Giant Prolactinoma Embedded by Pseudoaneurysm of the Cavernous Carotid Artery Treated with a Tailored Therapeutic Scheme

Valeria Mercuri1 Daniele Armocida2 Francesco Paglia2 Gargiulo Patrizia1 Antonio Santoro2 Luca D’Angelo2

1 Endocrinology Unit, Department of Experimental Medicine, ‘Sapienza’ University of Rome, Rome, Italy
2 Department of Human Neurosciences, Neurosurgery, ‘Sapienza’ University of Rome, Rome, Italy

Address for correspondence Daniele Armocida MD, PhD, 37, Via di Sacco Pastore, Rome 00141, Italy (e-mail: danielearmocida@yahoo.it).

J Neurosci Rural Pract 2022;13:358–369.

Abstract

The coexistence of intracranial aneurysm (IA) is generally thought to be highest in patients with pituitary adenomas (PAs). Different mechanisms may play a role in aneurysm formation, but whether the PA contributes to aneurysm formation is still unclear. In the literature, there are numerous reported cases of this association; however, the analyses of the characteristics of PAs, aneurysms, and treatment management are rare and limited to a restricted number of case reports. We report a rare case of an embedded aneurysm in a macroprolactinoma treated with therapeutic management tailored to the clinical, neurological, and radiological characteristics of the patient. To select the best treatment, we reviewed the literature and reported the only cases in which the radiological characteristics of aneurysms, PAs, therapeutic management, and patient outcome are described. We aimed to understand what are the variables that determine the best therapeutic management with the best possible outcome. The presence of a large pseudoaneurysm of the internal carotid artery completely embedded in a giant macroprolactinoma is rare and needs a tailored treatment strategy. The importance of the preoperative knowledge of asymptomatic IA coexisting with PA can avoid accidental rupture of the aneurysm during surgical resection and may lead to planning the best treatment. A high degree of suspicion for an associated aneurysm is needed, and if magnetic resonance imaging shows some atypical features, digital subtraction angiography must be performed prior to contemplating any intervention to avoid iatrogenic aneurysmal rupture. Our multimodal approach with the first-line therapy of low-dose cabergoline to obtain prolactin normalization with minimum risks of aneurysms rupture and subsequent endovascular treatment with flow diverter has not been described elsewhere to our knowledge. In the cases, we suggest adopting a tailored low-dose cabergoline therapy scheme to avoid rupture during cytoreduction and initiate a close neuroradiological follow-up program.

Keywords

► prolactinoma
► pituitary adenoma
► cerebral aneurysms
► internal carotid artery
► cavernous sinus
► flow diverter

DOI https://doi.org/10.1055/s-0042-1749662.
ISSN 0976-3147.
Introduction

Brain tumors and intracranial aneurysms (IAs) are the most common cerebral lesions, and these two pathologies frequently could coincide and occur concurrently. The incidence of such coexistence is approximately 0.5% of all intracranial tumors as reported, but the assessment of the real incidence rate is difficult, as angiography is not routinely performed for all brain neoplasms. Among all types of brain tumors, this coexistence is generally thought to be highest in patients with pituitary adenomas (PAs). There is a general consensus that IAs occur more frequently in association with PAs than among the general patient population. By mean of both autopic and retrospective studies, with incidence rates ranging from 0.5 to 7.4%, coincidental aneurysms are reported almost seven times more frequently in patients with PAs than in patients with other types of brain tumors.

Several mechanisms of aneurysm formation associated with PA have been proposed, including local circulatory stress, endocrine effect, mechanical effect, and direct invasion. It is possible that one or more mechanisms play a role in aneurysm formation at locations, but whether the PA contributes to aneurysm formation is still unclear. In the literature, over the decades, there have been sporadically numerous reported cases of this association, in some cases even very large series have been presented with more than 500 cases; however, the analyses of the characteristics of PAs, aneurysms, and treatment management are very rare and limited to a restricted minimum of case reports or clinical images. The great majority of these aneurysms are located outside the tumor itself. The presence of an internal carotid artery (ICA) aneurysm embedded within a PA located inside the sella turcica has rarely been reported. So, reported cases of giant PA are even rarer where extrasellar growth may result in fully embedded intracranial aneurysm (IA) in the tumor. Giant prolactinomas are a rare subset of macroadenoma characterized by large size (more than 40 mm in diameter), high aggressiveness, and massive extrasellar involvement. In this study, we report a rare case of an embedded aneurysm in a large PA treated with therapeutic management tailored to the clinical, neurological, and radiological characteristics of the patient. To select the best treatment for our case, we performed a review of the literature and reported the only cases in which the radiological characteristics of aneurysms, PA and therapeutic management, and patient outcome are described. With this study, we want to understand what are the main variables that determine the best therapeutic management with the best possible outcome of this uncommon but not even rare coexistence of pathologies.

Methods

We performed a review of the literature by analyzing all reported cases of PAs associated with IAs. We aimed to identify the clinical features of patients suffering from this unusual and coincidental relationship and to describe the best treatments proposed and performed. We also added our experience with an unusual case of carotid aneurysm embedded in PA.

Eligibility Criteria

Our target was to define the clinical and radiological criteria to deem a PA associated with IA by analyzing all cases reported in the relevant literature.

Therefore, while screening the literature, we adopted the following inclusion and exclusion criteria.

Inclusion criteria were meta-analysis, case series, clinical study, or clinical image reporting cases of patients who suffered from PA and IA.

Conversely, we excluded the following: cases reported without detailed clinical features of patients, cases reported without the description of radiological images, papers that report other pathologies (out of topic), papers written in languages other than English, papers published before 1985, and before the introduction of magnetic resonance imaging (MRI) and digital subtraction angiography for diagnosis and treatment.

Information Sources and Search

The English literature was systematically investigated using MEDLINE, the NIH Library, PubMed, and Google Scholar. The last search date was 15 February 2022. The following search terms were used: Pituitary Adenoma AND Intracranial aneurysm OR Cerebral Aneurysm. Duplicated articles were removed after the first investigation through the libraries.

Results

The search returned a total of 526 results, including radiological, molecular, and clinical studies. To this initial cohort, the aforementioned exclusion criteria for the title and abstract selection were applied, accordingly eliminating a total of 165 publications. The resulting 361 papers were included in our analysis. We subsequently excluded 315 articles after complete revision of the paper for inconsistent or incomplete case descriptions of cases reported, out of topic, or duplicated cases. A flowchart showing the article selection method is given in Fig. 1.

