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None relevant for the topic

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Background

Definition and epidemiology
- Primary angiitis of the central nervous system (PACNS) is a subtype of vasculitis with isolated involvement of the central nervous system (CNS).
- The diagnosis may be challenging at three overlapping levels: neuropathological, neuroimaging and clinical.
- Incidence: 2.4 cases per 1000000 persons/year
- M/F ratio 1:1
- Median age at diagnosis: 50 years

Diagnostic criteria
*Calabrese and Mallek 1988*
(1) history of clinical findings of an acquired, otherwise unexplained neurologic deficit,
(2) presence of classic angiographic or histopathologic features of angiitis within the CNS, and
(3) no evidence of systemic vasculitis or of any other disorder that could cause or mimic the angiographic or pathologic features.

*Birnbaum and Hellmann 2009*
- “Definite” PACNS if histopathological confirmation
- “Probable” PACNS if a high-probability angiogram (DSA) is associated with abnormal findings on MRI and CSF profile consistent with PACNS.

Limitations
- No strong data support the current diagnostic criteria
- Angiography-proven PACNS and biopsy-proven PACNS refer to large and medium-sized vessel involvement (LV-PACNS) and small vessel involvement (SV-PACNS), respectively
- The involvement of medium-sized vessels is a neglected issue
- New technologies and new differential diagnoses
Challenges in diagnosis and management

- The definite diagnosis therefore requires histopathological confirmation, but this is particularly challenging for CNS.

- The risk/benefit ratio of an invasive surgical procedure which may return a non-diagnostic or false-negative biopsy needs to be carefully considered.

- The increasing development and availability of non- or minimally invasive techniques means that the historical diagnostic criteria are not always fully adhered to.

- Given the lack of specificity of both the presenting symptoms and non-invasive investigations, confirmation of the diagnosis remains challenging and, even once the diagnosis is confirmed, the evidence base for therapeutic interventions is poor.

- Many areas regarding the diagnosis and management of PACNS lack of standardization and clinical evidence.

Why a guideline on PACNS?

The main purpose of these guidelines is to provide answers to predefined, clinically important questions regarding diagnosis and treatment for patients with probable or definite PACNS.
ESO Standard Operating Procedures

- P of the PICO is ‘probable’ and ‘definite’ PACNS
- Formulation of 17 main PICO questions focusing on accuracy of diagnostic techniques, differential diagnosis of PACNS subtypes, and the efficacy of treatment regimens
- The diagnostic PICOs were divided according to the techniques suggested by the diagnostic criteria:
  - CSF
  - neuroimaging findings
  - histopathological abnormalities
- The therapeutic PICOs were divided into:
  - disease-specific treatment (acute and maintenance therapy),
  - secondary prevention
  - acute stroke
- No RCT is available, but there are only small retrospective case series covering a wide years range
Relapse was defined as: (1) the reoccurrence or worsening of neurological symptoms attributable to active PACNS, or (2) worsening of existing and/or evidence of new abnormal neuroimaging findings on MRI consistent with PACNS activity, necessitating treatment change or escalation.

Remission was defined as the absence of relapse within 6 months after first-line therapy.

Clinically silent neuroimaging changes (e.g. new diffusion weighted imaging (DWI) findings, contrast-enhanced lesions or progressive intracranial stenosis) were considered as relapses, if reported as such in the selected manuscripts.

The definition of “induction” therapy was agreed as treatment in the acute phase. “Maintenance” therapy was defined as therapeutic interventions made after induction therapy.

Unfortunately, the timing of induction and maintenance therapy tended to be poorly defined and highly variable, so the MWG agreed to not consider these.
PICO 1: In adults with suspected PACNS, does CSF analysis for pleocytosis and hyperproteinorrhachia vs no CSF analysis improve the diagnostic accuracy?

