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Original Article

Area Postrema: Fetal Maturation, Tumors, Vomiting Center, Growth, Role in Neuromyelitis Optica

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ABSTRACT

Introduction: The area postrema in the caudal fourth ventricular floor is highly vascular without blood-brain or blood-cerebrospinal fluid barrier. In addition to its function as vomiting center, several others are part of the circumventricular organs for vasomotor/angiotensin II regulation, role in neuromyelitis optica related to aquaporin-4, and somatic growth and appetite regulation. Functions are immature at birth. The purpose was to demonstrate neuronal, synaptic, glial, or ependymal maturation in the area postrema of normal fetuses. We describe three area postrema tumors.
Methods: Sections of caudal fourth ventricle of 12 normal human fetal brains at autopsy aged six to 40 weeks and three infants aged three to 18 months were examined. Immunocytochemical neuronal and glial markers were applied to paraffin sections. Two infants with area postrema tumors and another with neurocutaneous melanocytosis and pernicious vomiting also studied.
Results: Area postrema neurons exhibited cytologic maturity and synaptic circuitry by 14 weeks'. Astrocytes coexpressed vimentin, glial fibrillary acidic protein, and S-100β protein. The ependyma is thin over area postrema, with fetal ependymocytic basal processes. A glial layer separates area postrema from medullary tegmentum. Melanocytes infiltrated area postrema in the toddler with pernicious vomiting; two children had primary area postrema pilocytic astrocytomas.
Conclusions: Although area postrema is cytologically mature by 14 weeks, growth increases and functions mature during postnatal months. We recommend neuroimaging for patients with unexplained vomiting and that area postrema neuropathology includes synaptophysin and microtubule-associated protein-2 in patients with suspected dysfunction.

Introduction

The area postrema (AP) is a paired structure in the floor of the caudal part of the fourth ventricle, extending almost to the calamus scriptorius where the fourth ventricular ependyma passes ventrally into the midline parenchyma to become the spinal central canal rostral to the medullospinal junction. The obex is a small, thin transverse membrane that overlies the posterior angle of the rhomboid fossa (fetal fourth ventricular floor) and may persist postnatally, reaching almost to the AP. Macroscopically in humans the AP appears as a bilateral, gelatinous structure protruding into the caudal part of the fourth ventricle on either side of the obex.[1] Microscopically its two components are vascular, consisting mainly of sinusoidal fenestrated capillaries, which form a portal system,[2] and cellular, composed of flattened ependymal cells, small neurons, and glial cells.[3,4] No histologic differences are seen in the AP of the neonate and of the elderly adult.[5] The cellular composition of the AP is similar in all mammals,[6] but the histologic compartments of the structure are more evident in humans than in rodents.[7] The lack of tight junctions between endothelial cells and the fenestration of capillaries enables peptides and other physiologic signaling molecules in the blood to have direct access to AP

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neurons that project to the brainstem autonomic centers.[7] The subcellular ultrastructure of AP neurons was described in 1974.[8]

The AP may not be uniform throughout. Price et al. identified distinct compartmentalization of the AP by zones that differ in what is the predominant cell type (neurons versus glia) and where the neurons project.[7] A funiculus separans, lying just beneath the rostralmost extent of the nucleus gracilis and just above the dorsal motor nucleus of the vagus, contains a layer of tanycytes (secretory cells that have a prominent long basal process, best known in the hypothalamus) that functions much like the blood-brain barrier that separates the AP from the nucleus solitarius.[7]

Fetal maturation of the human AP, using immunocytochemical markers of neuronal maturation[9,10] may be relevant in neonatal neurological conditions, both congenital dysgeneses and acquired hypoxic, endocrine, and metabolic disorders, as well as in intracranial hypertension. The application of some immunoreactivities related to blood-brain barrier function was reported in the AP of humans and dogs.[6] In the mouse, only after postnatal day seven there is increase in the volume and elaboration of synaptic input from *Phox2b*-derived neurons from brainstem autonomic nuclei, with a physiologic delay in maturation during the first postnatal week.[11] AP neurons are intensely reactive for dopamine-β-hydroxylase, the rate-limiting enzyme for norepinephrine synthesis.[11] However, most markers of neuronal maturation used in human neuropathology were not applied in these studies except for the glycolytic enzyme neuron-specific enolase (NSE) and glial fibrillary acidic protein (GFAP). Growth and volume increase of the AP in the human fetus and postnatal infant exceeds the growth rate of the surrounding brainstem structures.[5,6,11]

Despite its relatively small size, the connections of the AP with other structures of the brainstem and hypothalamus are widespread, analogous to the locus coeruleus, another small brainstem nucleus with extensive multiple connections. Afferent projections to the AP are from the glossopharyngeal and vagal nuclei of the medulla oblongata, including the almost adjacent nucleus solitarius.[12] Efferent serotonergic axons extend into the nucleus solitarius and the parabrachial nucleus.[13–15] These targets are part of the network of brainstem respiratory control and also play a role in cardiovascular regulation[16] and fetal weight gain.[17,18] From the periphery, blood-borne molecules received by the AP are integrated with signals from a variety of visceral organs, which are carried to the AP by vagal afferents, including baroreceptor information from the carotid sinus and aorta, osmoreceptor information from the liver, and mechanical information via stretch receptors in the stomach and lung.[7]

Although traditionally described in humans only from postmortem neuropathological examinations of the brainstem, the AP can be readily identified intraoperatively during endoscopy or surgery of the fourth ventricle of organs, carried out by injecting fluorescein sodium into the fourth ventricular cerebrospinal fluid (CSF) where lack of a blood-brain barrier enables signals to show good contrast with the surrounding brainstem structures in the ventricular floor that do possess this barrier.[19] Neuroimaging of the AP offers a less invasive but more limited option in living patients, despite the low resolution owing to its small size and that of the brainstem of neonates and infants. However, post-contrast three-dimensional fluid-attenuated inversion recovery magnetic resonance imaging (MRI) can demonstrate the AP and other circumventricular organs in human subjects.[20]

Historical background and syntax

The AP was originally described and named in 1896 by the illustrious nineteenth century Swedish neuroanatomist Magus Gustaf Retzius in his textbook of human neuroanatomy,[21] which was the most important text of this type of his century.[22] In his classical textbook published in the early twentieth century, Ramón y Cajal did not seem to have recognized the distinctiveness of the AP and included it with the rather nondescript medullary reticular formation.[23] Postrema is the superlative Latin irregular adjective of *posterus*, which means last or hindmost. Although the AP is located in the caudal half of the medulla oblongata, it is not at the extreme posterior end or medullospinal junction but rather is at the posterior extreme of the fourth ventricle, hence the term is imprecise.[22] The AP is a well-defined structure in mammals and birds, is uncertain in reptiles, and is not evident in amphibians or fishes.[24]

Materials and methods

Transverse sections of 6 μm of the medulla oblongata at the level of the inferior olivary nuclei and AP were taken in neuropathological autopsy of 24 human fetuses ranging in gestational age from six to 40 weeks.*

Sections at the level of the AP also were examined at autopsy in a seven-month-old infant, an eight-year-old child, and a 14-year-old adolescent, none of whom had neuropathological findings in the brain and had died of non-neurological disease. Of the three fetal cases here illustrated, the normal 15-week fetus had acute placental abruption, the 19-week fetus had kyphoscoliosis and visceral anomalies (gastroschisis and externalization of the intestines, imperforate anus, hypoplastic external genitalia) but a normal brain without hydrocephalus, and the 38.5-week neonate was large for gestational age, had polyhydramnios and postpartum respiratory distress, and lived only a few hours despite intensive medical support.

