eISSN 1303-1775

Neuroanatomy (2023) 11: 2-6

Review Article

Are We on the Way to Solving the "Mystery" of the Human Massa Intermedia?

Published online 10 January, 2023 © http://www.neuroanatomy.org

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Received 20.10.2021; accepted 22.02.2022

ABSTRACT

This concise review summarizes almost all aspects of the current state of knowledge of the human Massa intermedia (Adhesio interthalamica) research. Different issues and controversies about the human Massa intermedia (MI) development, anatomy, neurons, connectivity, potential functions, pathology, imaging, and their unclear interrelationships are included. The relevant data about all of these aspects are presented in this review, and the main issue about the MI presence or absence is emphasized and discussed. Some additional arguments in favor of the functional organization of neurons within the human MI are also given. It becomes apparent that the presence or absence of human MI cannot be explained by a single, uniform or simple mechanism, and that there are several more or less distinct morphological forms, isolated or combined with other brain variations and abnormalities. Therefore, detailed morphological classification of the human MI (including its absence/presence) into subtypes is strongly required. Finally, this review also indicates some directions for further studies of the human MI. **© NEUROANATOMY. 2023; 11: 2–6 ⋆ QROI.org/SFMDL**

Key words [Massa Intermedia] [Absence] [Human Neuroanatomy] [Connectivity] [Functions]

Introduction

Specific part of the diencephalon, the Massa intermedia (MI), synonymous with Adhesio interthalamica [1], in majority of humans connects the medial surfaces of the left and right thalamus. If there is this brain structure, variable in the size and shape, it bridges the cavity of the third ventricle. However, MI is not so rarely absent in humans, and this neuroanatomical fact raises many questions, yet without adequate explanations. Although known for a long time [2], it is an understudied neuroanatomical structure [3]. For example, "bilateral thalamic masses are connected by MI, which is relatively poorly developed in humans" is the only mention of the MI in an excellent book about the human nervous system [4]. However, MI is naturally absent, its true prevalence during life is unknown [5], and the large data variability about its presence/absence is caused by differences in samples studied (age, sex, handedness, brain size, regional and ethnic origin). Variability in size and shape of the MI (and consequently in the number of neurons) is well-known to neurosurgeons, especially when dealing with endoscopic third ventriculostomy [6]. How this phenomenon, that one structure is present in many but not all human brains affect healthy people, or what specific anatomic role is related to its presence/absence, and its possible consequences [7] is not yet known.

Anatomy

There is a general lack of consensus on the MI *prevalence* in the healthy population. Understanding the true prevalence is critical in providing context for future studies, as well as uncovering further clues regarding its function [8]. The data about the MI absence in various samples vary in a wide range, from 4% [3], 8.7% [9]. 9.5% [10], 12.7% [5], 12.9% [7], 19.51% of cases (21.05% in males and 18.18% in females) [11], up to 22% of persons [12].

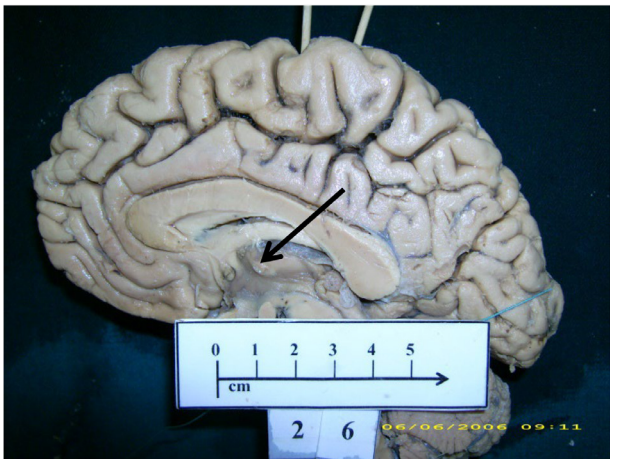

Figure 1. Midsagittal section of human brain with ovoid shaped section of massa intermedia (arrow).