Evidence-based Recommendation

In adults with suspected PACNS, there is uncertainty over the utility of CSF examination for pleocytosis and/or hyperproteinorrhachia as a diagnostic tool. This is due to the lack of specific comparative studies and to the heterogeneous data, regarding the diagnostic procedures and populations in the available studies.

Quality of evidence: -
Strength of recommendation: -

Expert Consensus Statement

For adults with a clinical suspicion of PACNS, we suggest CSF examination during the diagnostic workup to provide information relevant to the exclusion of conditions to be considered in the differential diagnosis (e.g. post-infectious vasculitis). CSF analyses should not be limited to determination of cell count and protein concentration and normal CSF analyses cannot, by themselves, exclude the diagnosis of PACNS.
PICO 1: In adults with suspected PACNS, does CSF analysis for pleocytosis and hyperproteinorrhachia vs no CSF analysis improve the diagnostic accuracy?

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Number of PACNS patients</th>
<th>Study duration</th>
<th>Age (mean or median)</th>
<th>Women (N)</th>
<th>Population with available CSF results (N)</th>
<th>PACNS with positive CSF (N)</th>
<th>CSF pleocytosis (&gt;5 cells/μL) (N)</th>
<th>CSF hyperproteinorrhachia (&gt;45mg/dL) (N)</th>
<th>PACNS with negative CSF (N)</th>
<th>Angiography proven with negative CSF (N)</th>
<th>Angiography proven with positive CSF (N)</th>
<th>Biopsy proven with negative CSF (N)</th>
<th>Biopsy proven with positive CSF (N)</th>
<th>Non-PACNS with positive CSF (N)</th>
<th>Non-PACNS with negative CSF (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvarelli et al., 2020b</td>
<td>Retrospective</td>
<td>191</td>
<td>1983–2017</td>
<td>49 (17–85)</td>
<td>92</td>
<td>148</td>
<td>120</td>
<td>63</td>
<td>49</td>
<td>28</td>
<td>23</td>
<td>67</td>
<td>5</td>
<td>53</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>de Boysson et al., 2017c</td>
<td>Retrospective</td>
<td>102</td>
<td>2010–2017</td>
<td>46 (18–80)</td>
<td>48</td>
<td>94</td>
<td>65</td>
<td>NR</td>
<td>NR</td>
<td>29</td>
<td>27</td>
<td>44</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Agarwal et al., 2022</td>
<td>Retrospective</td>
<td>82</td>
<td>2010–2019</td>
<td>34 (27.8–42)</td>
<td>14</td>
<td>48</td>
<td>42</td>
<td>17</td>
<td>32</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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</tr>
<tr>
<td>Schusser et al., 2017</td>
<td>Retrospective</td>
<td>31</td>
<td>2008–2014</td>
<td>44.5 (range 14.7–84)</td>
<td>18</td>
<td>31</td>
<td>29</td>
<td>11</td>
<td>19</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sundaram and Syiba, 2022</td>
<td>Retrospective</td>
<td>20</td>
<td>2016–2019</td>
<td>42.55 (=9.48)</td>
<td>6</td>
<td>20</td>
<td>14</td>
<td>3</td>
<td>14</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Wang et al., 2019a</td>
<td>Retrospective</td>
<td>18</td>
<td>2015–2016</td>
<td>30 (10–47)</td>
<td>8</td>
<td>18</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Abu-Shakra et al., 1994c</td>
<td>Retrospective</td>
<td>16</td>
<td>1984–1993</td>
<td>36.5 (26–53)</td>
<td>8</td>
<td>12</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Amin et al., 2021c</td>
<td>Retrospective</td>
<td>36</td>
<td>2012–2021</td>
<td>NA</td>
<td>80</td>
<td>36</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>9</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Raghavan et al., 2019</td>
<td>Retrospective</td>
<td>128</td>
<td>2005–2016</td>
<td>49.8 (±15.9)</td>
<td>128</td>
<td>113</td>
<td>10</td>
<td>24</td>
<td>24</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Becker et al., 2012a</td>
<td>Case-control</td>
<td>23</td>
<td>2013–2014</td>
<td>NA</td>
<td>23</td>
<td>23</td>
<td>16</td>
<td>NR</td>
<td>NR</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Torres et al., 2016</td>
<td>Retrospective</td>
<td>9</td>
<td>2005–2013</td>
<td>49 (35–70)</td>
<td>10</td>
<td>18</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Stegböhl et al., 2021a</td>
<td>Retrospective</td>
<td>7</td>
<td>2010–2017</td>
<td>67 ± 10</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Karman et al., 2021c</td>
<td>Retrospective</td>
<td>13</td>
<td>2018–2020</td>
<td>40 (12–58)</td>
<td>12</td>
<td>15</td>
<td>10</td>
<td>6</td>
<td>10</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
</tr>
<tr>
<td>Vera-Laterra et al., 2015c</td>
<td>Retrospective</td>
<td>12</td>
<td>2004–2010</td>
<td>32 ± 13.19</td>
<td>12</td>
<td>15</td>
<td>10</td>
<td>6</td>
<td>10</td>
<td>0</td>
<td>NR</td>
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<td>NR</td>
</tr>
<tr>
<td>Dura and Calabrese, 1995c</td>
<td>Prospective</td>
<td>7</td>
<td>2001–2007</td>
<td>49 (37–70)</td>
<td>10</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Singhal et al., 2016</td>
<td>Retrospective</td>
<td>47</td>
<td>1998–2015</td>
<td>51 ± 15</td>
<td>127</td>
<td>42</td>
<td>31</td>
<td>NR</td>
<td>NR</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kremer et al., 2011c</td>
<td>Retrospective</td>
<td>21</td>
<td>2003–2008</td>
<td>43 (11–65)</td>
<td>13</td>
<td>21</td>
<td>19</td>
<td>13</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
PICO 1: In adults with suspected PACNS, does CSF analysis for pleocytosis and hyperproteinorrhachia vs no CSF analysis improve the diagnostic accuracy?