From the final 46 articles enrolled, we selected 150 patients for this review, including our representative cases. The 150 patients are listed in Table 1.

The total number of patients was 150, with a mean age of 52.15 years (reported for 144 cases; minimum = 18, maximum = 73), 62 males (43.05%), and 82 females (56.94%). Details are given in Table 2.

The histological type of PAs reported document-wide variability, where nonsecreting adenomas accounted for the majority of cases (41 cases, 42.7%), followed by GH-secreting adenomas (33 cases, 34.4%), and prolactinomas (17 cases, 17.7%).

Description of aneurysm onset symptomatology and its correlation with diagnosis and management of PA was reported in 71/150 patients. We observed that in 36.62% (26/71 patients) of cases, the diagnosis of IA occurred incidentally following routine radiological examinations, and in
6/71 patients (8.45%), it occurred during the follow-up after the PA removal procedure, in the absence of symptomatology. In 16 patients, the presence of aneurysm was diagnosed after the persistence of symptoms after surgery or after abnormalities found during the transsphenoidal (TS) surgery procedure. From these, seven patients (9.86%) manifested progressive worsening of visual acuity after treatment of PA, three patients (4.23%) manifested acute headache in the absence of intracranial bleeding, three patients presented epistaxis (4.23%), and two patients (2.82%) exhibited severe intracranial hemorrhage symptoms with loss of consciousness and severe neurologic deficits. We report one patient with transient ischemic attack.

The most common location for an IA associated with a PA was the ICA with 89/126 cases reported (70.6%). The most frequent site of the aneurysm was at the intracavernous ICA (reported as carotid sinus ICA) with 50/126 reported cases (39.68%), followed by the supraclinoid ICA (37/126 patients, 29.37%) and the superior hypophyseal artery-ICA segment (2 cases, 1.59%). Other reported localizations were in decreasing order: anterior communicating artery (12/126 patients, 9.5%), anterior cerebral artery (9 patients, 7.14%), medium cerebral artery (8 patients, 6.35%), posterior cerebral artery (6 patients, 4.76%), and basilar artery (2 patients, 1.59%). The mean major dome diameter measured in the involved aneurysms was 2.69 mm (minimum 2.1 mm and maximum 14 mm).

The mode and timing of treatment was found to be highly variable and dictated, first, by the early and contextual diagnosis of the aneurysm along with the presence of PA and, second, based on the symptomatology and the presence of embedded aneurysm in PA.

In most of the reported cases (27/62, 43.5%), it was chosen to treat IA first by endovascular approach followed by the performance of TS approach for PA. In 12/62 patients (19.35%), the choice was made to treat the aneurysm and PA by a transcranial approach at the same surgical time.

In view of the fact that a considerable number of IAs were diagnosed during or after the procedure, a large number of PAs (12/62, 19.35%) were treated by the TS approach followed by the TC approach (5/62 patients 8%) and by the endovascular procedure in 4/62 patients (6.4%). In four cases, IA was not treated after TS surgery, and in another four cases, only a medical approach on PA was attempted before considering subsequent treatments. The other procedure modalities are shown in the tables.

Approaches on aneurysms were in most cases by the endovascular route, as also a consequence of the fact that most of them were located in the intracavernous compartment. Individual details of the procedures are given in the tables.

**Outcome Analysis**

The success rate of documented cases of aneurysm diagnosed at the same time as a PA was considered high with 60.41% of patients having an excellent outcome with endocrinological and neurological symptoms regressed or improving. The
## Table 1 Study selection

| Author            | Year | Patients | Sex | Age | Aneurysm location | Aneurysm symptoms | Aneurysm treatment | Embedding | Dimensions aneurism (mm) | Adenoma Symptoms | Type | Adenoma treatment | Timing-Modality | Outcome               |
|-------------------|------|----------|-----|-----|-------------------|-------------------|--------------------|-----------|-------------------------|------------------|------|---------------------|-----------------|-----------------------|
| Acqui et al^8     | 1987 | 2        | M   | 48  | AcoA              | Incidental        | Clipping           | No        | \                       | Acromegaly, visual loss | GH   | Transcranial        | Same            | Diabetes insipidus     |
|                    |      |          |     |     |                   |                   |                    |           | \                       |                   |      |                     |                 |                       |
| Onishi et al^16    | 1989 | 1        | F   | 31  | ICA               | Visual loss       | Clipping           | Yes       | \                       | Acromegaly       | GH   | Transcranial        | Same            | Good                  |
| Fudde et al^17     | 1990 | 1        |     |     | AcoA              | Incidental        | Clipping           | No        | \                       | Nonsecretory     | Transsphenoidal | TS-TC                | TCTS            | Good                  |
| Fujimura et al^18  | 1991 | 1        |     |     | ICA               | Hemorrhage        | Clipping           | \         | \                       | None             | GH   | Transcranial        | Same            | Good                  |
|                    |      |          |     |     |                   |                   |                    |           | \                       |                  |      |                     |                 |                       |
| Fedder et al^17    | 1990 | 1        |     |     | ICA               | Visual loss       | Clipping           | \         | \                       | Acromegaly       | GH   | Transcranial        | Same            | Good                  |
|                    |      |          |     |     |                   |                   |                    |           | \                       |                  |      |                     |                 |                       |
| Onishi et al^16    | 1989 | 1        | F   | 31  | ICA               | Visual loss       | Clipping           | \         | \                       | Acromegaly       | GH   | Transcranial        | Same            | Good                  |
| Fujimura et al^18  | 1991 | 1        |     |     | ICA               | Hemorrhage        | Clipping           | \         | \                       | None             | GH   | Transcranial        | Same            | Good                  |
|                    |      |          |     |     |                   |                   |                    |           | \                       |                  |      |                     |                 |                       |
| Acqui et al^8      | 1987 | 2        | M   | 48  | AcoA              | Incidental        | Clipping           | No        | \                       | Acromegaly, visual loss | GH   | Transcranial        | Same            | Diabetes insipidus     |
|                    |      |          |     |     |                   |                   |                    |           | \                       |                   |      |                     |                 |                       |
| Onishi et al^16    | 1989 | 1        | F   | 31  | ICA               | Visual loss       | Clipping           | Yes       | \                       | Acromegaly       | GH   | Transcranial        | Same            | Good                  |
| Fudde et al^17     | 1990 | 1        |     |     | AcoA              | Incidental        | Clipping           | No        | \                       | Nonsecretory     | Transsphenoidal | TS-TC                | TCTS            | Good                  |
| Fujimura et al^18  | 1991 | 1        |     |     | ICA               | Hemorrhage        | Clipping           | \         | \                       | None             | GH   | Transcranial        | Same            | Good                  |
|                    |      |          |     |     |                   |                   |                    |           | \                       |                  |      |                     |                 |                       |
| Onishi et al^16    | 1989 | 1        | F   | 31  | ICA               | Visual loss       | Clipping           | \         | \                       | Acromegaly       | GH   | Transcranial        | Same            | Good                  |
| Fujimura et al^18  | 1991 | 1        |     |     | ICA               | Hemorrhage        | Clipping           | \         | \                       | None             | GH   | Transcranial        | Same            | Good                  |
|                    |      |          |     |     |                   |                   |                    |           | \                       |                  |      |                     |                 |                       |