Its absence increased and its size decreased with age [5]. The prevalence of the "complete" MI was higher in

females than in males [7], and its presence was most strongly predicted by sex, loneliness, and inhibition, while age, handedness, race, and ethnicity were not predictors of MI presence [13]. Unusually large MI might hinder cerebrospinal fluid flow in the third ventricle and lead to misdiagnosis by radiologists [14]. Additionally, MI can be duplicated in 2% - 3.03% of persons [11;12], no clinical significance appeared to be ascribable to its duplication [15], but as a rare abnormality may occur in patients with additional defects [16].

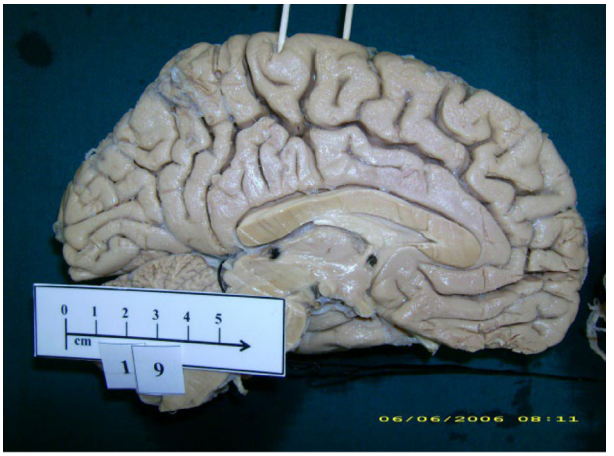

Figure 2. Midsagittal section of human brain without massa intermedia. (Black dots indicate anterior and posterior commissures).

Until the very end of the twentieth century, the MI was visible *in vivo* only by invasive radiological methods (pneumography or ventriculography) as a round or oval shadow, with variations at times so extensive as to simulate the tumor. The absent shadow corresponding to the MI was found in 16.9% of patients, MI was distinguished clearly in 75.9%, and presence of MI shadow with poorly defined borders was in 7.1% of patients [17]. Paradoxically, recent scientists using modern imaging [7] faced the same problem as authors [17] from fifty years ago, because they also were not always able to distinguish the MI [7]. Significantly more common was absence of the MI in males than in females, while significant age differences were in cases of MI absence (12.9%), and in the group with "complete" MI presence (32.9%). Finally, some cases (54.2%) were classified as "partial" MI because it was not possible to distinguish it in some slices [7].

Recent data

Recently, only 28 from 257 studies were included in the final review of the literature on the prevalence of MI. This review showed higher average MI prevalence than previously reported, and that the MRI studies rather than cadaveric reported higher rates of MI prevalence and among the females regardless of acquisition modality utilized [8]. Some data connect the size and presence of MI with age, so that in elder persons MI undergoes atrophy and may disappear [18]. Advanced ages presented decreased areas of sagittal sections [19] and decreased some of the MI diameters [9]. There was not significant relationship between the incidence of MI and gender, but MI was significantly larger in females (34.13 ± 11.57 mm^2), than in males (24.12 ± 11.34 mm^2) [11]. Other authors however, reported that females had 2.75 times higher likelihood of MI presence and MI size was best predicted by third ventricular width and age, mediating a larger MI with smaller third ventricular size and younger age [5]. The sex differences in size across the lifespan (larger female MI) were associated with the surrounding thalamic anatomy and neuropsychological functions, but without significant relationship between the incidence of MI and gender [3].

It is very probable that cadaveric samples generally originated from older subjects (related to brain atrophy) causing therefore the lower MI prevalence than *in vivo* imaging studies. The longitudinal studies are required to clarify possible speculations about potential "dynamic changes" of the MI during the life, because some data connect the size and presence of MI with age, so that in elder persons MI undergoes atrophy and may disappear [18]. However, this cannot be connected with the normal cases of, absent from birth, MI.