Tumors of area postrema

Postmortem brain tissue of a male child who died at age three years due to neurocutaneous melanocytosis with extensive melanocytic infiltration along the entire neuraxis of the meninges and central nervous system parenchyma (i.e., malignant melanoma), including the AP, was also available for examination. This child had continuous pernicious vomiting for several weeks before death; details of the neuropathological examination of this case were previously described.[25]

In two infants, with nearly identical histories of protracted vomiting and failure to thrive, a tumor of the AP was diagnosed by neuroimaging at age nine months; MRI was similar in both. Onset of repeated mostly daily vomiting was at seven months, followed by numerous gastroenterological and other investigations, including gastroduodenoscopy. Persistent weight loss prompted imaging (Fig 6 illustrates one case). The tumor was mainly extra-axial and did not result in obstructive hydrocephalus; it was successfully subtotally resected. Histologic examination revealed pilocytic astrocytoma.

Histopathological preparation

Formalin-fixed tissue was embedded in paraffin, and transverse sections of 6 μm were cut. In addition to routine hematoxylin-eosin histologic stain and luxol fast blue myelin stain, immunoreactivities

* In Canada, elective termination of pregnancy is legal and is performed in hospital by professional medical staff. The usual reason is for life-threatening maternal disease; fetal genetic, infectious, or malformative conditions not compatible with extrauterine survival; anticipated poor quality of postnatal life; or occasionally for social circumstances (e.g., unplanned teenage pregnancy, victim of rape). In the province of Alberta, after 24 weeks' gestation therapeutic abortions must be approved by the Hospital Medical Ethics Committee. Undesired fetal gender and familial socioeconomics are not acceptable reasons.

were performed using antibodies against (1) neuronal nuclear antigen (NeuN), (2) microtubule-associated protein-2 (MAP2), (3) calretinin, (4) synaptophysin, (5) GFAP (polyclonal antibody), (6) S-100β protein, (7) vimentin, (8) nestin, and (9) CD-68 microglial marker. These tests were performed not only for cellular lineage but also to confirm neuronal maturation.[9,10] The melanocytosis case had HMB45, Melan-A, and S-100β protein applied. Technical details of the specific antibodies, source, animal in which they were produced (mouse; rabbit), dilutions, and incubation conditions of each of these immunoreactivities are provided in another recent publication.[26] Three representative normal fetal cases were selected to illustrate.

Results

The AP was first recognized at 10 weeks' gestation as a cell-sparse, loosely organized zone in the caudal floor of the fourth ventricle on either side. In fetuses of six and eight weeks, the region at the caudal floor of the fourth ventricle was not histologically distinctive enough to specifically denote its differentiation. By 14 weeks' gestation and throughout the rest of prenatal life and postnatally, the AP is well recognized histologically in transverse or parasagittal sections of the medulla oblongata. The most impressive histologic change in the AP from 14 gestational weeks to term is the increase in its size with growth disproportionate to the growth of other brainstem nuclei (Fig 1). It appears throughout fetal life and postnatally as a loose structure with less cellular density than the underlying medullary tegmentum, but this appearance is deceptive because of its high vascularity (Fig 1), as confirmed by the density of small neurons (see below).

Immunocytochemical reactivities demonstrated that in the mid second and third trimesters and postnatally, neurons and glial cells showed mature expression. Neuronal markers such as MAP2 and NSE in particular confirmed a high concentration of small neurons,