- 17 papers (case series and cross-sectional studies) on 763 PACNS patients
- Lumbar puncture was performed in 588/763 (77%) patients
- CSF data were provided in 508/588 (86%) of patients who underwent a lumbar puncture
- The overall rate of positive CSF findings in PACNS patients was 77.8% (395/508), distributed as pleocytosis in 46% and hyperproteinorrhachia in 70% of patients

- Different thresholds for hyperproteinorrhachia: CSF protein > 45 mg/dl, > 50 mg/dl, > 80 mg/dl
- The diagnosis cannot be excluded or regarded as unlikely when CSF white blood cell counts are less than 5/mcl.
- A recent study evaluating total CSF protein levels in a community-based population of 633 participants (mean age 70.9 ±11.6 years), documented mean CSF protein 52.2 ±18.4 mg/dl (95% CI 24.0 - 93.4 mg/dl; range, 14.0-148.0 mg/dl) [Mayo Clin Proc 2023; 98: 239-251]
PICO 2: In adults with suspected PACNS, does assessing for predefined patterns of parenchymal abnormalities on brain MRI versus not assessing increase the diagnostic accuracy?

Evidence-based Recommendation

In adults with suspected PACNS, there is uncertainty regarding the clinical utility of identifying predefined patterns of parenchymal signal change to improve the diagnostic accuracy of PACNS and for differentiating SV-PACNS from LV-PACNS. This is due to underreporting and lack of specific comparative studies, as well as heterogeneity in the neuroimaging techniques employed and data reported in the available studies.

Quality of evidence: -
Strength of recommendation: -

Expert Consensus Statement

In adults with definite or probable PACNS, we suggest reporting neuroimaging findings in a standardized way, according to the described patterns of parenchymal involvement and contrast enhancement on MRI to collect relevant data prospectively. Given potential selection bias in those undergoing biopsy (i.e. those with tumefactive or contrast enhancing lesions), we suggest to be cautious in attributing some patterns (e.g. tumefactive patterns) to SV-PACNS or LV-PACNS.
In adults with suspected PACNS, does assessing for predefined patterns of parenchymal abnormalities on brain MRI versus not assessing increase the diagnostic accuracy?

