Giant Arachnoid Granulations

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Arachnoid granulations (AGs) are macroscopically visible arachnoid tissue outpouchings that protrude into bone, dura, and/or dural venous sinuses (DVSs).

Keywords: GAG ; giant arachnoid granulation

1. Introduction

Arachnoid granulations (AGs) are macroscopically visible arachnoid tissue outpouchings that protrude into bone, dura, and/or dural venous sinuses (DVSs) [1]. Historically, they have been defined by their juxtaposition and drainage into the superior sagittal sinus (SSS) and other DVSs. AGs primarily consist of collagen, immune cells, and cerebrospinal fluid (CSF)-filled spaces situated at brain borders [1]. These structures were described in 1543 by Vesalius [2] and were further characterized by Willis in 1664, Littre in 1684, Collins in 1685, Mery in 1701, and Pacchioni in 1705 [3][4][5]. However, they were only recently systematically characterized through detailed radiologic–pathologic investigation incorporating comprehensive analyses with cellular and molecular markers, thus enhancing knowledge of their anatomy and potential functions [1].

Typically, AGs are asymptomatic structures that abut dural tissues and measure only a few millimeters in diameter [1][6], but they occasionally enlarge to form so-called giant arachnoid granulations (GAGs) that may also associate with bone marrow spaces and, rarely, scalp dermal tissue. These structures may also cause clinical symptoms and/or nodular DVS filling defects on venography that manifest secondary to flow aberrations, DVS expansion, venous stenosis, and/or other suspected pathologies. GAGs have increasingly been reported in recent years with several cases involving the DVS and others found in extrasinus calvarial or diploic locations.

2. Reports and GAG Cases

The published literature from 1973 to 2023 yielded 41 publications describing GAGs in 169 persons [3][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46]. This incorporated reports of 146 persons each with a single GAG; 21 persons with at least two GAGs [7][8][9][10][11]; and 2 persons who each exhibited “multiple” GAGs, with three [12] or four [8] GAGs being discernible on presented imaging. Considering the above, the review yielded a total of at least 195 reported GAGs. Of these, 164 (84%) were intrasinus-type, 30 (15%) were calvarial-type, and 1 (1%) was mixed-type; the specific location was recorded in 182 (93%); clinical history was available for 92 (47%); imaging data were available in 140 (72%); and histologic data were available in 52 (27%) [3][9][10][13][14][15][16]. Sex was available for 147 of 169 persons (87%) [3][10][13][14][15][16]. Among the GAG cases with histology, 14 presented at surgery [3][12][13][14][15][16][45], and 27 presented at autopsy [9][10].

3. Demographic Features

Of the 147 persons with documented gender, GAGs involved 80 (54%) females and 67 (46%) males and were similarly distributed across sex (1.2:1 female-to-male ratio). The afflicted persons included infants [15], children [10][16][17][18][19][20], adolescents [17][21][22][23][24], and adults across a wide age spectrum [10][15][45] (range, 0.33 to 91 years; mean, 43 ± 20 years). Interestingly, one pediatric case was reported by parents since birth [16]. The mean number of GAGs per person was 1.0 and the overall number of GAGs recorded per decade of life is depicted in **Figure 1**A. Most persons with GAGs exhibited no comorbidities or past medical history but 4 of 169 persons (2%) were noted to be moderately obese or had cerebral small vessel disease [7][25][26]; 1 of 169 persons (1%) had a history of retrobulbar neuritis [3]; and 1 of 169 persons (1%) had staring episodes as well as a family history of seizures [10].