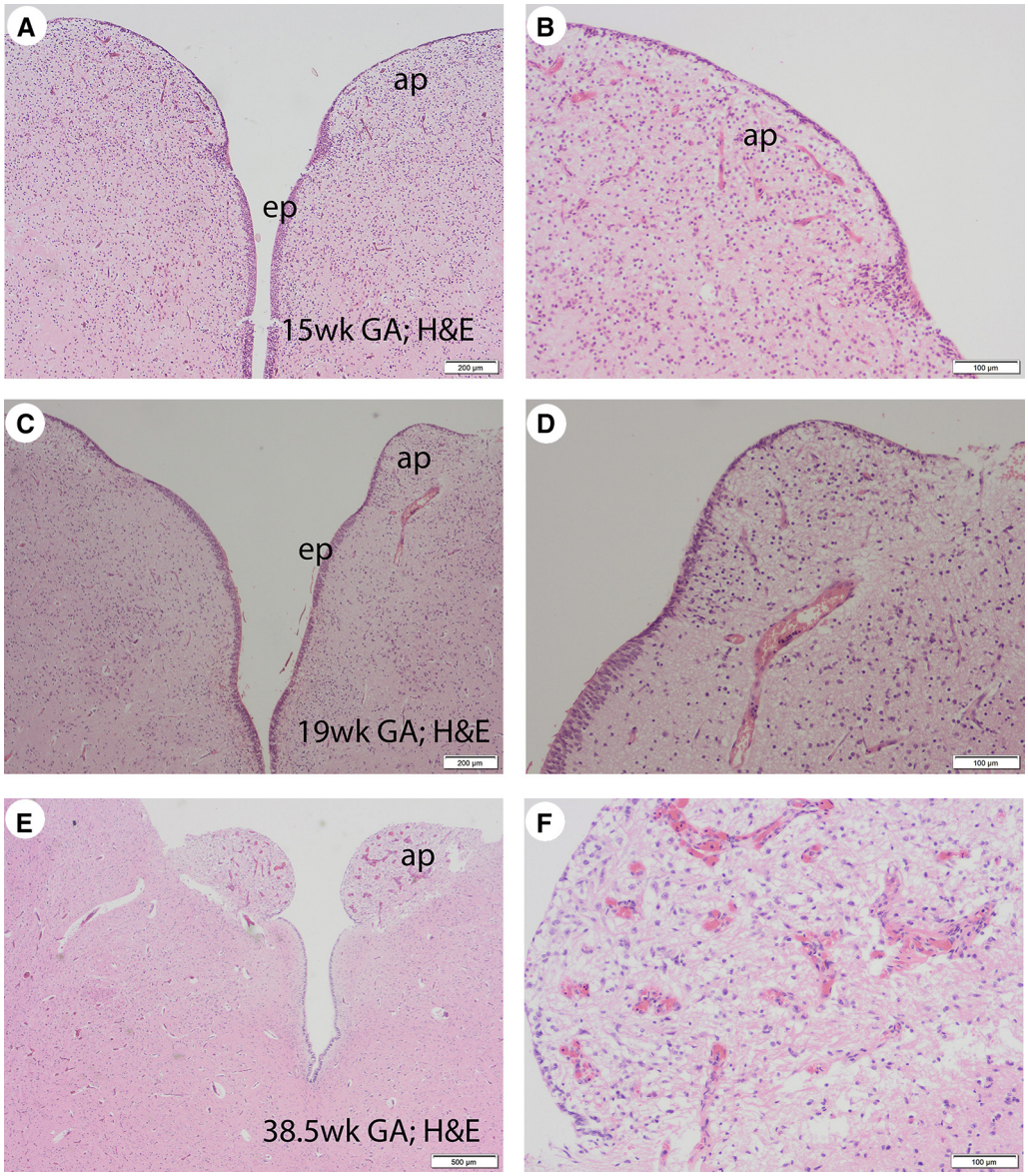

FIGURE 1. The area postrema (ap) increases in size disproportionately more than the underlying structures of the medulla oblongata during fetal life. (A,B) 15 weeks gestational age (GA), (C,D) 19 weeks GA, and (E,F) 38.5 weeks GA. Low-magnification views show the neuroanatomical relations to the fourth ventricle and size of the ap relative to the medulla oblongata. High-magnification views of the ap show an apparent loose tissue architecture and vascularity of this structure that belies the density of small neurons. Hematoxylin-eosin stain. ep, ependyma.

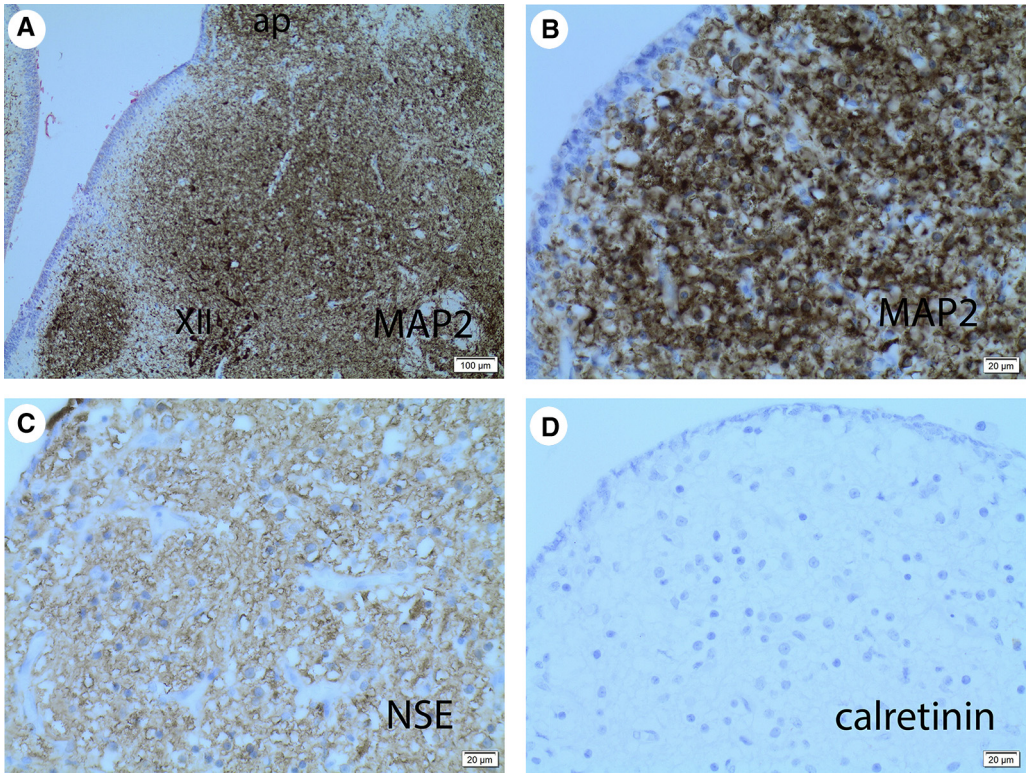

FIGURE 2. Neuronal markers confirm a high concentration of small neurons in the area postrema (ap) well demonstrated at mid gestation by (A,B) microtubule-associated protein-2 (MAP2) and (C) neuron-specific enolase (NSE). Low magnification of MAP2 (A) provides relative comparison with other medullary nuclei including the large hypoglossal motor neurons (XII). (D) Calretinin shows no reactive neurons, but GABAergic neurons are demonstrated by parvalbumin, another calcium-binding protein (not illustrated). At 15 weeks gestational age and at term, these neuronal markers are similar.

but margins of many small cells were difficult to discern with NSE (Fig 2A-C). Synaptophysin immunoreactivity demonstrated axons and synaptic contacts within the AP at all ages (Fig 3). NeuN was inconstant, and rare neurons were labeled in the AP. Calretinin, protein resistant to postmortem degradation, showed no reactive neurons at any age (Fig 2D), but parvalbumin was reactive in about one-third of neurons (not illustrated). In the same sections, calretinin was normally strongly reactive in neurons of the inferior olivary nucleus, providing an internal control that its lack of expression in the AP was not a technical artifact.

Glial cells within the AP exhibited coreactivity between vimentin and GFAP in fetuses and term neonates, and S-100β protein identified astrocytes and their radial processes with intense reactivity, including processing normally extending to capillaries (Fig 4).

Ependyma covers the AP in its margin at the fourth ventricle from about 12 weeks' gestation. At 15 weeks' gestation, the ependyma lining the fourth ventricle is a pseudostratified columnar epithelium, but the ependyma overlying the AP already is mostly a single-layered simple cuboidal epithelium, as seen in the same section, although a double layer occurs focally within the sheet of ependyma (Fig 1B). At 19 weeks' gestation this same condition of a simple ependymal epithelium persists. The pseudostratified ependyma of the fourth ventricular floor has coarse basal processes that extend into the parenchyma of the medulla oblongata as well, demonstrated by vimentin at mid gestation (Fig 4B,D,G); however, ependymal cells over the AP have only rudimentary basal processes at 15 weeks' gestation (Fig 4A) and no longer exhibit them by term (Fig 4C,F). With maturation the fourth ventricular ependyma eventually thins to a simple cuboidal epithelium in the mid to late third trimester (Fig 4F).

Ependyma at the junction of the AP with the medullary tegmental is thickened into multiple layers, especially at mid gestation (Fig 1B). The basal processes of the ependyma, together with astrocytic processes, form a barrier-like horizontal basal layer separating the AP from the underlying tegmentum of the medulla oblongata, at all ages (Fig 4A,B,F,G).

The distribution of neurons and glial cells was relatively uniform throughout the AP except for the glial layer at the basal surface of the AP as mentioned above. We were unable to identify compartmentalization or localization of cellular types to the medial or lateral sides of the AP. Although vimentin was positive in glial cells at all ages including postnatally, the more primitive protein of early cellular differentiation, nestin, was not immunoreactive in any cell (not illustrated). Ki-67 proliferating cell nuclear antigen was positive only in some endothelial cell nuclei, as expected. CD-68, a microglial and macrophage marker, showed no reactive cells within the AP at any gestational or early postnatal age (not illustrated).