(Continued)
| Author        | Year | Patients | Sex | Age | Aneurysm location | Aneurysm symptoms | Aneurysm treatment | Embedding | Dimensions aneurism (mm) | Adenoma symptoms | Type | Adenoma treatment | Timing-Modality | Outcome |
|---------------|------|----------|-----|-----|-------------------|-------------------|-------------------|-----------|--------------------------|-----------------|------|---------------------|-----------------|---------|
| Yu et al      | 2011 | 1        | F   | 54  | ICA               | Incidental        | Coiling          | Yes       | 5.3                      | Visual loss     | Nonsecretory | Transsphenoidal   | EV-TS           | Good    |
| Oh et al      | 2012 | 18       | F   | 52  | MCA               |                    | Coiling          | No        | 8                        |                 | Nonsecretory | Transsphenoidal   | EV-TS           |         |
|              |      |          |     |     | Basilar artery    |                    | Coiling          | No        | 3                        |                 | Nonsecretory | Transsphenoidal   | EV-TS           |         |
| F            |      |          |     |     | AcoA              |                    | Coiling          | No        | 2.8                      | GH             | Nonsecretory | Transsphenoidal   | EV-TS           |         |
| F            |      |          |     |     | AcoA              |                    | Coiling          | No        | 2.3                      | GH             | Nonsecretory | Transsphenoidal   | EV-TS           |         |
| F            |      |          |     |     | MCA               |                    | Coiling          | No        | 6                        | GH             | Nonsecretory | Transsphenoidal   | EV-TS           |         |
| F            |      |          |     |     | MCA               |                    | Coiling          | No        | 3.2                      | GH             | Nonsecretory | Transsphenoidal   | EV-TS           |         |
| F            |      |          |     |     | MCA               |                    | Coiling          | No        | 7;3;2.3                  | Nonsecretory   | Transsphenoidal | Transcranial       | Same            | Good    |
| F            |      |          |     |     | MCA               |                    | Coiling          | No        | 4.2                      | ACTH           | Transsphenoidal | Transcranial       | Same            | Good    |
| F            |      |          |     |     | ICA               |                    | Coiling          | No        | 7                        | GH             | Nonsecretory | Transsphenoidal   | EV-TS           |         |
| F            |      |          |     |     | ICA               |                    | Coiling          | No        | 6                        | GH             | Nonsecretory | Transsphenoidal   | EV-TS           |         |
| F            |      |          |     |     | ICA               |                    | Coiling          | No        | 7                        | GH             | Nonsecretory | Transsphenoidal   | EV-TS           |         |
| F            |      |          |     |     | ICA               |                    | Coiling          | No        | 5                        | GH             | Nonsecretory | Transsphenoidal   | EV-TS           |         |
| F            |      |          |     |     | ICA               |                    | Coiling          | No        | 6                        | Incidental     | Nonsecretory | Transsphenoidal   | EV-TS           |         |
| F            |      |          |     |     | CS-ICA            |                    | Coiling          | No        | 4.4                      | GH             | Nonsecretory | Transsphenoidal   | EV-TS           | Good    |
| F            |      |          |     |     | ICA-SHA           |                    | Coiling          | Yes       | 6.27;3.99                | Visual loss     | Nonsecretory | Transsphenoidal   | EV-TS           | Good    |
| F            |      |          |     |     | ACA A2            | TIA               | Bypass           | No        | Incidental               |                |                | Transcranial       | Same            | Good    |
| Author             | Year | Patients | Sex | Age | Aneurysm location | Aneurysm symptoms | Aneurysm treatment | Embedding | Dimensions aneurism (mm) | Adenoma Symptoms | Type | Adenoma treatment | Timing-Modality | Outcome |
|--------------------|------|----------|-----|-----|------------------|------------------|-------------------|-----------|-------------------------|-----------------|------|-------------------|-----------------|---------|
| Yoon et al41       | 2014 | 1        | F   | 44  | PCA              | Incidental       | Coiling           | No        | \           | \               | \               | Nonsecretory | Transsphenoidal | TS-EV          | Good    |
| Almeida Silva et al42 | 2014 | 1        | M   | 53  | AcoA             | Headache         | Clipping          | Yes       | 1          | \               | Hyperprolactinemia, visual loss | PRL          | Transsphenoidal | TS-TC          | Good    |
| Xu et al3          | 2015 | 1        | M   | 49  | AcoA             | Headache         | Clipping          | Yes       | \           | Note, in follow-up | PRL          | Transcranial | Same + gamma knife | Good    |
| Peng et al7        | 2015 | 1        | M   | 53  | CS-ICA           | Epistaxis, visual loss | Balloon           | Yes       | 14        | Incidental      | PRL          | Transsphenoidal | TS-EV+Medical | Good    |
| Tian et al47       | 2015 | 1        | F   | 63  | AcoA             | Postsurgery       | Coiling           | No        | 3.5;8       | \               | PRL          | Transsphenoidal | TS-EV          | Good    |
| Lee et al49        | 2015 | 1        | F   | 32  | PCA              | Postsurgery       | \                 | Yes       | 2.1;2.9     | Visual loss    | Nonsecretory | Transsphenoidal | TS-wait and see-EV | Good    |
| Habibi et al45      | 2015 | 1        | F   | 35  | SCA              | Postsurgery       | \                 | \         | \          | \               | Nonsecretory | Transsphenoidal | TS             | Good    |
| Khalsa et al46      | 2016 | 1        | M   | 61  | CS-ICA           | Hemorrhage        | Coiling + onyx    | Yes       | 1.2        | Hyperprolactinemia | PRL          | Medical       | Medical + Wait and see | Hemothage, died |
| Satyarthi and Raheja | 2017 | 1        | M   | 52  | ICA              | Worsening visual acuity | Clipping          | Yes       | 10.2;10.1 | Visual loss    | GH            | Transcranial | Medical + TC | Good    |
| Khachatryan et al42 | 2018 | 1        | F   | 37  | ICA              | Incidental       | Coiling           | Yes       | 2.5        | Acromegaly     | GH            | Medical       | Medical + TS + EV | Good    |
| Hu et al2          | 2019 | 36       | 21 M, 15 F | 58  | CS-ICA 13, ICA 17, ACA 8, MCA 1, PCA 3, Basilar artery 1 | \                 | \         | 3.1 (mean) | \           | \               | 21 | Nonsecretory, 9 GH, 5 PRL, 1 ACTH | Transsphenoidal | \      |
| Nakoha et al13      | 2019 | 1        | F   | 61  | CS-ICA           | Postsurgery       | Coiling           | Yes       | 11.9       | Headache       | PRL          | Transsphenoidal | Medical-EV | Good    |
| Morinaga et al48    | 2019 | 1        | M   | 68  | PcoP             | Postsurgery       | Coiling           | No        | \          | Acromegaly     | GH            | Transsphenoidal | TS-EV          | Good    |
| Inoue et al49       | 2019 | 1        | M   | 41  | CS-ICA           | Acute epistaxis after RT for surgery residual | Bypass           | Yes       | \          | Acromegaly     | GH            | Transsphenoidal | TS-TC          | Good    |
| Kino et al12        | 2020 | 1        | F   | 53  | ICA-SHA          | Incidental       | Clipping          | \         | 3.3;2.7     | Visual loss    | Nonsecretory | Transsphenoidal | EV-TS-TC       | Hemothage |
| Ogawa et al30       | 2021 | 24       | 10 M, 14 F | 56  | \                 | \                 | \         | \          | \           | \               | \               | \ | \ | \ | \ |
| Piper et al7        | 2021 | 1        | M   | 67  | CS-ICA           | Incidental       | Flow diverter     | Yes       | 3.7;3.4     | Incidental     | Nonsecretory | Transsphenoidal | EV-TS          | Good    |
| Wang et al51        | 2021 | 1        | F   | 38  | CS-ICA           | Incidental       | Wait and see      | Yes       | \          | Visual loss    | Nonsecretory | Transsphenoidal | TS             | Good    |
| Our case2022        | 2022 | 1        | F   | 73  | CS-ICA           | Visual loss      | Flow diverter     | \         | \          | \               | Headache, diplopia | PRL          | Transsphenoidal | TS-EV+Medical | Good    |

