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Trend of cerebral aneurysms over the past two centuries: need for early screening

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ABSTRACT

Objective Cerebral aneurysms (CAs) are linked to variations in the cerebral basal arterial network (CBAN). This study aimed to find the optimal age for screening to detect brain arterial variations and predict aneurysms before rupture.

Design An observational, quantitative and retrospective research.

Setting The study analysed 1127 cases of CAs published from 1761 to 1938. Additionally, CT angiography images of 173-patients at the Royal Adelaide Hospital (RAH), South Australia between 2011 and 2019 were examined for the presence and the location of aneurysms in CBAN.

Participants The data were collected from patients at RAH and 407 published sources, including males and females across the entire age range, up to 100 years old.

Outcome measures and results Data, CAs cases, from 1761 to 1938 included (526 males, 573 females and 28 unknown sexes). The age of these patients varied from 18 months to 89 years (mean age=42, SD=18). Approximately 11.5% of the CAs occurred in patients aged <20 years. Among the 1078 aneurysms whose location was reported, 76% were located in the internal carotid (IC), middle cerebral (MC) and anterior communicating artery complex (AcomAC) regions, while the remaining 24% were in the vertebrobasilar region. Among 173 patients from RAH aged between 18 and 100 years (male=83 and female=90, mean age=60, SD=16), 94% of the CAs were found in the IC, MC and AcomAC regions. The pattern of aneurysm occurrence, as indicated by values at the 25th, 50th and 75th percentiles, along with the minimum and maximum patient ages, has remained consistent from 1761 to 2019.

Conclusion The distribution pattern of CAs in relation to sex, age and locations in the CBAN, remained steady over the last 260 years resulting in risk of strokes early in life. Therefore, early screening for CBAN segment variations is advised for stroke prevention if possible.

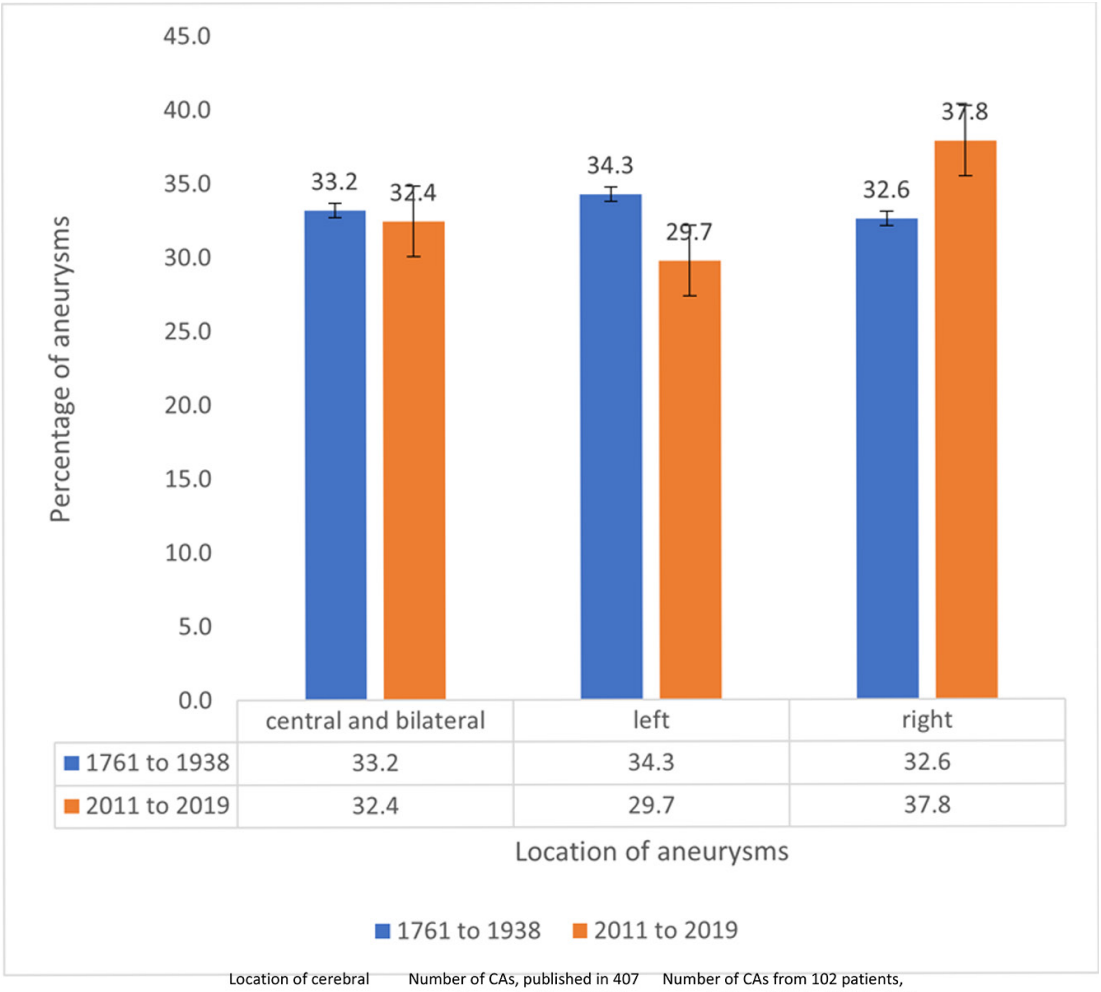
STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, the patterns of distribution and trends of occurrence of cerebral aneurysms have not been systematically studied over the past 260 years.
⇒ Aneurysms can develop at any age in the presence of variations in cerebral basal arterial network (CBAN).
⇒ Early detection of variations in CBAN in infant using non-invasive Doppler ultrasound technique is recommended and continuing screening regularly as needed.
⇒ Reported cases from the tertiary medical centres and 407 papers published over the past 260 years may not represent the general population precisely.
⇒ This investigation is not a continuous study.