- 18 studies
- 660 patients
- wide time range (1987 to 2020)
- 230 ‘definite’ PACNS, predominantly SV-PACNS (226)
- 303/398 patients with ‘probable’ PACNS had LV-PACNS

- acute ICH/SAH
- tumefactive pattern (t-PACNS)
- multiple acute/subacute ischemic lesions
- single acute/subacute ischemic lesion
- SVD pattern (according to the STRIVE criteria)
- parenchymal contrast enhancement
- spinal cord involvement

90/660 (13.6%)
27/660 (4.1%)
135/660 (20.45%)
42/660 (6.36%)
58/660 (8.79%)
135/660 (20.45%)
5/660 (0.76%)

- The available data were heterogeneous and reporting of many of the key features was incomplete
- This largely reflects the retrospective design of studies and the lack of a preplanned, standardized diagnostic work-up
- No neuroimaging pattern (including tPACNS) was reported to be indicative of a subtype of PACNS
- Whilst pre-biopsy parenchymal enhancement was positively associated with biopsy-proven PACNS compared with DSA-diagnosed patients (60% versus 23%; P=0.001), a potential selection bias was that contrast enhancement was a criterion for biopsy.
PICO 4: In adults with suspected PACNS, does cerebral computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) with high probability angiographic pattern vs digital subtraction angiography (DSA) with high probability pattern improve diagnostic accuracy?

**Evidence-based Recommendation**

In adults with suspected PACNS, we do not recommend using MRA routinely in place of DSA.

No recommendations can be drawn for CTA

Quality of evidence: Very low ⊕

Strength of recommendation: Strong against intervention ↓↓

**Expert Consensus Statement**

1. The clinical utility of CTA in PACNS has not been formally compared to MRA and DSA although it is widely used in the assessment of cerebrovascular disorders. We suggest that it could be comparable to MRA if multislices (>128) technique is employed

2. DSA has a higher sensitivity and specificity in detection of medium-sized vessel involvement in PACNS and it is less invasive than brain biopsy. It is suggested that DSA is considered in patients with clinical suspicion of PACNS, when the MRA/CTA does not show compatible neuroimaging features.
PICO 4: In adults with suspected PACNS, does cerebral computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) with high probability angiographic pattern vs digital subtraction angiography (DSA) with high probability pattern improve diagnostic accuracy?

- 5 papers
- 186 patients with PACNS

- 109/186 (58.6%) underwent DSA
- 122/186 (65.6%) MRA or CTA

- Direct comparison MRA (1.5T and 3T) vs DSA in 31 patients
- Among the 25/31 patients (81%) with abnormal DSA findings, all but one had changes on 3D-TOF-MRA
- In a per-segment analysis, the concordance between 1.5T 3D-TOF-MRA and DSA was 0.82 (95% CI, 0.75– 0.93), and between 3T 3D-TOF-MRA and DSA, it was 0.87 (95% CI, 0.78 – 0.91)
- Detection of vessel stenosis in predefined segments of the large intracranial vessels, rather than detection of the high probability angiographic pattern

PICO 5: In adults with suspected PACNS and normal MRA does performing a DSA versus not performing a DSA improve the diagnostic accuracy?

Evidence-based Recommendation

In adults with suspected PACNS, we suggest performing a DSA if the MRA is normal.

Quality of evidence: Very low ⊕
Strength of recommendation: Weak for intervention ↑?
PICO 5: In adults with suspected PACNS and normal MRA does performing a DSA versus not performing a DSA improve the diagnostic accuracy?