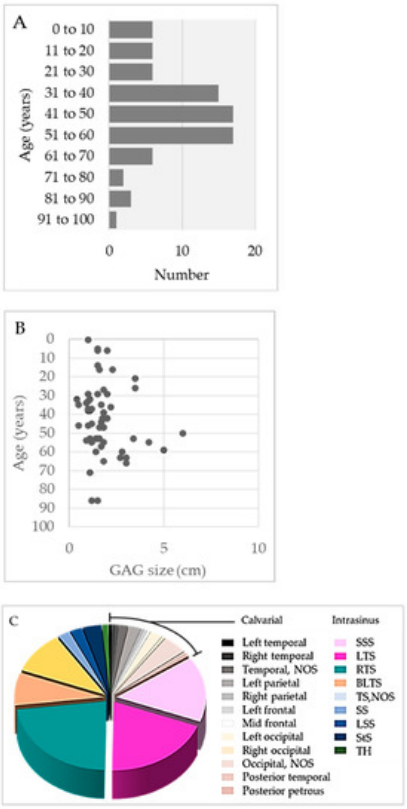

Figure 1. (**A**) Summary of the age distribution of persons with GAGs, according to decade of life. (**B**) GAG size distribution according to age. (**C**) Summary of GAG distribution by location.

4. GAG Size and Morphology

The size distribution of GAGs is summarized in **Figure 1**B. The mean diameter of GAGs was 1.9 cm ± 1.1 cm (standard deviation), though diameters ranged from 0.4 to 6.0 cm. Notably, five reported GAGs measured less than 1 cm in diameter (range: 4 to 9 mm) [26][32][33]. There was no direct correlation of GAG size with age [11]. The person's age and GAG size were recorded for only 24 persons with recorded gender. Analyses among these cases revealed no statistically significant difference in mean age across male versus female individuals (females, 38 years; males, 45 years). However, a statistically significant difference was noted for GAG diameter across sex (females, 1.78 cm; males, 3.39 cm; $p < 0.05$) [3][13][15][16][20][23][26][27][28][29][30][31][32][33]. GAGs also varied in shape. Typically, GAGs were well-defined, nodular, round-to-ovoid structures, but others were irregular and a discrete, oblong vermiform shape was also characterized in one person (1%) [31].

5. Anatomical Distribution and Frequency

The majority of GAGs presented along SSS or transverse sinuses, or in parasagittal brain regions, whereas a subset involved the temporal bone (**Figure 2**C) and caused the compression of inner or middle ear structures [14][37]. Postmortem DVS studies reveal GAGs in 3.68–20% of adolescent and adult autopsies [9][10]. However, these analyses likely underestimate the true number of GAGs since they did not examine calvarial-type GAGs. Although imaging series are on record [11][18], no imaging study has analyzed the true prevalence of GAGs in live persons.

7. Reported GAG Histology

Fourteen calvarial-type or mixed-type GAGs were evaluated histologically [3][13][14][15][16][45]. Surgically resected bone and soft tissue elements from these structures were studied with routine hematoxylin and eosin (H&E) staining following the decalcification of bone tissues and revealed collagen and meningothelium. The workup of two cases incorporated immunohistochemistry analysis [13][45]. Both of these cases were analyzed with the use of the anti-EMA label, which confirmed the meningothelial component [13][45]. One case that underwent comprehensive immunohistochemistry workup additionally revealed the presence of S100-positive nerve twigs; CD68-positive, CD138-positive, or CD45-positive immune cells (consistent with the presence of foam cells or monocytes/macrophages, plasma cells, or lymphocytes, respectively) (**Figure 2**); and CD31-positive, CD34-positive, and D2-40-positive capillary vessels within the GAG (consistent with blood capillary vessels and/or lymphatic capillary vessels). A thrombosed vein, hemorrhage, lymphatic vascular obliteration, and meningothelial hyperplasia were also present within this reactive GAG (**Figure 2**) [45]. Histology

on 8 of 14 (57%) GAGs confirmed diploic space infiltration by GAGs [3][13][14][15][16]. In 5 of 14 (36%) cases, a large CSF-filled central cavity was reported rather than a dense collagen core, and these were therefore reported to mimic unilocular cysts [3][13][15]. In 14 of 14 (100%) cases, the outer GAG surfaces were covered by arachnoid or dural cells, rather than by endothelium [3][13][14][15][16]. On a retrospective review of published histological images, 3 of 14 (21%) cases demonstrate apparent mononuclear immune cell infiltrate within the GAG core, though this was not characterized as immune cells in the original reports [14][15]. Moreover, 2 of 14 (14%) described the presence of fat cells, though a retrospective review of published histology images suggests that these were instead foam cells (i.e., lipid-laden monocytes/macrophages) that had been misinterpreted on histologic assessment [16].