Developmental and comparative data

Generally, MI fuses during the 13th or 14th weeks of gestation (18) and its absence identifiable in very early years of life, suggests a congenital cause [5]. The name "adhesion" may lead someone to think that MI presence is the result of mechanical fusion of both the thalami. However, in brain regions where adjacent parts of the CNS are in contact, which otherwise are separated by liquor, after fusion a visible band of ependyma remains [20], which is not the case in human MI [21]. In rats ependyma disappeared with age by adhesion and fusion. Fusion appears as convergence of the two-cell-layer seam into a one-cell-layer seam, followed by disruption. At the sites of fusion fragmentary ependymal seams remained detectable (more than 50%) among the neuropil, even in adults [20]. We never could observe any trace of ependymal presence or strikes within the human MI which, as a whole, had subependymal features [22].

In any of the veterinary anatomy (even basic) and Zoology textbooks it is striking that in mammals (including marine mammals) the MI is always present, that is much larger than in humans, and that contains numerous nuclei. Frauchiger [23] questioned the significance of a huge MI and of incomplete separation of the thalami and suggested that failure of the thalami to separate mimicked the anatomy of chimpanzee and other inferior animals. He emphasized that "thalamoschisis" occurred only in humans and that the process of separation of the two thalami could be at the base of the superior organization of the human brain as compared to anthropoids [23]. Contrary to this, the absence of MI has been considered as well-established marker of (abnormal) neurodevelopment in midline structures such as the MI, but not consistently replicated in schizophrenia [10;24;25].

Neurons

The human MI contains the nucleus reuniens (medioventral nucleus) [1], and the parts of other

periventricular thalamic nuclei [26]. Terminology is confusing because human MI nuclei were labeled differently by different authors and in diverse mammals [26;27;28]. Since the analogy between the eponymous has not been confirmed for thalamic midline nuclei in animals and in humans, one must be very careful in extrapolating these to humans [27]. The question is what happens to the nucleus reuniens (medioventral nucleus) in the absence of MI [29], and some believe that just strong development of nucleus reuniens causes MI to develop [26]. The approximate number of neurons in the "average" human MI (3000 – 5000; Malobabić's unpublished study) is for example larger than in very important human nucleus ambiguus (left -1942 neurons; right -1836 neurons) [30]. The future is not too far away when the imaging methods will show the details in brain, such as neurons. Polymorphism of neurons in the adult human MI is present and rare detailed descriptions of the human MI neurons were based on the Nissl-stained material. By the Golgi impregnation in the adult human MI were shown the isodendritic type neurons (fusiform neurons-most characteristic, multipolar neurons and rare triangular neurons), as well as the neurons with oval perikaryon which do not belong to this type [31]. In the fusiform neurons were shown somatostatin, ghrelin, L-enkephalin, in triangular neurons neurotensin, in multipolar neurons neurotensin and L-enkephalin, and in the neurons with oval perikaryon somatosatin and L-enkephalin [22]. The specific circular organization of neurons found in frontal sections of human MI suggests its functional significance. Similar, but smaller circular groups of neurons were also present in the periventricular region of the thalamus. According to their actually subependymal location, to their size and form, these circular groups could represent *in vivo* correlates of neurospheres [32].