Abbreviations: ACA, anterior cerebral artery; AcoA, anterior communicating artery; ACTH, adrenocorticotropic hormone; CS-ICA, carotid sinus internal carotid artery; EV, endovascular; F, female; FSH, follicle-stimulating hormone; GH, growth hormone; ICA-SHA, internal carotid artery–superior hypophyseal artery; M, male; MCA, medium cerebral artery; PRL, prolactin; RT, radiography; Same, during the same surgery; TC, transcranial; TS, transsphenoidal; TSH, thyroid-stimulating hormone.
Table 2 Population study

| Patients reported 150 |  
|---------------------|-----------------------|
| Sex (144) | F = 82/144, 57.94% |
| Age (144) | Mean age = 52.15 minimum = 18, maximum = 73 |
| Adenoma histology (reported in 96 pts) |  
| Nonsecreting = 41/96, 42.7% |
| GH = 33/96, 34.4% |
| PRL = 17/96, 17.7% |
| TSH = 2/96, 2% |
| ACTH = 2/96, 2% |
| Craniopharyngioma = 1/96, 1% |
| Aneurysm symptomatology |  
| Incidental = 26/71, 36.62% |
| Visual loss = 7/71, 9.86% |
| Postsurgery = 6/71, 8.45% |
| Epistaxis = 3/71, 4.23% |
| Headache = 3/71, 4.23% |
| Hemorrhage = 2/71, 2.82% |
| TIA = 1/71, 1.41% |
| Aneurysm location |  
| CS-ICA = 89/126, 70.6% |
| AcoA = 12/126, 9.5% |
| ACA = 9/126, 7.14% |
| MCA = 8/126, 6.35% |
| PCA = 6/126, 4.76% |
| Basilar artery = 2/126, 1.59% |
| Aneurysm dimension (113) |  
| Mean = 2.69 mm (minimum = 2.1, maximum = 14) |
| Treatment modality |  
| EV-TS = 27/62, 43.5% |
| TC in same procedure = 12/62, 19.35% |
| TS-TC = 5/62, 8% |
| TS-EV = 4/62, 6.4% |
| TS-wait and see = 4/62, 6.4% |
| TG-TS = 4/62 - 6.4% |
| EV-TG-Gamma-knife = 1/62, 1.6% |
| Medical + TC = 1/62, 1.6% |
| Medical + TS + EV = 1/62, 1.6% |
| Medical + Wait and see = 1/62, 1.6% |
| Medical + EV = 1/62, 1.6% |
| TC + Medical = 1/62, 1.6% |
| Aneurysm treatment (86) |  
| Coiling = 33/86, 38.37% |
| Clipping = 19/86, 22.1% |
| Balloon occlusion = 4/86, 4.65% |
| Pipeline = 2/86, 2.33% |
| Wait and see = 2/86, 2.33% |
| ICA aneurysm embedded | 24/67, 35.8% |

Table 2 (Continued)

| Patients reported 150 |  
|---------------------|-----------------------|
| Adenoma treatment (101 pts) |  
| Medical = 4/101, 3.9% |
| Transcranial = 12/101, 11.9% |
| Transsphenoidal = 84/101, 83.1% |
| None = 1, 0.9% |
| Outcome (43 pts) |  
| Good = 29/43, 60.41% |
| Hemorrhage/rupture = 5/43, 11.62% |
| Adenoma regrowth = 3/43, 6.98% |
| Aneurysm rehabilitation = 3/43, 6.98% |
| Worsening visual acuity = 1/43, 2.33% |
| Diabetes insipidus = 1/43, 2.33% |
| CSF leak = 1/43, 2.33% |

Abbreviations: ACA, anterior cerebral artery; AcoA, anterior communicating artery; ACTH, adrenocorticotropic hormone; CSF, cerebrospinal fluid; CS-ICA, carotid sinus internal carotid artery; EV, endovascular; GH, growth hormone; MCA, medium cerebral artery; PCA, posterior cerebral artery; PRL, prolactin; TC, Transcranial; TIA, transitory ischemic attack; TS, transsphenoidal; TSH, thyroid-stimulating hormone.

most common complications reported were hemorrhage from aneurysm rupture in the postoperative phase or if the patient refused treatment (five cases, 11.62%), followed by incomplete regression of endocrinological symptoms or mass effect of the adenoma on parasellar structures (two cases, 4.65%). One patient died before the procedure, and one patient was not treated and was managed (at his preference) with wait-and-see management.