INTRODUCTION

Anatomical variations among components of the cerebral basal arterial network (CBAN) in addition to the trauma, infection, spontaneous dissections and collagen disorders have been linked to the formation of cerebral aneurysms (CAs)[1–3] and such variations develop during the period of embryonic life.[2] The period taken for the development of CAs may vary among individuals and once formed they may enlarge, compress the surrounding tissues and rupture leading to subarachnoid haemorrhage (SAH).[3]

CAs of all sizes have been observed to cause SAH in adults[4] (incidence 6–10/100 000), however, they also occur in the age group 0–20 years (incidence rate=1.4–2 per 100 000).[5–7] It is not clear that the occurrence of anatomical variation-related aneurysms is limited to any specific age. The management of complicated CAs is costly and the CAs can leave permanent disabilities or even become fatal costing millions of dollars to families and governments.[7–12] The majority of childhood SAH (ie, incidence 1.4–2 per 100 000 children) are caused by the pre-existing CAs.[13] About 5% of the total cerebral aneurysmal cases diagnosed in the clinical setup were in the age group 0–19 years and the incidence of childhood SAH is significantly greater in the older age children.[13] The clinical manifestation of aneurysmal cases seen later in life might be the consequence of aneurysms that developed in early childhood. Therefore, this study aims to review cases of CAs using data collected from a tertiary medical centre (Royal Adelaide Hospital (RAH), South Australia) and published sources to investigate the recent pattern of CAs and how it has changed over the past 260 years. The null hypothesis is that the advancement of



Location of cerebral aneurysms	Number of CAs, published in 407 papers[14], recorded from 1761 to 1938	Number of CAs from 102 patients, recorded from 2011 to 2019 in RAH
central and bilateral	374	44
left	386	40
right	367	51
Total	1127	135

Figure 1 Comparison of the location of cerebral aneurysms (CAs) between Royal Adelaide Hospital (RAH) sample (2011–2019) (n=135 CAs from 102 patients, orange colour) with those recorded in 407 publications (1761–1938) (n=1127 CAs, blue colour).[14]

medical science did not lead to a reduction in the prevalence of aneurysms by age.