Table 7. PICO 4 and PICO 5 summary of data. Neuroimaging of brain vessels.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Study duration</th>
<th>Mean Age (years)</th>
<th>PACNS pts/W (N)</th>
<th>Test performed (N)</th>
<th>PACNS (N)</th>
<th>Probable PACNS (N)</th>
<th>MRA high probability (N)</th>
<th>CTA high probability (N)</th>
<th>DSA high probability (N)</th>
<th>MRA Positive</th>
<th>MRA Negative</th>
<th>True positive</th>
<th>False positive</th>
<th>True Negative</th>
<th>False Negative</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becker et al. Case-control 2017</td>
<td>Case-control</td>
<td>2013–2014</td>
<td>NR</td>
<td>25/NR</td>
<td>14 DSA, 18 MRA or CTA</td>
<td>10</td>
<td>10/18</td>
<td>NR</td>
<td>10/14</td>
<td>10/18</td>
<td>8/18</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cosottini et al. Retrospective et al. 2013</td>
<td>Case-series</td>
<td>NR</td>
<td>49.13 ± 6.22</td>
<td>8/6</td>
<td>8 DSA, 6 MRA</td>
<td>0</td>
<td>8</td>
<td>4 (1.5T), 6 (3T) for proximal vessels</td>
<td>NR</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Geri et al. Retrospective 2014-40</td>
<td>Retrospective</td>
<td>1990–2009</td>
<td>Median age 45 (37-54)</td>
<td>18/9</td>
<td>10 DSA, 7 MRA</td>
<td>1</td>
<td>17</td>
<td>NR</td>
<td>NR</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>de Boysson et al. Retrospective 2017</td>
<td>Retrospective</td>
<td>2010–2017</td>
<td>Median age 46 (18-80)</td>
<td>102</td>
<td>91 MRA, 87 DSA</td>
<td>26</td>
<td>76</td>
<td>57/91 (62%), SV 0/23, LV 57/68 (84%)</td>
<td>NR</td>
<td>NR</td>
<td>67/87 in the whole group (0/19 in SV and 67/68 in LV)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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</tr>
<tr>
<td>Thaler et al. Retrospective 2019</td>
<td>Retrospective</td>
<td>2009–2014</td>
<td>43 [±15.3]</td>
<td>33</td>
<td>17 (8 were defined as SV)</td>
<td>11 (25 were defined as LV)</td>
<td>17</td>
<td>NR</td>
<td>11</td>
<td>25</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
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</tr>
</tbody>
</table>

NR: not reported/retrievable.
The main limitation of MRA is in the evaluation of medium size vessels and DSA is known to have the greatest spatial resolution.

CTA has not been evaluated in this setting but the known limitation of CTA (without CT perfusion) in identifying medium vessel occlusion in acute stroke would contribute to lack of confidence in the technique as a substitute for DSA when MRA is normal and the clinical suspicion of PACNS persists.

There is one study directly comparing MRA and DSA in a small sample of 31 patients from the French registry, but the comparison focused on stenosis and not on the high probability pattern and the definition of DSA and MRA findings was “abnormal” vs “normal” without further grading of the “abnormal” category.

24/25 false negative MRA segments could be defined as “medium sized vessels” and MRA had 7 false positive segments too.

Atherosclerosis is the main differential diagnosis in patients with multifocal involvement of large and medium-sized vessels and DSA has the higher accuracy for evaluating the burden and pattern of involvement.

The “high probability angiographic pattern” was originally proposed for a broader differential diagnosis, including atherosclerosis, than the one outlined by the Birnbaum and Hellmann’s criteria.
PICO 6: In adults with probable LV-PACNS, does performing High Resolution Vessel Wall Imaging-MRI (HRVWI-MRI) vs performing a digital subtraction angiography (DSA) increase the diagnostic accuracy?

Evidence-based Recommendation

In adults with probable LV-PACNS, there are insufficient data on HRVWI-MRI to determine whether the technique improves the diagnostic accuracy of PACNS when used with DSA

Quality of evidence: -

Strength of recommendation: -

Expert Consensus Statement

HRVWI-MRI is a promising but not yet validated technique. We suggest that it should be investigated and validated in prospective multi-center trials.