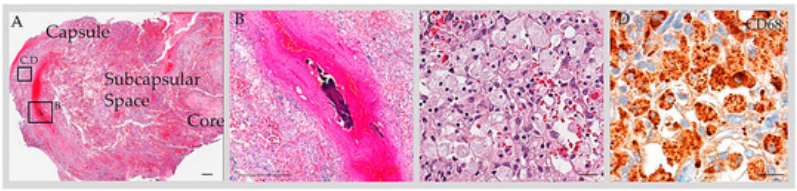

Figure 2. Anatomy of GAG. H&E-stained section of a GAG dome that was resected from an adult patient with post-traumatic headache revealed a multilaminar structure composed of a capsule, subcapsular space, and core (**A**). The subcapsular space contained blood and cells. On a high-power exam, a thrombosed vein (**B**) and foam cells (**C**) were present within the structure. Immunohistochemistry for CD68 highlighted a prominent number of cells, consistent with macrophages (**D**). Scale bars = (**A**,**B**), 100 µm; (**C**,**D**), 10 µm. Copped areas (black boxes in (**A**)) are shown in (**B**–**D**). Images reproduced from *Int. J. Mol. Sci.* **2023**, *24*, 11410 [45].

At least 27 DVS-type GAGs were identified on postmortem DVS examination [9][10][15]. However, their tissue composites were not analyzed in detail. The largest population-based anatomical study of DVS-type GAGs consisted of a postmortem investigation published by Haybaeck et al. [9] and incorporated data from H&E and Elastica van Gieson stains as well as immunohistochemistry preparations incorporating labels for vimentin, desmin, EMA, and S100. In this series, intrasinus GAGs were reported to consist of dense collagen and meningothelial cell clusters covered by an endothelial cell layer. Mamourian et al. [10] describe large, centrally-placed blood vessels within three DVS-type GAGs from two patients although characterization of the tissue component was limited.

8. Signs and Symptoms

While some reports define GAGs as normal AG variants of no known clinical significance [10][34], heterogeneous acute, subacute, and/or chronic signs and symptoms have been reported in association with many GAG cases. The most common presenting signs in persons with GAGs included headache (32 of 169 persons, 19%), vision change (10 of 169 persons, 6%), hearing change (9 of 169 persons, 5%), vertigo (6 of 169 persons, 4%), papilledema, and intracranial hypertension (each in 4 of 169 persons, 2%). Interestingly, 1 of 169 patients (1%) presented with a so-called laughing headache [7]. More ominous symptoms such as a change in consciousness, loss of consciousness, or seizure (each involving 2%) and meningism, neck pain, fever, and facial droop (each involving 1%) were also noted. Interestingly, 1 of 169 patients (1%) presented with repetitive hemorrhagic episodes, and 38 of 169 patients (22%) exhibited the herniation of brain parenchyma into a calvarial-type or DVS-type GAG, with involvement of cerebral cortical and/or cerebellar foliar tissue. A significant proportion of patients with herniated brain tissue, including one 5-year-old child, exhibited evidence of brain injury [8][17][18][20][38]. In a series of 27 patients, Gozgec et al. [17] reported a statistically significant positive correlation between the frequency of herniated brain damage and GAG size ($p < 0.05$).

Some afflicted persons indicated that symptoms had been ongoing for several years, or for decades prior to diagnosis [26][29][45]. Acute clinical events that exacerbated GAG symptoms were present in 9 of 169 persons (5%) and a relieving factor, i.e., internal jugular venous compression that mitigated pulsatile tinnitus, was noted in 6 of 169 persons (4%). A total of 3 of 169 (2%) patients with auditory changes complained of pulsatile tinnitus with “whooshing”, “swooshing”, or “sloshing” sounds [26][28][29]. All of these patients had transverse sinus or posterior temporal bone involvement by GAG [26][29], and one patient indicated that the frequency of the perceived auditory change was constant with her heartbeat [29]. Several patients indicated that GAG-associated symptoms had a significant impact on their quality of life or interfered with activities of daily living [7][17][26][29][45].