MATERIALS AND METHODS

Study design and setting

Two types of data were used in this study:

1. Type 1 data are composed of 1127 cerebral aneurysmal cases that were published in the 407 papers from 1761 to 1938, as compiled by McDonald and Korb.[14] These CAs were identified at autopsy and included patients of all ages (average age=41.7 years, mode age=41 years, median age=41 years, SD=17.7, age range 1.5–89 years) (online supplemental files 1 and 2).
2. Type 2 data were cerebral CT angiography (CTA) images obtained from 173 randomly selected patients, who visited RAH, South Australia, between January 2011 and December 2019 for a variety of cranial pathologies; their age ranged from 18 to 100 years, males=83, females=90, mean age=60 years, median age=62 years, mode age=61 years, SD=15.72) with (n=102) or without (n=71) aneurysms (online supplemental files 2 and 3). These images were anonymised, stored in the Carestream data registry system. The consent documents taken from each patient were not provided to the researchers to ensure privacy. The research materials used in this study comprised 1229 observed cases of CAs that spread across all age groups, spanning a period of approximately 260 years.

Data sources and size

Type 1 data: a range of variables (such as, the year CAs was detected, age, sex, location of the aneurysm) related to 1127 cases of CAs reported in publications from 1761 to 1938,[14] were transferred into an excel data file, rearranged and subjected to analysis (online supplemental

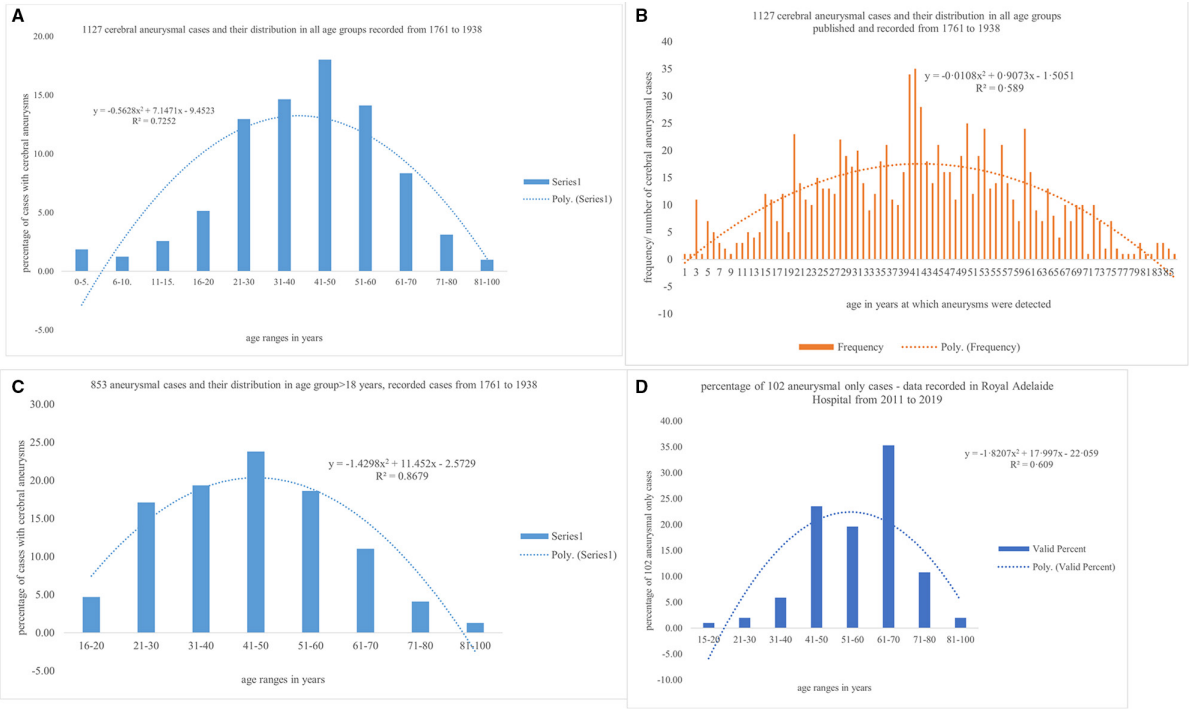


Figure 2 Figures displaying the distribution patterns of cerebral aneurysms (CAs) in different age groups recorded from 1761 to 1938 and from 2011 to 2019. A polynomial regression lines show the number and distribution of CA cases across all age groups. (A) The distribution of cerebral aneurysmal cases (n=1127) in various age groups, recorded from 1761 to 1938.[14] (B) The frequency of cerebral aneurysmal cases and their distribution (n=1127) across all age groups recorded[14] from 1761 to 1938. (C) Age-related (≥18 years) distribution of individuals affected with CAs over the past 260 years (1761–1938) (n=853), recorded[14] from 1761 to 1938, and (D) age-related (18–100 years) prevalence (%) of CAs in Royal Adelaide Hospital (RAH) sample from 2011 to 2019 (n=102). The peak prevalence occurred between 31 and 60 years (p<0.001).