In the meantime, we suggest that use of HRVWI-MRI should be limited to expert centers and the interpretation of a positive finding should not be the unique neuroimaging modality supporting the diagnosis of PACNS.
PICO 6: In adults with probable LV-PACNS, does performing High Resolution Vessel Wall Imaging-MRI (HRVWI-MRI) vs performing a digital subtraction angiography (DSA) increase the diagnostic accuracy?

- 3 papers
- 73 patients with PACNS [29 (40%) with LV-PACNS], included between 2009 and 2020
- All described vessel wall enhancement (VWE) as the main finding, co-localizing with MRA/DSA arterial stenoses when present
- Concentric VWE was more common than eccentric VWE (85-95%)
- There were insufficient data to assess for other HRVWI-MRI derived biomarkers, including pre-contrast thickening, and spontaneous T2 signal of the vessel wall
- Selection bias (availability of HRVWI-MRI)
- The change in PACNS diagnostic accuracy due to HRVWI-MRI remains unknown
- No study provided adequate information regarding the change in diagnostic accuracy provided by HRVWI-MRI when compared with DSA.
PICO 9: In adults with definite PACNS, does the presence of MRI leptomeningeal enhancement (LME) vs positive biopsy findings change the diagnostic accuracy?

Evidence-based Recommendation

In adults with definite PACNS there is persistent uncertainty regarding the effect on diagnostic accuracy of the presence of MRI leptomeningeal enhancement (LME).

Quality of evidence: -
Strength of recommendation: -

Expert Consensus Statement

Although a very low quality of evidence, we suggest proceeding to biopsy where there is clinical suspicion of PACNS, LME and normal findings on DSA. If there is no LME, we suggest that targeted biopsy of gadolinium-enhanced lesions may increase the diagnostic accuracy of the biopsy in comparison to blind biopsy.
PICO 9: In adults with definite PACNS, does the presence of MRI leptomeningeal enhancement (LME) vs positive biopsy findings change the diagnostic accuracy?

- 2 descriptive cohorts with available information regarding the neuroimaging features of biopsy-proven PACNS patients
- 203 PACNS patients were analyzed and LME was reported in 33/203 patients (16.3%)

- Two main limitations explain the low level of evidence
  - Information regarding GBCA administration is not provided in all studies.
  - In patients with LME and positive biopsy, information regarding the location of the sample, i.e. whether the biopsy was guided on a LME and whether the biopsy collected meningeal and/or brain tissue, is often lacking, precluding any precise analysis of the link between LME and the biopsy result.
PICO 12: In adults with probable/definite PACNS, does using glucocorticoids + any further immunosuppressive drug vs glucocorticoids alone improve outcome?

Evidence-based Recommendation

In adults with probable/definite PACNS there is uncertainty regarding the clinical benefit associated with use of immunosuppressive drugs in addition to glucocorticoids.

Quality of evidence: -
Strength of recommendation: -

Expert Consensus Statement

Given the potential severity of PACNS, the relapsing course of the disease, and the well-known glucocorticoid-related toxicity, we suggest consideration of adding an immunosuppressant to glucocorticoid therapy in most patients with PACNS.
We also suggest that in milder disease phenotypes, use of glucocorticoids alone might be discussed in a multidisciplinary team with relevant expertise and/or an expert in the diagnosis and management of PACNS.
PICO 12: In adults with probable/definite PACNS, does using glucocorticoids + any further immunosuppressive drug vs glucocorticoids alone improve outcome?