Connectivity and functions

Decussating and commissural fibers of the human MI connect some thalamic nuclei [28] and have wide ranging terminations, with a strong predilection for limbic structures [5;34]. Immunoreactivity for neuropeptide Y, substance P and adrenocorticotropic hormone was present only in the fibers and not in the neurons of human MI [22]. Tractography showed in the MI fibers of the stria medullaris [33] and extensive connections between MI and limbic, frontal and temporal lobes, as well as the insula and pericalcarine cortices, with stronger connectivity in women via their MI [34]. This supported the role of MI as a midline commissure with strong connectivity to the amygdala, hippocampus, and entorhinal cortex [34]. Controversies are present about the functional significance of MI, and its absence has been linked to cognitive differences and psychiatric disorders [5;34]. The MI size statistically mediated the relationship between age and attention among females [3]. Brains with absent MI were associated with lower gray matter volume in the premotor cortex, inferior frontal gyrus, and anterior temporal cortex. This may be related to the proximity of the MI to medial thalamic nuclei connected to these cortical areas and MI may be functionally related to emotional and cognitive control processes [7]. Subjects with the MI (56%) had more developed complex simultaneous processing (ability of spatial visualization in particular), and subjects without the MI (44%) had more developed simple perceptive processing (ability of perceptual identification and synthesis) [35]. The non-systematic results of less developed non-verbal ability in males with MI, and of no difference in female subjects [36] could be explained by the fact that the non-verbal ability is actually composed of the spatial and perceptual ability which stand in opposite functional relation to the presence of the MI [35].

Clinical evidence

In mesial temporal epilepsy patients, the absence of the MI was linked to lower scores on verbal memory and executive function tests [37]. A neglected structure of possible relevance for complete failure of callosotomy in some patients is the thalamic commissure in the MI. It would be of interest to know, whether it is the patients with a large diameter MI who do badly after callosotomy [38]. Males without the MI die earlier than males with MI, but such a finding has not been reported for females, the MI was absent in 31.7% of predominantly psychiatric patients [26] and its absence has been linked to cognitive differences and psychiatric disorders [5;34]. Later by MRI were repeated findings of absent or reduced MI in association with neuropsychiatric disorders. The first-episode psychosis patients with a history of cannabis use had a significantly lower prevalence of absent MI than first-episode psychosis subjects without a history of cannabis use, and significantly shorter MI than controls [25]. Well-established marker of abnormal neurodevelopment in midline structures such as (absence of) MI has been implicated in schizophrenia, while its genetic mechanism is unknown [9;24]. The MI absence in about twice more schizophrenia patients than in healthy controls was not statistically significant, but residual subtype of schizophrenia was associated with higher rate of MI absence [39]. Significant difference was in absence of MI in schizophrenia patients (24.2%) and in controls (9.5%), with shorter MI in patients, and in males than in females [10]. However, even if volumetric thalamic abnormalities in schizophrenia in concordant twins may mark the substantial genetic contribution to the illness, the MI is unlikely to be affected in schizophrenia [40]. Also, the subjects with high-risk genotypic combination of dopamine D3 receptor and of brain-derived neurotrophic factor had a shorter MI than those without MI in the healthy controls, but not in the schizophrenia patients, what does not support its specific role in the pathogenesis of schizophrenia [24]. Between the patients of Alzheimer's disease and controls, there were not differences in prevalence (79%) and size of the MI [19].

Conclusion

It is still not known how the absence of MI in many human brains affects healthy people [7], but its presence/absence, and variations in its size and shape, could be a marker of differences between human brains [22].

Therefore, its morphological variations, including its size and shape, should be further more used in various diagnostic classifications. The functional significance of MI remains largely unknown and its role is poorly understood in humans [34]. Even without resolving the question whether the MI is a vestigial or functional structure, its presence or absence could be a marker for other, genetic or functional differences between the human brains [32].

After all, we can conclude that all kinds of presence/absence MI are not caused by the same fundamental mechanism. Beside obvious diseases, genetic and developmental types, the changes of size of the MI and whatsoever, its absence/presence, can be in unknown percentage related to the aging processes. However, is still unknown the meaning of absence/presence of the MI in generally normal people. It appears necessary to differentiate potential various types of absence/presence of the MI in humans, what should include longitudinal studies. Therefore, much more investigations are required to elucidate the "mystery" of the human MI, and after recent beginning steps we still have a long way to go to clarify the multiple aspects of the MI morphology and functions.

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