The AP of the child with pernicious vomiting for several weeks before death and neurocutaneous melanocytosis revealed extensive infiltration of this structure by melanocytes (Fig 5) in which most foreign cells were reactive for the melanoma markers HMB-45 and Melan-A. S100β protein, which marks melanocytes as well as astrocytes and ependymocytes, was also positive. Most melanocytes were amelanotic (nonpigmented), typical of the central nervous system in this neurocutaneous disease.

The two infants with primary AP neoplasms had neuroimaging demonstration of the lesions, one of which is illustrated in Fig 6. The lesions were confirmed at surgical exploration as pilocytic astrocytoma of the AP and were neither metastatic nor infiltrative from primary brainstem glioma deeper within the brainstem. These children had intractable vomiting or hiccups as their predominant

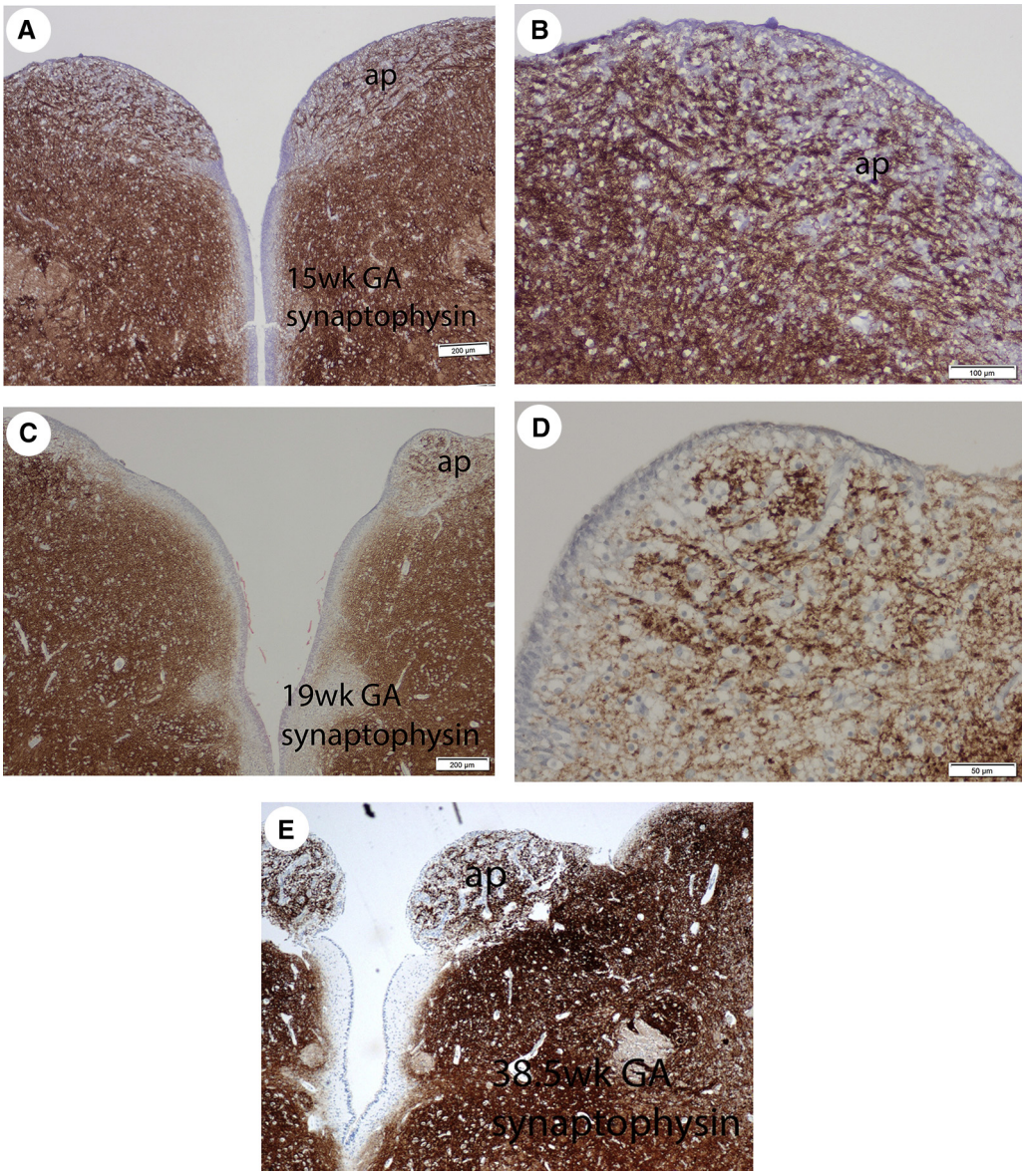

FIGURE 3. Synaptophysin immunoreactivity demonstrates development of synaptic plexi within the area postrema (ap) beginning at 14 weeks GA. Synaptic reactivity within the medullary parenchyma is more intense at all fetal ages than in the area postrema, as shown in low-magnification views, but synaptic vesicles are formed by 15 weeks. (A,B) 15 weeks gestational age (GA), (C,D) 19 weeks GA, and (E) 38.5 weeks GA.

symptoms. Neither had obstructive hydrocephalus at the level of the fourth ventricle.

Discussion

Our findings of maturation of morphogenesis of the AP in human fetuses correspond to those previously reported by Castañeyra-Perdomo et al.[5] and thus are confirmatory, particularly with respect to pre- and postnatal growth in size of the AP in relation to growth of the brainstem in general. We supplement these histologic observations with immunocytochemical findings not previously described. The early fetal neuronal maturation in the AP in relation to its functional immaturity at birth and in early infancy contrasts with data that both the human and murine AP exhibit delayed maturation of synaptic input from *PHOX2B*-derived neurons.[11] All autonomic afferent and efferent circuits, and especially the specification of noradrenergic neurons of neural crest origin, require the paired homeobox gene *PHOX2B* to develop properly.[11,27–32] *Phox2b* deficiency in mice and human results in central hypoventilation syndrome, dysautonomia, or embryonic lethality, at least in part due to the crucial role of this gene in the maturation of neural crest cells.[11,33–35] The human olfactory bulb is another example of neuronal and synaptic immaturity yet functional to detect and distinguish odorous molecules from 30 weeks' gestation,[36] and this highlights an important general developmental principle that function can precede neuronal cytologic maturation.

Examination of aborted fetuses is the only practical means of studying human fetal developmental neuroanatomy. The risk exists that the tissue being examined is not entirely normal because of the circumstances leading to spontaneous fetal death or induced abortion, but if the brain has a normal weight and gross and microscopic morphology for the gestational age, and there is no evidence of chromosomopathy or genetic or metabolic disease or congenital infection, it may be assumed that individual brain structures, such as the AP, also are normal or near-normal.