file 1). Type 2 data: the cerebral CTA of 173 patients recorded from 2011 to 2019 in RAH were accessed to study the presence and absence of CAs in different locations of CBAN based on diagnoses made by clinicians. Some cases had multiple aneurysms located in the various segments of CBAN (online supplemental file 3).

The above cases of CAs were grouped into age ranges 0–5, 6–10, 11–15, 16–20, 21–30, 31–40, 41–50, 51–60, 61–70, 71–80 and >81 years and transferred into the SPSS V.25 software, for analyses (online supplemental file 1). The observation error has been tested by repeating the observation of the location of CAs in the cerebral CTA images in 20 cases, a month after the first study. There was 100% agreement of repeated observations with those of the first one. The sites of the formation of aneurysms were recorded as the left and right, internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), anterior communicating artery complex (AcomAC), posterior communicating artery, posterior cerebral artery, vertebral artery, basilar artery, posterior inferior cerebellar artery, anterior inferior cerebellar artery, superior cerebellar and pial arterial regions. In some cases, the areas of location of aneurysms seemed not to have been mentioned and those cases were tabulated under the heading of 'aneurysms located in CBAN'. Overall, the locations of nearly 1229 aneurysmal cases from both datasets were broadly divided into four categories: central and bilateral, left and right (figure 1) before being plotted in the bar charts to study the location and distribution trends of aneurysms in the arterial network over the past 260 years (figure 2). The aneurysms located in the AcomAC, and basilar arterial regions were classified as the central group of aneurysms. Additionally, in a few cases aneurysms were located simultaneously on left and right sides and those cases were grouped as 'bilateral' (online supplemental files 1 and 3 and figure 1).

Statistical methods

Data were analysed using Excel and Statistical Package for the Social Sciences (SPSS-IBM, V.25) program (eg, descriptive and χ^2 tests). The p values <0.05 were considered as statistically significant.

Patient and public involvement

Involving patients was challenging for conducting and planning this research, since researchers were allowed the access only to anonymised raw data recorded in the database. As per the ethics permit, we accessed retrospective anonymised data, precluding patient involvement in research planning and execution. The shared outcome of this study will be informed to the public, families and patients who attend medical centres for various clinical visits, through a series of meetings, seminars and media releases.