Two of these cases were reported in cases where only PAs were treated, two were evidenced after endovascular treatment with coiling and TS surgery, and one patient had rupture before starting any form of treatment. The only reported case of cerebrospinal fluid (CSF)-leak after procedures was reported in the case where the EV approach was performed after the TS approach.

During the follow-up, the presence of aneurysm grown in size, rehabilitated, or with the presence of bleeding was identified in 3/42 cases, 2 of which were in situations where only TS treatment for the PA had been opted for; in 1 case, only aneurysm rehabilitation occurred after the coiling procedure.

Representative Case

A 73-year-old woman with a history of arterial hypertension and amenorrhea since the age of 27 with no further investigation was admitted to our Hospital for headache and diplopia. Ophthalmological examination confirmed horizontal diplopia on the extreme lateral gaze. Examination of the fundus oculi ruled out papilledema. Apart from a slight left hemifacial hypoesthesia in the territory of V2, neurological examination was unremarkable. A gadolinium-enhanced brain MRI was performed and showed an intracranial lesion involving the left cavernous sinus and carotid internal
carotid artery. Gadolinium-enhanced T1 sequences documented a more parenchymatous area of the lesion that constituted the periphery of the neoformation. The inner portion of the lesion presented signs of flow in continuity with the cICA (►Fig. 2A–D). A digital subtraction angiography confirmed the presence of a giant pseudoaneurysm of the cICA (►Fig. 2E–F). Pituitary hormones blood levels were tested: prolactin (PRL) > 4,000 ng/mL, follicle-stimulating hormone 1.2 mIU/mL, luteinizing hormone 0.1 mIU/mL; thyroid-stimulating hormone, free triiodothyronine, free thyroxine, adrenocorticotrophic hormone, cortisol, growth hormone, and insulin-like growth factor 1 were all within normal limits. An endoscopic endonasal three-dimensional-navigated paraseptal approach was performed to collect samples of the lesion abutting in the sphenoethmoidal recess. We deemed any further resection pointless because the likelihood of a histological diagnosis of prolactinoma was extremely high and, to mitigate the risk of aneurysm rupture, increased by any decompressing surgical maneuvers around the aneurysm itself. Histological examination confirmed the diagnosis of a PRL-secreting adenoma with an accumulation of amyloid-like amorphous material, expression of estrogenic receptors, with a Ki-67 of 2%. We decided to treat the cICA aneurysm in case of any further neurological deterioration. Low-dose cabergoline (0.5 mg twice a week) treatment was started. At discharge, visual symptoms were stable and headache responded well to common analgesics. After 6 months of medical therapy, the patient was stable and serum PRL was 45 ng/mL. After 1 year following the same regimen, serum PRL normalized (16 ng/dL).

Approximately, 12 months later, the patient was referred to our institution for a sudden severe headache, associated with nausea and photophobia, and deficiency of abduction of the left eye. A head computerized tomography scan was performed and excluded a subarachnoid hemorrhage (SAH). A control brain MRI showed no changes in tumor size but an increase in the size of the cICA pseudoaneurysm. Endovascular occlusion of the left ICA was not viable because occlusion tests revealed an insufficient contralateral blood supply, so a flow diverter (FD) (Pipeline embolization device) was deployed along the left cICA after adequate loading doses of aspirin and clopidogrel. The patient tolerated the procedure and discontinued clopidogrel 3 months afterward. At discharge, visual symptoms remained stable.

Five months after, diplopia completely regressed, and we observed a reduction in the size of the pathological tissue at the edges of the aneurysm. The dose of cabergoline was reduced to 0.5 mg 1/2 cp twice a week. Control brain MRI at 1 year revealed almost complete regression of the prolactinoma (►Fig. 3).

**Fig. 2** (A) Head CT scan three-dimensional volume reconstruction showing the cICA pseudoaneurysm, the petrous internal carotid artery (pICA), the basilar artery (BA), and anterior cerebral artery (ACA). Note the fetal origin of the left PComA (#) and hypoplastic left A1 segment (‘) and the extensive erosion of the middle cranial fossa caused by the giant prolactinoma (white arrows); (B–D) gadolinium enhanced brain MRI T1-weighted sequences in the three planes showing a voluminous neoformation packing the sphenoid sinus (white arrows) with an extension into the cavernous sinus, infiltration of the mesial temporal dura, middle cranial fossa, and initial involvement of the infratemporal fossa presenting an inner portion with flow signal in continuity with the ICA. (E–F) Digital subtraction angiography demonstrating a large pseudoaneurysm of the cICA.
Discussion

PA with coexisting IA is not uncommon. The clinical symptoms are mainly caused by hormones secreted by PAs or by compression on the surrounding brain tissues and optic nerve, while for associated IA, the diagnosis is often incidental (51/94, 54.26%). It seems that older age and cavernous sinus invasion increase the rate of coexistence; some studies have also hypothesized that female sex may be a risk factor for AIs in patients with pituitary tumors, but the reported data do not suggest this difference.

There are many explanations regarding the causes of so high association between PAs and IAs. The mass effect and invasion of tumors change the hemodynamics and vascular structure, respectively, of the intracranial arteries. As PA is a hormone-secreting tumor, the secreted hormones can induce aneurysm occurrence and growth. Among the full-detailed reported cases, the most commonly detected endocrinopathies were hyperprolactinemia (58/96, 60.4%) and GH-secreting tumors (33/96, 34.4%). ICA aneurysms have been correlated to hyperprolactinemia in the so-called vasculogenic hyperprolactinemia, much more than the presence of a true prolactinoma (reported in 17.7% of cases).