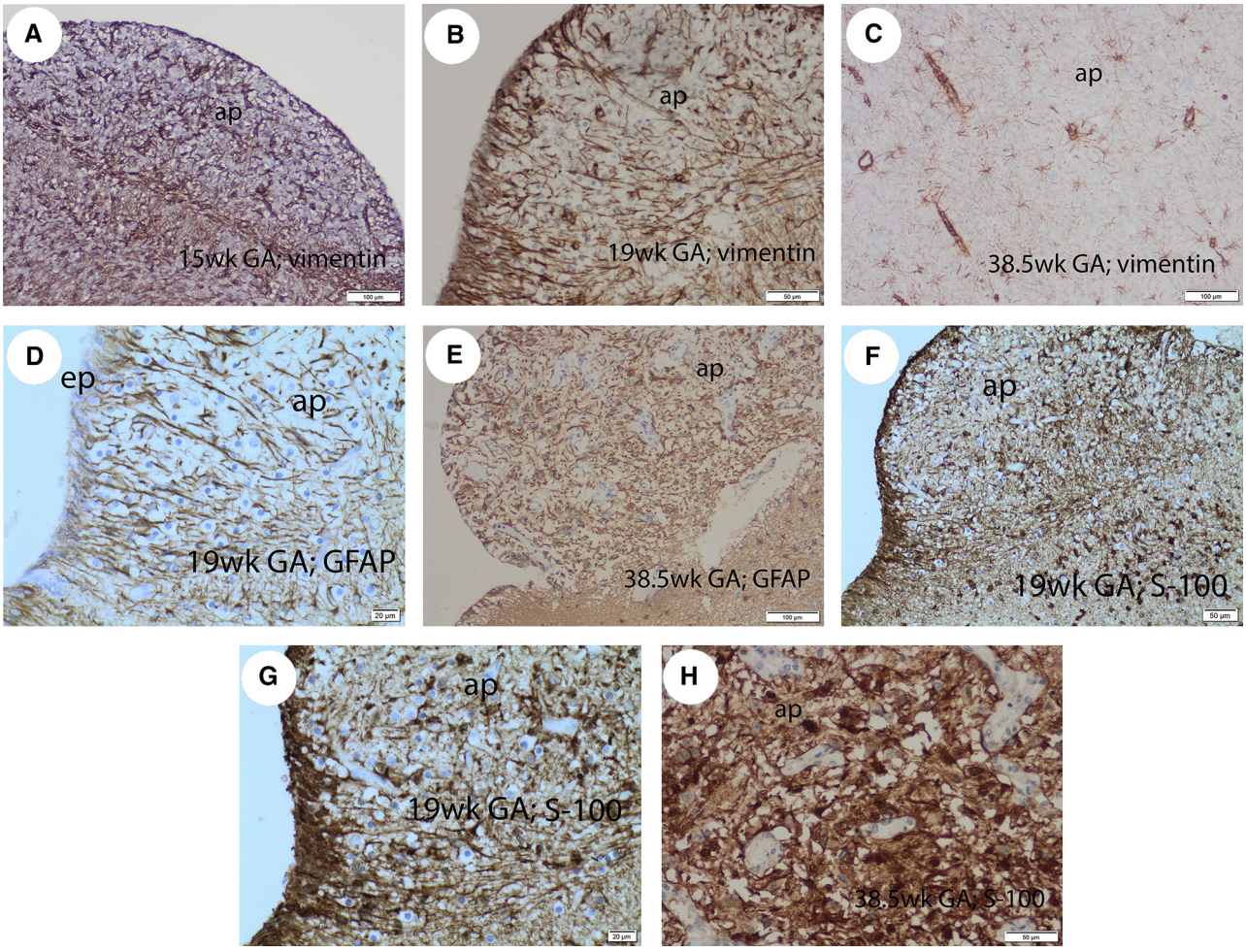

FIGURE 4. Glial cell density and distribution within the area postrema (ap). Vimentin immunoreactivity (A–C) at (A) 15 weeks gestational age (GA) and (B) 19 weeks GA shows many astrocytes; at (C) 38.5 weeks GA astrocytes still express this transitory fetal intermediate filament. Vascular endothelial cells normally express vimentin at all ages including in the adult, not only in the ap but also throughout the body. Ependymal cells (ep) over the ap are reactive at all gestational ages, but at (B) 19 weeks GA they exhibit coarse basal processes extending into the ap. (D,E) Glial fibrillary acidic protein (GFAP), a more mature astrocytic intermediate filament protein, is coexpressed with vimentin in astrocytes and ependymal cells including ependymal basal processes at all fetal ages; astrocytic processes are seen extending to capillaries (normal), a site of aquaporin-4 secretion; (D) 19 weeks GA and (E) 38.5 weeks GA. (F–H) S-100β protein expression is intense in astrocytes and ependyma including basal processes and astrocytic end-feet on capillaries. (F,G) 19 weeks GA and (H) 38.5 weeks GA. A horizontal layer of ependymal and glial processes forms a barrier-like separation of the ap from the underlying medullary tegmentum, as seen with all of these astrocytic markers.

Extrapolation from animal studies also carries the risk that the corresponding human structures may not be entirely equivalent.

Fetal cellular maturation in the area postrema

Our demonstration of similar immunoreactivities of synaptophysin in fetuses of 14, 19, and 38.5 weeks' gestation as seen in Figs 1-3 indicated similar early maturation at all these gestational ages. Synaptophysin is important not only as a late marker of neuronal maturation but also in confirming the establishment of synaptic contacts and circuitry within the AP. Axoplasmic flow of the synaptophysin molecule from the perinuclear somatic cytoplasm to the axonal terminals was also seen. We were unable to confirm the report of compartmentalization of the AP with aggregation of certain types of neurons or glial cells.[7] In our cases, the distribution of cellular types appeared qualitatively uniform; we did not, however, perform serial sections through the entire AP, which might have shown better evidence than the random sections we examined. Calretinin failed to show the number of GABAergic neurons that were anticipated; however, other calcium-binding proteins give different immunoreactive neuronal specificities (e.g., parvalbumin, calbindin D28k), and one of these other antibodies (parvalbumin) better demonstrates these inhibitory neurons, consistent with a specificity of these calcium-binding molecules.[9,10]

NeuN, being a nuclear marker with the cytoplasmic epitope expressed much later, is a fragile molecule vulnerable to postmortem autolytic degradation, unlike robust molecules that resist autolysis, such as synaptophysin and vimentin.[9,10] In addition, NeuN is not expressed at any age in certain specific neurons, namely, Purkinje cells of the cerebellum, inferior olivary and dentate nuclear neurons, mitral cells of the olfactory bulb, retinal photoreceptor neurons, and sympathetic neurons of the paravertebral chain. To this list, AP neurons may now be added, although further study of postmortem brains with short times from death to tissue fixation is needed to confirm this conclusion.