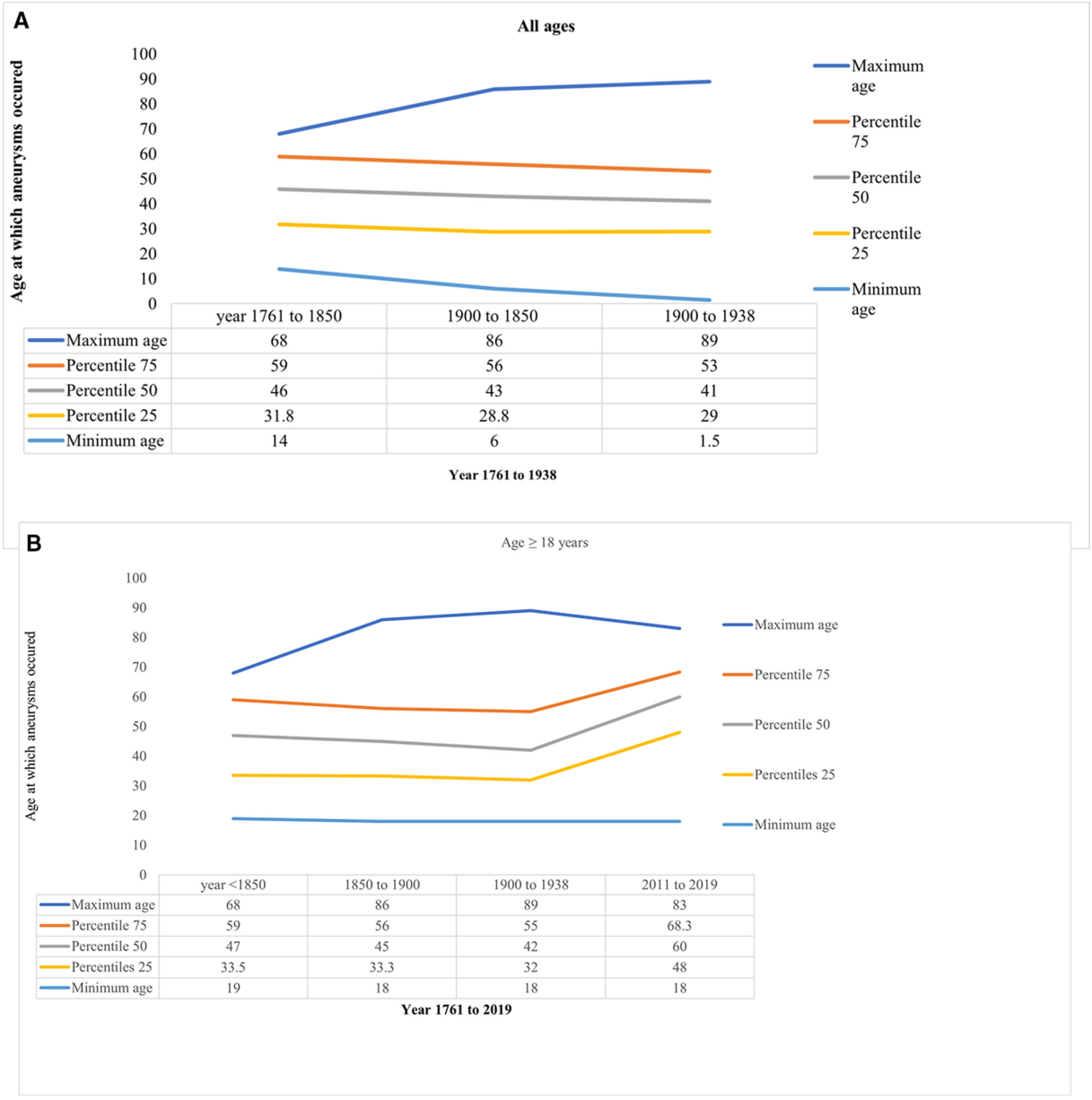


Figure 3 Comparison figures showing the trend of occurrence of cerebral aneurysms at different age group (n=1127) from 1761 to 2019. (A)The values of the 25th, 50th and 75th percentiles, as well as the minimum and maximum observed all ages of patients with aneurysms, from 1761 to 1938.[14] (B) The values of the 25th, 50th and 75th percentiles, as well as the minimum and maximum observed patients with >18 years of age with aneurysms, recorded from 1761 to 1938[14] and 2011 to 2019 in Royal Adelaide Hospital.

Findings

This study reviewed 1127 aneurysmal cases of patients of all ages from a total of 407 published articles prior to the year 1939. The ages of these patients (males=526, females=573, unknown sex=28) ranged from 18 months to 89 years of age with an average of 41.70 years, mode of 41 years and median of 41 years (SD=17.7) (online supplemental file 2, figure 2A–C and online supplemental file 1). The second group of patients with CAs (44 males and 58 females, and n=102) from RAH (2011–2019) with the age range 18–100 years showed that the most common age for diagnosis or complication of CAs ranged from 31 to 60 years with the calculated mean, median, mode and SD of 57.60, 60.00, 48.00 and 13.12 years, respectively (figure 2D and online supplemental file 4). Analysis of both sets of data revealed that the majority of the patients who presented with complicated aneurysms were in their third to sixth decades of life (online supplemental file 2).