GH-secreting tumors could be considered an independent risk factor for IA formation. A prolonged elevated GH level can induce arteriosclerosis, degenerative changes in the arterial wall, and collagen metabolism, but considering that in the majority of cases (42.7%) PAs are inactive, this role in the pathogenesis of IAs, thus, remains to be fully elucidated.

Another explanation for the high coexistence between PA and IA lies in the size and invasiveness of pituitary tumors. PAs occur the majority of times near the intracavernous segment of the ICA; as a tumor grows, it may compress or invade the cavernous sinus, potentially changing the hemodynamics of the ICA and inducing the formation of an IA. Neoplastic infiltration over the cavernous sinus might strongly influence the incidence rate of IAs, especially in the case of pseudaneurysms involving the cICA as in our presented case. IA with coexisting PA can be classified as nonadjacent, adjacent, intradenoma types. In nonadjacent types, the aneurysm is located apart from the adenoma such that they are not in direct contact and are separated by other tissues. These are the cases where IA were outside the cavernous sinus (37 cases, 29.37%); in adjacent types, PAs and aneurysms were in close or partial contact, and the capsule of PA was intact; in intraadenoma types, the aneurysm body was partially or completely embedded in the PA (reported in 24/150, 16%). The last situation refers especially to the giant PAs that represent approximately 6–10% of all pituitary tumors. This rare subtype of PA is characterized by high aggressiveness and massive extrasellar involvement. They are usually associated with high serum PRL levels (>1,000 ng/mL, so they are also defined as giant prolactinomas).

The method for treating a PA associated with a cerebral aneurysm is controversial, and the problem occurs especially in cases with cerebral aneurysms embedded in PAs or in cases where the IA is not radiologically identified. The best strategy has to be tailored to the patient to adopt the best medical treatment, avoid accidental rupture of IA during the surgical procedure, and plan treatment for the removal of the adenoma. The choice for the best procedure also has to take into account the need for long-term antiplatelet drugs before surgery.
the removal of the PA. The strategies outlined in the various reports are numerous and varied, of these the four main and most used are treatment of the IA using the endovascular procedure before transsphenoidal surgery for the PA, transsphenoidal surgery as the first treatment step, the use of a combined surgical treatment for both pathologies, and the choice to adopt a medical treatment for PA before the decision on surgical procedures. In our analysis, the most adopted strategy in the last years was to subject the patient first to endovascular treatment (41.9%).

Management strategies for the treatment of cerebral aneurysms have greatly expanded, and endovascular therapy has almost replaced direct clipping in the last years, but the strategy treatment for this occurrence partially depends on the angiographic features of the aneurysm and ability to tolerate single or dual antiplatelet agents to prevent thromboembolic complications in the presence of a PA. In general, the preferred treatment for aneurysms associated with a PA was the endovascular coiling and, more recently, the FD device. The endovascular procedure has been performed in the majority of cases (28/62, 45.52%) prior to tumor resection and has led to avoid long-term antiplatelet drugs. In these procedures, antiplatelet therapy is generally not required and this intervention has been shown to provide aneurysm protection with low morbidity and facilitate transsphenoidal resection of the adenoma. For these reason, the treatment of the coexistence pathology can be performed within the same procedure (in this study is reported in 19.35% of cases). In cases of direct clipping, the surgical approach and the timing become problems (it was performed just in 11 cases reported). Performing both treatments with a transcranial approach is an alternative choice, but tumor resection via the endoscopic endonasal approach has more advantages than the transcranial approach in terms of preservation of endocrinological and ophthalmological function.

Regarding the outcome of patients, the results of the various treatments reported were good, with functional recovery and complete exclusion of the aneurysm achieved in 74.42% of cases. The most frequently reported complication was hemorrhage from aneurysmal rupture occurring during TS surgery (in only one case) and during the time between the two treatments.

If ICA-cavernous aneurysms rarely rupture because the aneurysm is surrounded by hard tissues such as the dura and other bony structures, the risk of rupture may increase if there is no longer the protection exerted by the presence of the tumor mass near or around the aneurysmal dome or in case of a rapid change in the intra- and parastellar pressure conditions. With this condition, the rupture could become dramatic once rupture and hemorrhage occur; the aneurysm may not be confined inside the tumor and may enter into the subarachnoid space to combine with SAH.

So, the most important risks could be apoplexy combined with SAH, severe epistaxis (reported in one case), or the genesis of a carotid-cavernous fistula.

In our case, we considered the possibility of aneurysm rupture during endovascular internal trapping because the prolactinoma might have invaded and increased the fragility of the aneurysmal wall. For these reasons, we suppose that in case of giant PAs, medical treatment of PA (in case of prolactinoma) must be performed at first. Objectives of the medical treatment include shrinkage of the lesion and normalization of serum PRL. First-line therapy is conducted with dopamine agonists, among which cabergoline is the most widely adopted. Some giant prolactinomas are responsive to a low dose of cabergoline; in this case, we observed normalization of serum PRL within 1 year. The average time needed to obtain a normalization of PRL levels is approximately 2 years. This variability is not associated with tumor size or baseline PRL serum level, and it is not correlated with tumor shrinkage. In this particular case, our therapeutic strategy was strongly influenced by the coexistent cICA aneurysm. The decision to use the minimum effective dose of cabergoline was determined by the need to avoid rapid shrinkage of the lesion, which could have induced aneurysm rupture.

After the occlusion test, in our case we preferred to select the use of FD as an approach for the IA. FD represents the mainstay of treatment of IAs not manageable with traditional coiling, as well as for the treatment of iatrogenic or posttraumatic pseudoaneurysms. FDs might be used in association with endosaccular coiling or to manage aneurysms already treated with coils. The use of FDs to treat cICA aneurysms embedded in pituitary macroadenoma has been already described and recently reported in a similar case.

**Conclusion**

IA are more frequently associated with PAs than with other tumor types, and the underlying reasons for this require continued exploration and study. Their diagnosis and management are extremely varied and poorly described in the literature. The importance of the preoperative knowledge of asymptomatic aneurysms coexisting with PA can avoid accidental rupture of aneurysm during surgical resection of PA and/or may lead to the planning of a special medical and surgical strategy to deal with both pathologies simultaneously. High degree of suspicion for associated aneurysm is needed, and if MRI shows some atypical features, DSA must be performed prior to contemplating surgical intervention to avoid iatrogenic aneurysmal rupture. The presence of a large pseudoaneurysm of the cavernous segment of the ICA (cICA) completely embedded in a giant macroadenoma is exceedingly rare and needs a tailored treatment strategy.