Amongst glial markers, S-100β protein had the strongest reactivity to both glial somata and radiating glial processes (Fig 1G, H). Of note is the fact that vimentin was equally reactive as GFAP. Vimentin is an immature transitory intermediate filament protein replaced by GFAP in maturing astrocytes and ependymal cells, and GFAP then disappears from ependymocytes but persists in mature

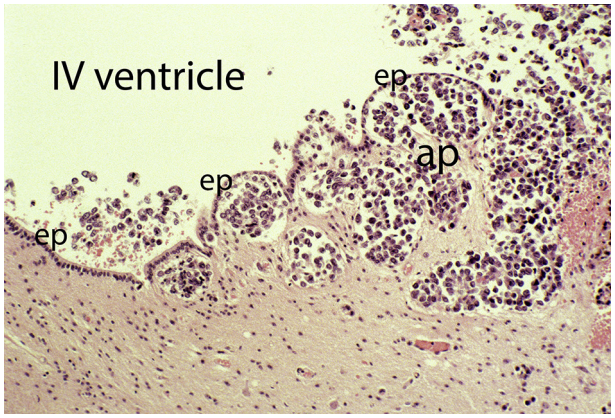

FIGURE 5. Parasagittal section of the floor of the fourth ventricle of a three-year-old boy who died of neurocutaneous melanocytosis after three weeks of pernicious vomiting refractory to antiemetic medications. At autopsy, there was severe melanocytic infiltration in the area postrema (ap) on both sides. Most melanocytes were unpigmented (amelanotic), but the majority of cells were reactive with one or both of anti-melanoma antibodies HMB45 and Melan-A, as well as against S-100β protein (not illustrated). The ependyma (ep) is preserved over most the ap, and melanocytes appear to infiltrate through an ependymal gap. Hematoxylin-eosin stain.

astrocytes.[37–41] In radial glial fibers of the cerebrum and Bergmann glial cells of the cerebellar cortex, vimentin continues to be co-expressed with GFAP until radial glial processes are retracted after neuroblast migration in complete and in Bergmann cells of the adult cerebellum. This rare mature Bergmann cell coexpression can now be seen to similarly include the AP.

The simple cuboidal ependymal epithelium of the mature brain lacks basal processes of immature ependymal cells, whereas the less mature pseudostratified ependyma lining the fourth ventricular floor in the late first, second, and early third trimesters shows such processes, similar to those seen in the ependyma of the lateral ventricles.[40–42] These ependymal basal processes do not guide migratory neuroblasts as do radial glial fibers, but rather are secretory; in dorsal and ventral median septa of the early fetal spinal cord and brainstem, they are important in axonal guidance, repelling longitudinal- but facilitating commissural-growing axons, and in the immature ependyma of the fourth and lateral ventricles, they may serve to facilitate neuroblast migration by helping attach neuroblasts to radial glial fibers. Basal ependymal processes are well formed in the AP at mid gestation, but what function they serve in that site is unknown. Ependymal cells are strongly reactive with anti-AQP4 antibodies,[5] and their basal processes may be secretory for AQP4.

Evidence for the role of AP as the emetic "vomiting center"

The AP is traditionally considered to be clinically important as the "vomiting center" of the brainstem. It was first identified as a chemoreceptor trigger zone in vomiting responses in the cat by Borison and Brizzee in 1951.[43] The AP and the almost adjacent nucleus or tractus solitarius are involved in nausea and vomiting in humans and animals[5,17,18,44–49] and to food craving and body weight in rodents.[18,50] Some patients with AP dysfunction present intractable hiccups rather than vomiting.[50]

Severe vomiting in pregnancy, termed *hyperemesis gravidarum*, was described as early as 2000 BC in ancient Egypt.[51] This unpleasant symptom is common but not universal in pregnancy and is particularly severe in the late first trimester. The mature AP is sensitive to circulating levels of certain hormones in early pregnancy. Catechol-estrogen steroids and irregular liver metabolites, both of which are elevated in early pregnancy, have emetic properties, and the AP is implicated as the origin.[51–53] The AP is not essential for motion-induced (vestibulogenic) vomiting from vestibular stimulation, however.[47] Vomiting induced by certain neurotoxic drugs, such as those used in chemotherapy as antimetabolites, mediate these side effects in part by acting on the AP[54,55] and also in familial dysautonomia (Riley-Day syndrome) by activation of dopamine receptors in chemoreceptor trigger zones.[53,54] Some chromosomopathies, such as 22q11.2 deletion (DiGeorge syndrome) may present intractable vomiting as a seizure type[56] that also involves the AP, although the seizures do not likely originate there. In other patients with seizures, intractable ictal vomiting may be reflexive epilepsy.[55]

Tumors of the AP

Persistent, often intractable vomiting is a cardinal symptom of tumor of the AP, and such patients require MRI with special attention to the caudal fourth ventricular area. We here demonstrate neoplastic processes of the AP in three patients, one with pernicious vomiting in the weeks before death and two cases of focal gliomas in patients who survived. Other cases of primary gliomas of the AP have been published, also with pilocytic astrocytoma as the neuropathological diagnosis.[50,57] These lesions of the AP can cause obstructive hydrocephalus at times, unlike AP involvement in non-neoplastic conditions.

The AP is an "exquisite" region of the brain where surgery has a high risk of intraoperative death, but in experienced neurosurgical hands it is feasible, as demonstrated in one of our cases (Fig 6) and in many successfully surgically treated cases of hemangioblastoma.[58] This vascular tumor is an integral component of von Hippel-Lindau disease, for which there is now a specific genetic marker, and the AP is a frequent primary site of this lesion.[58]

AP as a circumventricular organ for vasomotor regulation and transfer of molecules between brainstem and cerebrospinal fluid

Circumventricular organs are midline or parasagittal structures around the third and fourth ventricles that lack a blood-brain barrier: the pineal, median eminence, neurohypophysis (posterior pituitary), and subcommissural organ are secretory, whereas the subfornical organ, organum vasculosum of the fetal lamina terminalis, and the AP are sensory.[59] Neurons are present in all circumventricular organs except the pineal and neurohypophysis, although the former contains neuroendocrine cells that secrete melatonin, and the latter contains axons from hypothalamic neurons. These two exceptions are also the only components that lack an ependymal lining. Astrocytes and microglial cells (resident cerebral macrophages) occur in all. The circumventricular organs are sites of communication with the CSF as well as between the brain and peripheral organs via blood-borne products.[59] The lack of a blood-brain barrier within the AP, despite the small size of this structure, is associated with a prominent capillary network and its position just beneath the fourth ventricular ependyma, which facilitates transfer of molecules, hormones, transmitters, and electrolytes between the brainstem and CSF. Each of the circumventricular organs has its own unique function and structure; for these reasons and because of their neuroanatomical dispersion in various parts of the brain, no single unifying feature characterizes their development.[60]

The circumventricular organs in general and AP in particular are closely related to angiotensin II and oxytocin[5,6] and vasopressin for vasomotor regulation.[16,61,62] Angiotensin II would not likely have an important role in the autoregulation of cerebral blood flow in the fetus because the development of the smooth muscular layer around parenchymal arterioles is relatively late in the third