The most important aspect of the two sets of data was the wide age range of occurrence of CAs and the fact that some of the complicated aneurysmal cases appeared at an early age (figure 2A,B, online supplemental file 1). A separate analysis was conducted for 853 out of the 1127 cases of CAs recorded before 1938 (males=409, females=438, unknown sex=6), specifically focusing on the age range of 18–89 years to align the age groups with

Table 1 Prevalence of cerebral aneurysms in males and females: a comparison of the recent hospital-based data recorded in RAH from 2011 to 2019 with the autopsy data published before from 1761 to 1938

Sex	N=173, cases with or without cerebral aneurysms recorded in RAH from 2011 to 2019	N=1127 aneurysm cases (from 1761 to 1938) recorded in 407 publications[14]
Sex not defined	0	28
Female	90	573
Male	83	526
Female-to-male sex ratio	1.08	1.09

*This study investigated the prevalence of cerebral aneurysms in both males and females, drawing a comparison between recent hospital-based data recorded in RAH (2011-2019) and autopsy data published between 1761 and 1938.
N, Number of aneurysmal cases; RAH, Royal Adelaide Hospital; RAH, Royal Adelaide Hospital.

the RAH recorded data from 2011 to 2019 (online supplemental file 2, figure 2C,D). The similarities of SD (15.45) of those 853 cases (from 1761 to 1938) and the cases that were recorded from 2011 to 2019 in RAH (13.12 years) validated the comparability of our data and the findings (online supplemental file 2). The values of the 25th, 50th and 75th percentiles, as well as the minimum and maximum observed ages of patients with aneurysms, remained relatively stable from 1761 to 1938 (figure 3A). Some of these percentile values increased slightly as life expectancy extended from 1761 to the 21st century (figure 3B). Therefore, the SD, and age distribution of adult patients with ruptured or diagnosed CAs presented in the 2011–2019 dataset were consistent with those cases reported before 1938, indicating persistence of a pattern (table 1, figures 2 and 3). Specifically, aneurysms are being frequently diagnosed in individuals aged 30–60 years, and this age range has remained relatively unchanged over the past 260 years (table 1, figures 2 and 3). Forty-nine out of 1127 cases recorded across 407 publications from 1761 to 1938 seemed not to have information about the location of aneurysms in the CBAN, however, 818 out of 1078 identified aneurysms (76%) were in the ICA, MCA and AcomAC regions and rest of them were in the vertebrobasilar region (online supplemental file 1). The location and distribution pattern of aneurysms from 102 patients recorded in RAH was consistent with 1078 cases recorded from 1761 to 1938 (online supplemental files 1–3).

In the type 2 dataset, a total of 135 aneurysms were identified in 102 individuals, with ages ranging from 18 to 83 years, across various components of CBAN (figure 2D and online supplemental file 3). Among these aneurysms, 38 (28.14%) were detected in the right MCA region, while 17 (12.6%) were in the right ICA region. In comparison, the left MCA and ICA regions had 27 (20%) and 12 (8%) aneurysms, respectively, which appeared to be lower in number compared with the right MCA and ICA regions. When considering the distribution of aneurysms based on territory, 55 out of 135 aneurysms (40.74%) in 50 patients were found in the right ICA and MCA territories, whereas 39 out of 135 aneurysms (28.88%) in 37 patients were detected in the left ICA and MCA regions (online supplemental file 3). Out of the 102 individuals with aneurysmal cases included in the study, 33 (24.44%) had aneurysms located in the AcomAC region, accounting for 33 out of the total 135 aneurysms. An additional 5.9% of the total aneurysms (8 out of 135 aneurysms) were found in the vertebral and basilar arterial regions, as indicated in the online supplemental file 3. A majority of the CAs, 127 out of the total 135 (94% of the total), were in the MCA, ICA and AComAC regions (online supplemental file 3). Some cases had multiple aneurysms, for example, 2 cases had right ICA and MCA aneurysms, while 10 cases had left ICA and MCA aneurysms (online supplemental file 3).

There were no significant differences between male and female patients affected with CAs in all 1229 cases analysed in those two datasets (χ^2 statistic=0.83, p≥0.36) (table 1). The sex, age of occurrence and location of CAs appear to have remained steady over the past 260 years across all age groups (table 1 and online supplemental file 2, and figure 3). The mode, mean and median age and SD of patients with ruptured or diagnosed CAs studied from 2011 to 2019 in RAH matched well with the cerebral aneurysmal cases recorded in the past considering the difference in life expectancy between the two time periods studied (1761–1938 and 2011–2019) (figure 3 and table 1).