9. Imaging Features

Diagnosis of GAG on imaging workup was accomplished by visualization of round-to-ovoid, irregular or oblong, unilocular or multilocular cystic-appearing structures with or without internal septations, and with internal CSF-like density or signal intensity and communication with the subarachnoid space on MRI with and/or without contrast [8][13][15][17][19][20][22][23][24][25][26][28][30][31][36][37][38][39] (**Figure 3**A), MR angiogram/venogram [10][23][25][34][35][36][39][40][41][42], CT with and/or without contrast, or CT angiogram [8][21][25][27][28][31][34][35] (**Figure 3**B). GAGs were also identified as well-delineated focal calvarial defects on plain X-ray [13][15] or as focal filling defects within the DVS on conventional angiography and/or on cross-sectional studies [11]. GAGs with bone involvement caused smooth, evenly marginated impressions on the inner table of the skull and sometimes expanded into the diploic space, rarely eroding the outer skull table. Eight extrasinus-type GAGs that exhibited large “erosive” or “destructive” osteolytic calvarial defects were suspected to be malignant tumors [3][12][13][15][16]. MRI was the test of choice for differentiating GAGs from DVS thrombosis.

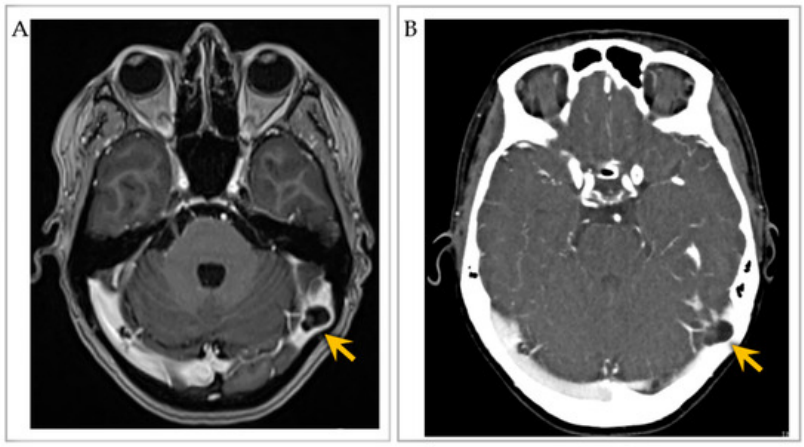

Figure 3. Imaging of an individual with multiple intrasinus-type GAGs. (**A**) Post-contrast T1-weighted brain MRI axial image shows two GAGs along the right and left lateral transverse sinuses, with severe sinus narrowing on the left (arrow). (**B**) CT venogram axial image further depicts the two GAGs with severe left lateral transverse sinus luminal narrowing (arrow). Images reproduced from *Int. J. Mol. Sci.* **2023**, *24*, 11410 [45].

While the internal GAG characteristics generally paralleled those of CSF on CT and MRI, GAGs more commonly demonstrated internal vascular (i.e., presumed veins) and/or soft tissue elements that were not easily observable in smaller AGs. In an imaging review, brain parenchymal herniation into GAGs was found in 22% of DVS-type GAGs [18]. The internal MRI signal was CSF-incongruent in a majority of GAG cases [11][18] and this differential signal was most commonly identifiable on high-resolution T2-weighted or T2-FLAIR sequences [18]. In a retrospective MRI analysis of DVS-type GAGs published by Ogul et al. [18], vessels were identified in 33 of 45 GAGs (73.3%) and were best observable by contrast-enhanced dynamic MR venography or post-contrast high-resolution T1-weighted MPRAGE sequences. An internal GAG vein was demonstrated in 22 out of 26 (84.6%) female patients by dynamic MR venography and was significantly more common than in males ($p = 0.04$), although the reason for this sex difference is unclear [18].

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