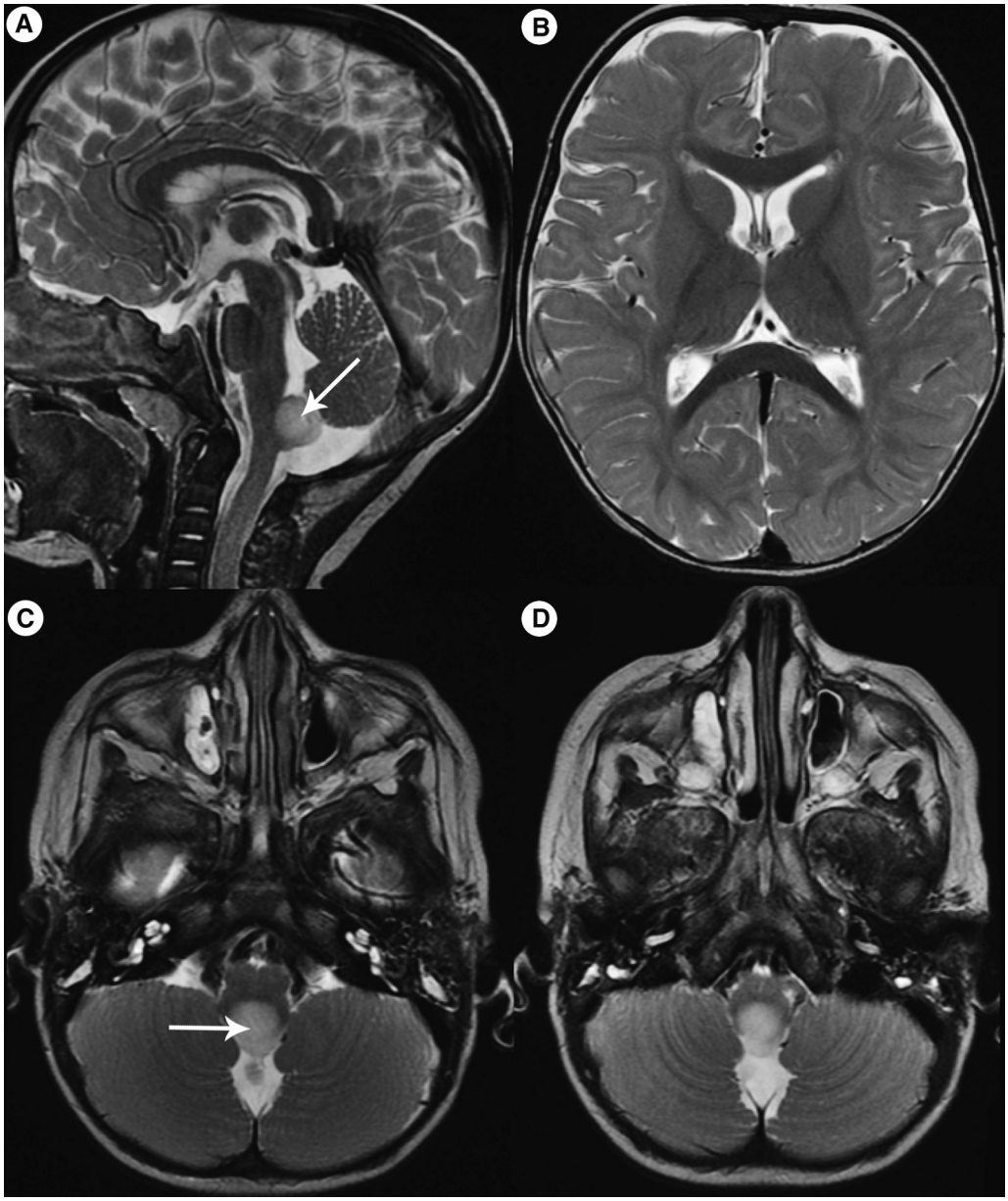

FIGURE 6. T2 magnetic resonance imaging of nine-month-old infant with primary astrocytoma of area postrema. (A) Sagittal and (C, D) axial T2 images demonstrate a homogeneous noncystic tumor mass (arrows) in the midline of the caudal posterior fossa. It distorts the fourth ventricle but does not obstruct CSF flow. (B) Axial image of supratentorial space shows normal lateral ventricles, confirming absence of obstructive hydrocephalus.

trimester, so that in younger fetuses there are no vascular receptors to respond to angiotensin except the major cerebral arteries before their branches penetrate the brain tissue. Genetic transcriptome microarrays of the AP of hypertensive rats show multiple AP alterations compared with normotensive controls.[63]

Area postrema syndrome in neuromyelitis optica spectrum disorder

Neuromyelitis optica (first described clinically by Eugen Devic, 1858–1930) is a relapsing but ultimately progressive demyelinating leukoencephalopathy that seems to selectively involve the optic nerves and spinal cord, although it is not restricted to these sites and can involve diencephalic structures, particularly the hypothalamus as well. Although early believed to be a variety or phase of multiple sclerosis, neuromyelitis optica is now regarded as a distinct disease that does not progress to become multiple sclerosis as shown in long-term neurological follow-up.[64] Onset usually is in mid adult life with a female:male predominance of 10:4,[64,65] but pediatric cases also are reported.[66] It is more common in patients of African or Caribbean origin than in those of European descent; the earliest and most frequent clinical symptoms are frequent episodes of nausea and vomiting or sometimes intractable hiccups, a clinical picture sometimes termed the *area postrema syndrome*.[64,67]

The AP is the site most involved in pathogenesis, however unlikely it might seem by its small size and location. The mechanism involves aquaporin-4 immunoglobulin-G (AQP4-IgG).[67–71] AQP1 and AQP4-IgG can be demonstrated immunocytochemically as water transporter channel markers in capillary endothelial cells of the AP in microscopic sections.[6] AQP4 is secreted by ependymal cells and astrocytic end-feet on capillaries in the AP (Fig 4E,H) and also in some peripheral organs such as the proximal gastric mucosal cells. Laminin immunoreactivity was demonstrated as a

double basement membrane surrounding different-sized capillaries in the AP with a wide perivascular space between the two layers but was not visualized in capillaries of the surrounding medullary brain tissue in which only a single basement membrane is present, confirmed with collagen IV immunoreactivity.[6]

Disruption of the blood-leptomeningeal and blood-brain barrier at the AP is seen in patients with neuromyelitis optica and AQP4-IgG by gadolinium-enhanced MRI.[67–69,72] As with all circumventricular organs, the AP normally lacks a blood-brain barrier. Some patients with nausea, vomiting, or hiccups who do not have optic nerve and spinal cord demyelination also have elevated circulating levels of anti-AQP4 antibodies.[73] Another antibody sometimes demonstrated in blood in conjunction with AQP4 in neuromyelitis optica is myelin oligodendrocyte glycoprotein.[73] About two-thirds of children with symptoms and neuroimaging signs of neuromyelitis optica show elevation of one or both of these antibodies, and these immunoserological data are useful diagnostically in distinguishing neuromyelitis optica from childhood multiple sclerosis.[74–76] Myelin oligodendrocyte glycoprotein antibodies are found in other acute demyelinating syndromes, particularly in children, including acute demyelinating encephalomyopathy followed or not by optic neuritis but not in multiple sclerosis. APQ4-IgG can be measured in CSF and also in serum.[77] APQ4-IgG may also be demonstrated in tissue sections by applying an immunocytochemical antibody.[6]

Apart from the clinical presentation of relapsing and progressive visual impairment due to optic neuritis and longitudinally extensive transverse myelopathy,[76] some patients and also rats have unprovoked and sometimes pernicious neurogenic nausea and vomiting during relapse,[48,63,64,78,79] sometimes designated *area postrema syndrome* and now is one diagnostic criterion for neuromyelitis optica spectrum disorder.[80] MRI shows demyelination in the optic nerves and spinal cord, sometimes producing images of tumefactive demyelination closely resembling those of classical multiple sclerosis[68,76]; brain biopsy shows demyelination with reactive astrocytes but preserved surface AQ4 immunoreactivity.[80] It is difficult to have direct histopathological examination of the AP because it is not easily accessible for biopsy (although tumors are successfully resected), and generally it is not specifically examined at autopsy.