DISCUSSION

The age and locations at which CAs occur in the CBAN has not changed over past 260 years (figures 1–3, table 1) despite the life expectancy has increased over time worldwide and the progress in medicine. In the past people had shorter life span on average, and yet the CAs occurred at the same ages as they do now.[15] The life expectancy recorded at below 50 years in 1940 and even below 40 years in 1850 was way lower compared with the one recorded above 80 years of age since the year 2000 in Australia.[15] A separate analysis was done for 853 out of the 1127 CAs recorded[14] before 1938 focusing on the age range of 18–89 years to align the age group with the currently RAH recorded data from 2011 to 2019, since there were no aneurysmal cases of children (age <18

years) in the RAH dataset. In Adelaide, there is a separate hospital for children where aneurysmal cases would have been treated, but the authors had no access to these data (online supplemental file 3). RAH is a general hospital, thus individuals aged 18 years and less are not admitted. Current study compared the cases of CAs diagnosed by CTA imaging technique (from 2011 to 2019) with those verified by surgery and autopsy,[14] since there were no cerebral angiogram facilities in early years (ie, before 1938). The cases of aneurysms are commonly diagnosed, when the patients are presented at medical centres after attacks of stroke.[16] CAs in the past seemed to be ruptured and complicated as early as 18 months of age and as late as 89 years of age with a wide range of age (online supplemental file 1). The findings suggested that the change in lifestyle or medical practice had no effect at the age/time of formation of CAs in general population. Clinical investigation of lipid profiles in patients commenced after 1950,[17] and they started attributing arterial diseases and aneurysms to the hyperlipidaemia, however, the manifestation of occurrence of aneurysms by age in the past 260 years seems not to be different from the current age of occurrence. Although the lifestyle and the external influences, including medical practice, changed over more than two centuries, aneurysms still occur at approximately the same age. Therefore, aneurysms occur and rupture on their own internal circumstances and are not related to the diet, environmental and external factors.[18] The most likely internal factor is the severity of the variation on the segments of CBAN that adversely affects the haemodynamics resulting in the formation of aneurysms.[1 19] The condition of the arterial wall should not have changed over the last 260 years and that seems to be less significant than the variation in the components of CBAN. The segmental and communicating arteries play a crucial role in dampening the systolic pressure within the CBAN and reducing the likelihood of aneurysm formation.[1 19] The severity of arterial variation can have negative effects on the blood flow dynamics through the variant segment of the component of the CBAN.[1 19] The incidence of CAs is about 3.3% in the general population and may not be diagnosed, until they get enlarged as the size of the aneurysm <3 mm in diameter can be missed.[20] Imaizumi *et al* found that the prevalence rate of CAs was 4.32% in Japan.[12] The incidence rate of CAs in childhood (age <18 years) has been reported to be 0.5%–4.6%, which is almost as common as the incidence rate observed among adults.[13] Treating cases of CAs with a diameter <3 mm requires careful consideration, as pre-existing small aneurysms of ≤3 mm could rupture, resulting in spontaneous SAH.[21] The majority of CAs are detected only when they cause a stroke or other pathological effect (eg, compression of the optic tract).[4] Individuals >18 years are no longer considered children.[6 13]

Most of the symptomatic cases of CAs in the paediatric age group were observed in older children (15+ years),[13] and only complicated cases of CAs were generally diagnosed and reported.[22 23] If the incidence of childhood CAs described (ranges from 0.17% to 4.6%)[24] is corrected for number of years lived, it would be 18.4% of the total aneurysmal cases among adults. The adult patients included in CAs studies ideally have an age range of 18 years and above, which can include individuals up to the age of 100 years.[12 15] In contrast, the childhood group included in aneurysmal studies typically ranges from birth up to 18 years of age and a few studies have categorised patients who are 18 years or older under the adult group.[6 13] When the age range, 0–18 years and 19–100 years is considered, the incidence of childhood CAs, that should be multiplied by 5 times to correct for the number of years lived, can be comparable to that in adults because the childhood period of life is much shorter than the adulthood. Therefore, the age range of adult group (≥20 years up to 100 years) included in the CAs and stroke studies would be about 5 times more than the age range of children (ie, ≤18 years).[22 23] That means adults have 5 times more years to develop CAs compared with children. Therefore, the incidence of childhood CAs per year is almost equivalent to adult.[21 25] Hence, CAs could develop in early childhood in the presence of a significantly variant component of cerebral arterial anatomy,[1 2] and it could take years for them to balloon before becoming symptomatic and being observed in a tertiary medical centre. The overall pattern of location and distribution of childhood CAs was similar to adult as they commonly occurred in ICA, MCA and AcomAC regions.[3] Therefore, the development of CAs is not age related and found to be prevalent in all age ranges.[10 12 13 26] CAs may not always be associated with the advanced age, history of smoking, drinking alcohol but start forming as early as in the childhood in the presence of variant components of cranial blood vessels.[27] The mean age at which people were affected by CAs was reported to be 55–57 years of age in a study conducted using 1085 aneurysmal cases from 2008 to 2016.[28] There are a few reports of CAs published between 1938 and 2011 that could have been compiled for statistical analyses. However, their inclusion into this study would not have changed its basic conclusions, that is, large age range and no change through time in the occurrence of CAs.