Our multimodal approach with the first-line therapy of low-dose cabergoline to obtain PRL normalization with supposedly minimum risks of aneurysms rupture and subsequent endovascular treatment with FD upon neurological deterioration has not been described elsewhere to our knowledge.

**Authors’ Contributions**

All authors have contributed equally to the draft of this manuscript.
Conflict of Interest
None declared.

References
1 Satyarthee GD, Raheja A. Unruptured internal carotid artery aneurysm associated with functional pituitary adenoma: a true association. Asian J Neurosurg 2017;12(04):701–704
2 Hu J, Lin Z, Zhang Y, et al. Prevalence of unruptured intracranial aneurysms coexisting with pituitary adenomas. World Neurosurg 2019;126:e526–e533
3 Xu K, Yuan Y, Zhou J, Yu J. Pituitary adenoma apoplexy caused by rupture of an anterior communicating artery aneurysm: case report and literature review. World J Surg Oncol 2015;13:228
4 Housepian EM, Pool JL. A systematic analysis of intracranial aneurysms from the autopsy file of the Presbyterian Hospital, 1914 to 1956. J Neuropathol Exp Neurol 1958;17(03):409–423
5 Wakai S, Fukushima T, Furuihata T, Sano K. Association of cerebral aneurysm with pituitary adenoma. Surg Neurol 1979;12(06):503–507
6 Piper KJ, Karsy M, Barton B, et al. Management of coincident pituitary macroadenoma and cavernous carotid aneurysm: a systematic literature review. J Neurol Surg Rep 2021;82(03):e25–e31
7 Peng Z, Tian D, Wang H, et al. Epistaxis and pituitary apoplexy due to ruptured internal carotid artery aneurysm embedded within pituitary adenoma. Int J Clin Exp Pathol 2015;8(11):14189–14197
8 Acquini M, Ferrante L, Fraioli B, Cosentino F, Fortuna A, Mastronardi A. Association between intracranial aneurysms and pituitary adenomas. Aetio-pathogenetic hypotheses. Neurochirurgia (Stuttg) 1987;30(06):177–181
9 Oh MC, Kim EH, Kim SH. Coexistence of intracranial aneurysm in 800 patients with surgically confirmed pituitary adenoma. J Neurosurg 2012;116(05):942–947
10 Saad AF, Syed A, Marashi KB, et al. Endovascular therapy using flow diversion for giant internal carotid artery pseudoaneurysm arising in the setting of an invasive pituitary macroadenoma. Proc Bayl Univ Med Cent 2017;30(01):47–49
11 De Sousa SMC, Meyer EJ, Rankin W, Brautigan PJ, Burt MG, Torpy D. Vasculogenic hyperprolactinemia: severe prolactin excess in association with internal carotid artery aneurysms. Pituitary 2017;20(06):676–682
12 Kino H, Ito Y, Akutsu H, et al. Combined endoscopic endonasal and bilateral subfrontal approach for a nonfunctioning pituitary adenoma associated with an internal carotid artery-superohipphysial artery aneurysm. World Neurosurg 2020;134:297–301
13 Nakahara M, Uozumi Y, Chiba Y, Miyake S, Fujita A, Kohmura E. Direct carotid cavernous fistula due to rupture of a cavernous carotid aneurysm embedded within a prolactinoma after cabergoline administration. World Neurosurg 2019;122:495–499
14 Paglia F, et al. Preoperative 3D volume reconstruction of the posterior wall of the sphenoid sinus with Horos: A free, simple and reliable tool in endoscopic endonasal trans-sphenoidal surgery. Neurocirugia (Astur) 2021 (e-pub ahead of print). Doi: 10.1016/j.neucir.2021.04.005
15 Kulseng B, Myhre HO. Is insulin growth factor-1 (IGF-1) playing a role for aneurysm formation in patients with pituitary gland tumors? Int Angiol 2006;25(04):433–435
16 Onishi H, Ito H, Kuroda E, Yamamoto S, Kubota T. Intracranial mycotic aneurysm associated with transsphenoidal surgery to the pituitary adenoma. Surg Neurol 1989;31(02):149–154
17 Fedder SL, Barnett TP, Curtin A. Pituitary macroadenoma and anterior communicating artery aneurysm. AJR Am J Roentgenol 1990;155(01):200–201
18 Fujiwara S, Fujii K, Nishio S, Fukui M. Diagnosis and treatment of pituitary adenoma with adjacent carotid artery aneurysm. J Neurosurg Sci 1991;35(01):41–46
19 Weir B. Pituitary tumors and aneurysms: case report and review of the literature. Neurosurgery 1992;30(04):585–591
20 Hermier M, Turjman F, Torrent P, et al. Intracranial aneurysm associated with pituitary adenoma shown by MR angiography: case report. Neuroradiology 1994;36(02):115–116
21 Salpietro FM, Longo M, Alafaci C, Cervasio O, Tomasello F. Coexisting pituitary tumour and intracavernous asymptomatic aneurysm: management implications. Acta Neurochir (Wien) 1997;139(08):791–792
22 Pant B, Arita K, Kurisu K, Tominaga A, Eguchi K, Uozumi T. Incidence of intracranial aneurysm associated with pituitary adenoma. Neurosurg Rev 1997;20(01):13–17
23 Imamura J, Okuzono T, Okuzono Y. Fatal epistaxis caused by rupture of an intratumoral aneurysm enclosed by a large prolactinoma—case report. Neurol Med Chir (Tokyo) 1998;38(10):654–656
24 Dolenc VV, Lipovsek M, Slokan S. Traumatic aneurysm and carotid-cavernous fistula following transsphenoidal approach to a pituitary adenoma: treatment by transcranial operation. Br J Neurosurg 1999;13(02):185–188
25 Revuelta R, Arriada-Mendicco N, Ramirez-Alba J, Soto-Hernandez JL. Simultaneous treatment of a pituitary adenoma and an internal carotid artery aneurysm through a supraorbital keyhole approach. Minim Invasive Neurosurg 2002;45(02):109–111
26 Sade B, Mohr G, Tampieri D, Rizzo A. Intrasellar aneurysm and a growth hormone-secreting pituitary macroadenoma. Case report. J Neurosurg 2004;100(03):557–559
27 Pany A, Sobri M, Valarmathi S, Nazihah M, LatifAZ, Adnan JS. Giant aneurysm or pituitary macroadenoma: a diagnostic dilemma. Med J Malaysia 2004;59(01):123–125
28 Yang MY, Chen C, Shen CC. Cavernous aneurysm and pituitary adenoma: management of dual intrasellar lesions. J Clin Neurosci 2005;12(04):477–481
29 Chuang CC, Chen YL, Pai PC. A giant intracavernous carotid artery aneurysm embedded in pituitary macroadenoma presenting with pituitary apoplexy. Cerebrovasc Dis 2006;21(1-2):142–144
30 Bulsara KR, Karavadi SS, Powers CJ, Paullus WC. Association between pituitary adenomas and intracranial aneurysms: an illustrative case and review of the literature. Neurol India 2007;55(04):410–412
31 Curto L, Squadrito S, Almoto B, et al. MRI finding of simultaneous coexistence of growth hormone-secreting pituitary adenoma with intracranial meningioma and carotid artery aneurysms: report of a case. Pituitary 2007;10(03):299–305
32 Soni A, De Silva SR, Allen K, Byrne JV, Cudlip S, Wass JA. A case of macroadenoma encaSing an internal carotid artery aneurysm, presenting as pituitary apoplexy. Pituitary 2008;11(03):307–311
33 Seda L Jr, Cukiert A, Nogueira KC, Huayllas MK, Lipovsek M. Intracranial internal carotid artery aneurysm coexisting with GH-secreting pituitary adenoma in an acromegalic patient. Arq Neuropsiquiatr 2008;66(01):99–100
34 Wang CS, Yeh TC, Wu TC, Yeh CH. Pituitary macroadenoma coexistent with supraclinoidal internal carotid cerebral aneurysm: a case report and review of the literature. Cases J 2009;2:6459
35 Rustagi T, Uy EM, Rai M, Kannan S, Senatus P. Intracranial hemorrhage from undetected aneurysmal rupture complicating transsphenoidal pituitary adenoma resection. Conn Med 2011;75(07):393–398
36 Yu K, Herwadkar A, Kearney T, Gnanelingham KK. Pituitary adenoma and incidental superior hypophyseal aneurysm. Br J Neurosurg 2011;25(03):432–433
37 Yamada S, Yamada SM, Hirohata T, et al. Endoscopic extradural removal of pituitary adenoma: the importance of pretreatment of an adjacent unruptured internal carotid artery aneurysm. Case Rep Neurol Med 2012;2012:891847