Body weight, lipid metabolism, and somatic growth

Regulation of body weight and fat may be one of the important functions of the AP during prenatal development.[17] The greatest rate of fetal weight gain is between the third and fourth months of gestation, when body weight increases from 20 to 120 g.[81] Castañeyra-Pedomo et al. noted that this period coincides with the early maturation of the AP,[5] and we make this same correlation based on our studies.

Serotonergic afferent axons entering the AP were mentioned in the Introduction. Leptin is an adipocyte-derived peptide hormone that communicates levels of fat stores in the body to the brain for long-term regulation of energy balance, and AP neurons possess leptin receptors.[82] Leptin and amylin influence a subpopulation of AP noradrenergic neurons with either a depolarizing or a hyperpolarizing effect, suggesting that the AP is a site of central modulation of energy metabolism and lipid metabolism in particular.[82–86] Amylin and leptin may even facilitate the development of axonal projections from the AP to the nucleus solitarius.[85]

Receptors for amylin and calcitonin (a potent amylin agonist) peptides are targets for treating obesity, diabetes mellitus, and osseous disorders, and calcitonin receptors are demonstrated in the AP and in other medullary centers, including the nucleus solitarius.[87,88] Ghrelin (growth hormone secretagogue receptor) accesses the AP but not the nucleus solitarius, and this receptor is essential for fasting-induced activation of AP neurons.[88] Ghrelin modulates electrical excitability in AP neurons[88]; ghrelin-sensitive neurons of the AP are GABAergic (calretinin-immunoreactive neurons) and mediate ghrelin-induced gastric emptying.[88] Cholecystokinin is a gut hormone with anorexigenic effects via action at both central and peripheral receptors; the AP is a target of cholecystokinin-8 that mediates appetite suppression with the participation of AP by glutamate release onto AP neurons, as determined in fresh rat brain slices.[89] In this same context, the diazepam-binding inhibitor is another anorexigenic factor, mediated through an endozepine octadecaneuropeptide, and is strongly expressed in ependymal cells lining the fourth ventricle (that cover the AP), as well as in some astrocytes between the AP and adjacent nucleus solitarius, that strongly inhibits appetite and the swallowing reflex when microinjected into that medullary region of rats.[90] Noradrenergic neurons of the AP are also activated by satiety-promoting action of oleoylethanolamide, not requiring afferent input from the nucleus solitarius or other vagal nuclei.[91]

In addition to the effects of benzodiazepines, cocaine- and amphetamine-regulated transcript peptides suppress gastric emptying and nutritional intake following fourth ventricular injection in rats and activate neurons of the AP and nucleus solitarius.[92] Hepatoma tumor-bearing rats develop anorexia and body weight loss for which the AP is invoked in a mechanism involving tumor-initiated macrophage inhibitory cytokine-1.[93] Rats injected intraperitoneally with human macrophage inhibitory cytokine-1 also showed activation of AP and nucleus solitarius neurons.[94] Microglial cells (resident brain macrophages) are activated by acid-sensing ion channel type I in the AP and nucleus solitarius.[95]

Other possible functions

A role of the AP in taste aversion learning in rats and cats is postulated to be mediated by angiotensin II,[61] but this report requires further confirmation; no human data are available. Afferents from the glossopharyngeal nerve,[12] which mediates taste in the posterior third of the tongue and oropharynx, provide a neuroanatomical basis for this function. The nucleus solitarius is the principal brainstem respiratory center, paired longitudinal columns in the dorsal part of the medullary tegmentum near the AP.[96] It has reciprocal connections with the vagal nucleus ambiguus for coordination of breathing and swallowing to avoid aspiration, in conjunction with the pre-Bötzinger nucleus, which projects serotonergic axons that also express the modulating neuropeptide somatostatin to the AP.[97]

Non-neoplastic pathologic lesions of the area postrema

The AP is within the watershed zone of usually symmetrical brainstem infarcts in the pre- or postnatal periods due to transitory hypotension and poor perfusion from the basilar artery.[98] Rare structural lesions are also described, such as a neurenteric cyst in an adult.[99] Hemangioblastoma of the lower brainstem involving mainly the AP was described in 14 patients with von Hippel-Landau disease, with vomiting and aversion to food being prominent symptoms.[58]

Among posterior fossa malformations, there are a few descriptions of the AP by either neuroimaging or postmortem neuropathological examination in dysgeneses of the brainstem, cerebellum, or fourth ventricle. Data are incomplete largely because the AP is not a structure routinely examined at autopsy and brainstem sections that include it usually are not taken. Fetuses and infants with Dandy-Walker malformation, Joubert syndrome,

Chiari II malformation, rhombencephalosynapsis, and others theoretically could harbor developmental anomalies of the AP. Even in cases of congenital hydrocephalus, it would be important to know whether increased intraventricular pressure during fetal development alters the AP. Vomiting is a prominent symptom in infants and children with hydrocephalus, regardless of the level of obstruction of CSF flow.

Excessive and repeated use of a neurotoxic insecticide in the house resulted in the sudden death of a seven-month-old infant; at autopsy the AP could not be demonstrated in its expected site on either side of the medulla oblongata, but apoptotic neurons were identified in the surrounding region in the posterior floor of the fourth ventricle.[100]

Recommendations

(1) *Neurologists and neuroradiologists:* In patients with protracted or recurrent vomiting or hiccups, MRI with special attention to the lower medulla oblongata should be performed for tumors, neuromyelitis optica, or malformation of the AP. Serum and CSF aquaporin-4-IgG can be reliably measured.
(2) *Neurosurgeons:* Tumors of the AP at times can be safely resected with expectation of good outcome in skilled and experienced hands.
(3) *Neuropathologists:* At autopsy in fetuses, neonates, and children who presented clinical signs consistent with a possible lesion of the AP, a transverse section should be cut at the level of the caudal end of the fourth ventricle to include the AP; histopathological examination should include synaptophysin, MAP2, and GFAP immunoreactivity in sections that include this nucleus with secondary consideration of APQ4, vimentin, and S-100β protein.

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