Ultrasonographic video screening by placing the probe in the fontanelles of babies before they close has been found to be safe and effective in studying brain vessels[26 29] and can be incorporated as a screening tool to detect variations in intracranial vessels that could predispose to the development of CAs later in life. One illustration of such possibility is that individuals with the left and right ACA proximal segment diameter ratio >1.4 have a 27-fold increased risk of developing CAs in the AcomAC region.[1] Parents of children found to have variations in CBAN could be advised to schedule follow-up screening periodically, especially if a more affordable and convenient technology

for detecting brain aneurysms becomes available. The current screening recommendation is based on the congenital variations of segments of CBAN, but such variations could occur later on life in cases of pathology like atherosclerosis and could cause aneurysms. Future studies to test the association of presence of anatomical variations in CBAN in infancy and future risk of both unruptured and ruptured intracranial aneurysms in adulthood are recommended.

The estimated cost of a single stroke is approximately $A300 000 in Australia.[9] With a haemorrhagic stroke incidence of 10 per 100 000, the total cost amounts to $A45 million per year in a city like Adelaide,[1] South Australia, which has a population of 1.5 million. Regular screening for individuals with significantly variant brain arteries identified, representing 50% of the population, once every 5 years, and assuming the cost of a single CTA or magnetic resonance angiogram is about $A100 each, the total screening cost would be $A1.5 million per year, that means 30 times reduction in cost of strokes. Additionally, the government would receive millions of dollars in return as tax revenue from working individuals who would survive with little to no disability from potential strokes resulting from aneurysms. This study was not designed to examine the characteristics of aneurysms, but the focus was on the distribution of aneurysms in different segments of CBAN, trend of occurrence of aneurysms over the past 260 years and the comparison of CAs in all age ranges.

Limitations

The insufficient data on the lack of personal and family history, history of smoking, lipid profile and blood pressure are limitations of this study. A larger survey and a prospective study could be conducted. A prospective study could involve using ultrasound techniques to identify variations in brain vessels among infants.

CONCLUSION

Brain arterial aneurysms can develop early in the presence of variant arterial components. Screening children under 24 months using transcranial ultrasonography for variant cerebral arteries may be practical. Those with variations should undergo periodic tests for aneurysms, aiming to prevent some haemorrhagic strokes if an affordable and convenient technology for detecting brain aneurysms becomes available.

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Contributors AB is responsible for the overall content as the guarantor and accepts full responsibility for the work and the conduct of the study, has access to the data ands control the decision to publish. AB conceived the idea, collected and analysed both sets of data, took pictures, recorded videos, contributed to conceptualisation, prepared and drafted the manuscript. JK conceived the idea, contributed to the concept, aided in data interpretation, editing and the revision of the manuscript and approving the article. JT conceived the idea, contributed to the concept, aided in data interpretation, editing and the revision of the manuscript and approving the article. MH conceived the idea, masterminded and helped in statistics, data analysis and interpretation, editing and approving the article.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The Human Ethics permit (approval number: H2014176, Research Ethics Committee, Office of Research Ethics, Compliance and Integrity, Faculty of Health Sciences, University of Adelaide) granted permission to access and use the de-identified dataset from the Carestream data registry system (Vue-RIS-version-11.0.14.35) for research. The patients gave their consent to use their clinical information for research activities.

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