the central nervous system (CNS) do not exist. In fact, dura mater is not a component of the neuraxis but covers, along with the other meningeal layers, both the brain and the spinal cord.
3. The so-called blood–brain barrier (BBB) (an anatomical structure that, despite its name, is present in all parts of the neuraxis, with some small exceptions) prevents the formation of transudate (interstitial fluid) in the nervous tissue, thus preventing any change in the volume of these structures that would interfere with the functioning of the nervous cells; e.g. disruption of the BBB is the main cause of cere-

bral oedema, a very severe pathological condition. As transudate does not form in the CNS, it is not necessary to have any lymphatic vessel in this part of the human body.

4. In the two most recent papers (Aspelund et al. 2015; Louveau et al. 2015), the experiments were performed on mice. Lecco (1953) examined the dura mater of 30 human subjects and found lymphatics structures in four of them. Hence he concluded that these lymphatics probably developed in the dura mater of these subjects for functional reasons, independently of the age of the subjects.
5. Dural lymphatics, when present, can take part in the absorption of cerebrospinal fluid (CSF), produced by the choroid plexus, a dedicated region of the CNS cavities ('ventricles') covered by ependymal cells, which lack the BBB, and the formation of a transudate is a prerequisite for formation of this fluid. Lymphatic cells may migrate through the ependymal cell layer to the CSF, in turn reaching the dural lymphatics.

We agree with the authors of the two most recent studies (Aspelund et al. 2015; Louveau et al. 2015) who believe that a better knowledge of dural lymphatics can shed light on the circulation of lymphatic cells from the arachnoid liquid to the venous bloodstream; and, as these cells may be a hallmark of disease, such as neuroinflammatory or neurodegenerative pathologies, the study of these cells may open up new scenarios in the context of CNS disease pathogenesis, early diagnosis, follow up and therapy. We would also like to thank the authors of both papers (Aspelund et al. 2015; Louveau et al. 2015) for having directed their attention to a sometimes forgotten chapter of human anatomy. However, in our opinion, their work has not resulted in a new discovery, nor can they claim that these lymphatics are present in the entire central nervous system, but only in its covering layers. We would like to make these observations known for the benefit of our students and colleagues.

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PARS PRIMA SECTIO VII.

63

ART. VI.

De lymphaticis profundis capitis, & colli.

Lymphatica profunda capitis dividi possunt in ea, quæ ex cerebro, ac in ea, quæ ex aliis partibus profundis capitis, & colli proficiunt. Hæc ut in aliis partibus vasa sanguinea sequuntur. Glutine absque colore post sanguineorum injectionem replentur, & tunc optime conspiciuntur. In truncos majores facilè tubulus introducitur.

Quæ ex musculo temporali, ex parte interna ac externa masseteris, ex pterygoideis, ex maxillæ foramine inter processum coronoideum, ac condyloideum locato, & ex canali infraorbitario adveniunt in glandulas post, ac infra parotidem, & ad divisionem jugularis internæ positas commeant. Ea quæ ex narium cavitatibus derivant numerosissimis furculis ex omni membranæ pituitariæ ambitu, ac ex ipsius folliculis glandulosis nascuntur. Hi in trunculos rediguntur, qui cum vasis sanguineis per eosdem canales, ac per eadem foramina egrediuntur, eorumque decursum legunt. Interim dividuntur denuò, & aliqui cum superioribus in ramos conflunt, reliqui dumtaxat cum iisdem consociantur quousque vel in communes glandulas se immittant, vel iter introrsum paullisper desistant, ut ad glandulas tendant, quæ ad latus internum carotidis internæ resident propè ipsius ingressum in canalem caroticum. In has glandulas concurrunt pariter ii lymphaticorum trunci, qui ex palato, & ex parte superiore pharyngis proficiuntur.

Rami, qui ex linguæ superficie, ac substantia nascuntur, diversos formant truncos, quorum aliqui in ramos divisi ad duas glandulas juxta sanguineorum decursum positas, atque ex his ad glandulas circum divisionem jugularis interpositas producuntur, reliqui verò huc directè concurrunt.

Ex larynge, ex parte inferiore pharyngis, ac superiore glandulæ thyroideæ adeunt glandulas, quæ aut inter jugulares & glandulam thyroideam, aut supra jugulares jacent, vel directè, vel aliis prius trajectis glandulis, quæ cartilagini thyroidi, atque cricoidi accumbunt. Cætera ab ima glandulæ thyroideæ sede, vel coadunantur in glandulas tracheæ supernè accumbentes, ut cum iis consociantur, quæ ex pulmonibus, & ex glandula juguli huc adveniunt, ac dein truncis communibus sub jugularem internam in glandulas inferiores colli se immittant, vel directè antè aut ponè jugularem internam ad has glandulas tendunt.

Dura matris lymphatica sanguineorum decursum sequuntur, ac cum iis per foramen spinosum exeunt ex cranii cavitate, dein iis copulantur, quæ ex musculis pterygoideis promanant, ac glandulas petunt divisioni jugularis internæ appositas. Aliqui trunculi inter laminas duræ matris juxta sinum longitudinalem se demergunt. Dura meninge a cranio avulsa postquam lymphatica per injectionem coloratam in vasa sanguinea glutine absque colore intumescere, multi se offerunt trunculi, qui in externa ipsius superficie reserti apparent. Ex hoc autem conjiciendum puto eos immitti in cranii foramina ut per extimam ipsius superficiem egrediantur. Verum ut hæc vascula glutine absque colore replentur necesse est, ut sanguineorum injectio optime cedat, quod hic loci perardè evenire expertus sum. Attamen id quandoque mihi contigit ut horum truncos juxta arterias, ac venas meningæas oculo vitris adjuto usque ad foramina spinosa sequi potuerim, atque hinc in glandulas usque, quæ adjacent jugularis internæ divisioni.

Lymphatica in cerebri superficie simili modo glutine absque colore repleta vidi. Cum in cadaveribus sanguinis effusiones inveniebantur nonnumquam repleta conspexi vascula quædam, quæ ex nodulis, cursu aliisque qualitatibus ita lymphatica æmulabantur, ut, si quid longa docet experientia, ejusdem esse indolis vocare in dubium nequiverim. Sed exilissima hæc vascula maxima ex parte cum inter laminas duræ matris unà cum venis sanguineis se demergant juxta sinus longitudinalis ductum oculis tandem se subducunt. Idque iis evenit, quæ ex hemisphæris in cerebri basim reclinantur cum circa carotides coadunantur. Hæc autem tam excellunt tenuitate ut ipsa numquam injicere potuerim mercurio.

Sed injeci alia vascula satis ampla in arachnoide sita, quæ aut acre, aut glutine post

Fig. 1 This picture shows the reproduction of the first page of the chapter of the book 'Vasorum lymphaticorum corporis humani historia et ichnographia' in which Paolo Mascagni first described the presence of lymphatics in the cerebral dura mater. The arrow shows the incipit of the sentence in which Mascagni describes the course of these lymphatic vessels.

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