Journal of Neurosciences in Rural Practice Vol. 13 No. 3/2022 © 2022. Association for Helping Neurosurgical Sick People. All rights reserved.
38 Xia X, Ramanathan M, Orr BA, et al. Expanded endonasal endoscopic approach for resection of a growth hormone-secreting pituitary macroadenoma coexistent with a cavernous carotid artery aneurysm. J Clin Neurosci 2012;19(10):1437–1441
39 Choi HS, Kim MS, Jung YJ, Kim OL. Incidental superior hypophyseal artery aneurysm embedded within pituitary adenoma. J Korean Neurosurg Soc 2013;54(03):250–252
40 Takeuchi S, Wada K, Sakakibara F, Nawashiro H, Mori K. Anterior cerebral artery dissecting aneurysm associated with untreated craniopharyngioma. Br J Neurosurg 2013;27(01):102–104
41 Yoon KW, Cho CS, Lee SK. Large intracranial aneurysm after transsphenoidal surgery for pituitary macroadenoma. J Korean Neurosurg Soc 2014;55(03):160–163
42 Almeida Silva JM, Campos RR, Souza RR, Sette Dos Santos ME, Aguiar GB. Spontaneous subarachnoid haemorrhage from rupture of an anterior communicating artery aneurysm in a patient with pituitary macroadenoma. Neurocirugia (Astur) 2014;25(02):81–85
43 Tian X, Shu H, Zhang H, Wang H, Guo L. Intracranial hemorrhage due to rupture of an anterior communicating artery aneurysm in a patient with pituitary adenoma. J Craniofac Surg 2015;26(02):e154–e155
44 Lee CH, Chen SM, Lui TN. Posterior cerebral artery pseudoaneurysm, a rare complication of pituitary tumor transsphenoidal surgery: case report and literature review. World Neurosurg 2015;84(05):1493.e1–1493.e3
45 Habibi Z, Miri SM, Sheikhzadeh A. Pituitary macroadenoma coexistent with a posterior circulation aneurysm leading to subarachnoidal hemorrhage during transsphenoidal surgery. Turk Neurosurg 2015;25(03):469–474
46 Khalsa SS, Hollon TC, Shastri R, Trobe JD, Gemmete JJ, Pandey AS. Spontaneous subarachnoid hemorrhage due to ruptured cavernous internal carotid artery aneurysm after medical prolactinoma treatment. J Neurointerv Surg 2017;9(03e9
47 Khachatryan T, Khachatryan M, Fanarjyan R, Grigoryan M, Grigorian A. Enlargement of an incidental internal carotid artery aneurysm embedded in pituitary adenoma associated with medical shrinkage of the tumor: Case report. Surg Neurol Int 2018;9:30
48 Morinaga Y, Nii K, Sakamoto K, Inoue R, Mitsutake T, Hanada H. Stent-assisted coil embolization for a ruptured posterior communicating artery pseudoaneurysm after endoscopic transsphenoidal surgery for pituitary adenoma. World Neurosurg 2019;123:301–305
49 Inoue H, Kawano T, Ohmori Y, et al. Internal carotid artery aneurysms diagnosed after stereotactic radiosurgery for a growth hormone-secreting pituitary adenoma: a case report and literature review. Acta Neurochir (Wien) 2019;161(06):1191–1195
50 Ogawa Y, Watanabe M, Tominaga T. Pituitary adenomas associated with intracranial aneurysms: the clinical characteristics, therapeutic strategies, and possible effects of vascular remodeling factors. J Neurol Surg A Cent Eur Neurosurg 2021 (e-pub ahead of print). Doi: 10.1055/s-0041-1739232
51 Wang T, Hu Y, Qiu Y. A giant pituitary adenoma can coexist with an incidental aneurysm: look beyond the pituitary adenoma and don't miss the diagnosis. World Neurosurg 2021;156:92–94