Table 13. Summary of the extracted data for PICO 12, Therapy: induction phase.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Study duration</th>
<th>Follow-up period</th>
<th>Mean Age (years)</th>
<th>PACNS/ Definite PACNS</th>
<th>Probable PACNS</th>
<th>Treatment type</th>
<th>Glucocorticoids + any immunosuppressant drug</th>
<th>Glucocorticoids alone</th>
<th>Cyclophosphamide + Glucocorticoids</th>
<th>MMF + Glucocorticoids</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Boysson et al. 2017&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>2010–2017</td>
<td>median months 52.5 (7–198)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>median 46 (18–80)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>102/48 (12 SV + 36 LV)</td>
<td>26</td>
<td>76</td>
<td>Induction&lt;sup&gt;4&lt;/sup&gt;</td>
<td>(SV 21, LV 63)</td>
<td>16</td>
<td></td>
<td>4 (biopsy proven)</td>
</tr>
<tr>
<td>Saver et al. 2020&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>1983–2007</td>
<td>Median 19 months (range: 0–26.1 years)</td>
<td>49 (17–65); biopsy 50 (17–84) and angiography</td>
<td>19/(NR)</td>
<td>129 (9 with positive angiogram and positive biopsy)</td>
<td>Induction&lt;sup&gt;6&lt;/sup&gt;</td>
<td>72</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sundaram and Syal 2016&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>2016–2019</td>
<td>409 days, range (118–240)</td>
<td>42.55 (9.48)</td>
<td>20/6</td>
<td>1</td>
<td>Induction</td>
<td>12</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
<td>15</td>
</tr>
<tr>
<td>Schuster et al. 2018&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>2008–2017</td>
<td>median age 43.5 (range 14–83)</td>
<td>44/26</td>
<td>25</td>
<td>19</td>
<td>Induction</td>
<td>39</td>
<td>5</td>
<td>33</td>
<td>0</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported/retrievable.

<sup>a</sup>SV 67 (11–198) LV 74.5 (0–189).

<sup>**</sup>SV-PACNS 41.5 (18–61), LV-PACNS 48.5 (19–80).

<sup>***</sup>At last FU 58 (57%), SV 13 (50%) and LV 45 (59%).

<sup>1</sup>6–145 months after diagnosis, mainly in patients with isolated SV PACNS (14 (54%) with isolated SV PACNS vs 18 (24%) with demonstration of large/medium vessel involvement; p = 0.004.

<sup>4</sup>in 96, IV pulse methylprednisolone therapy (from 3 to 42 pulses, median 5 pulses, mostly 1 g/pulse), preceded the beginning of oral prednisone (PDN) therapy.
The literature search identified no relevant RCTs
- 4 papers suitable for data extraction
- 357 PACNS patients
- 181/357 (50.7%) had definite PACNS
- 207/357 (58%) had combined therapy with glucocorticoids and immunosuppressants
- 29/357 (8.1%) had glucocorticoids alone
- The predefined outcomes were largely underreported
- The rate of prolonged remission without relapse seemed to be lower in patients treated with glucocorticoids alone in comparison with those who received glucocorticoids combined with an immunosuppressant
- There is also a possible selection bias regarding mild disease phenotypes treated with corticosteroids alone versus more aggressive presentations treated with combinations treatment
PICO 14: In adults with probable/definite PACNS do antiplatelets versus no antiplatelets improve outcomes?

Evidence-based Recommendation

In adults with PACNS, there is uncertainty regarding the routine use of antiplatelets.

Quality of evidence: -
Strength of recommendation: -

Expert Consensus Statement

Aspirin may have a beneficial effect in PACNS, which may be due to a combined antithrombotic and anti-inflammatory effect and its possible complementary action with glucocorticoid therapy. In patients with large/medium vessel involvement we suggest including aspirin therapy.
### Table 15. PICO 14 summary of data. Therapy: secondary prevention.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Study design duration</th>
<th>Follow-up period</th>
<th>Mean Age PACNS/ Women (N)</th>
<th>PACNS/ Definite PACNS</th>
<th>Treatment type</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Boysson et al., 2017</td>
<td>Retrospective 2010–2017</td>
<td>Median months 52.5 (0–198)</td>
<td>Median 46 (18–80)</td>
<td>102/48 (12 SV 26 + 36 LV)</td>
<td>Secondary prevention 39 (all LV PACNS)</td>
<td>Death at 3 months (number/hazard ratio)</td>
<td>63</td>
</tr>
<tr>
<td>Salvanesi, 2020</td>
<td>Retrospective 1983–2017</td>
<td>Median 19 months (range: 0–28.1 years)</td>
<td>49 (17–85); biopsy 58 (17–84) and angiography 49 (17–85)</td>
<td>129 (9 with positive angiogram and positive biopsy)</td>
<td>Secondary prevention 41</td>
<td>Death at 12 months (number/hazard ratio)</td>
<td>134</td>
</tr>
<tr>
<td>Kraemer and Berlin, 2011</td>
<td>Retrospective cohort 2003–2008</td>
<td>NR</td>
<td>42.48 years (median 43, range 11–65 years).</td>
<td>21/13 (6 biopsy positive, 13 angiography positive and 2 angiography negative)</td>
<td>Secondary prevention 12</td>
<td>mRS 0–2 at 12 months (number)</td>
<td>9</td>
</tr>
</tbody>
</table>

NR: not reported/retrievable.
Three retrospective studies investigated the use of antiplatelet agents in patients with PACNS which was either biopsy- or angiography-proven.

The therapy was initiated or continued in 25% to 57.1% of patients at diagnosis, mainly in LV-PACNS.

The efficacy and safety of aspirin were assessed in only one retrospective study at a single center over a 29- to 35-year period (1983–2017).

Aspirin was not significantly associated with severe disability (mRS 4–6: 36% vs vs 30%) or mortality (23% vs 23%).

There was also no significant difference in the prevalence of intracranial hemorrhage (6.5% vs 13%).

After adjustment for age, aspirin therapy was found to be positively associated with long-term remission (OR 2.59, 95% CI 1.21–5.52, p = 0.013).

The quality of evidence for all reported outcomes was low.
PICO 15: In adults with probable/definite PACNS does long-term immunosuppression versus no long term immunosuppression improve the outcomes?

Evidence-based Recommendation

In adults with probable/definite PACNS there is uncertainty regarding the use of long-term immunosuppression.

Quality of evidence: -
Strength of recommendation: -

Expert Consensus Statement

We suggest initiating maintenance therapy when no recurrence has been registered after the induction therapy. We suggest continuing maintenance therapy for at least 2 years before considering cessation in patients without recurrences.
PICO 15: In adults with probable/definite PACNS does long-term immunosuppression versus no long term immunosuppression improve the outcomes?

Table 16. PICO 15 Summary of data. Therapy: maintenance phase.

<table>
<thead>
<tr>
<th>Study author, year</th>
<th>Study design</th>
<th>Study duration</th>
<th>Follow-up period</th>
<th>Mean Age PACNS/ Women (N)</th>
<th>Definite PACNS</th>
<th>Probable PACNS</th>
<th>Treatment type</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Boysson et al., 2017</td>
<td>Retrospective</td>
<td>2010–2017</td>
<td>median months 52.5 (0–198); SV 67 (1–198); LV 47.5 (0–188)</td>
<td>102/48 (12 SY + 36 PACNS 41.5 LV)</td>
<td>76</td>
<td>Long term immunosuppressive treatment</td>
<td>Death at 3 months (number/hazard ratio)</td>
<td>mRS 0–2 at 3 months (number)</td>
<td>Stroke (first or recurrence)</td>
</tr>
<tr>
<td>Salvarani, Retrospective</td>
<td>1993–2017</td>
<td>Median</td>
<td>19 months (range: 0–28.1 years)</td>
<td>191/NR</td>
<td>71</td>
<td>Maintenance phase</td>
<td>After induction, 48 (47%) patients received maintenance therapy (AZA, MTX and MMF in 38, 6 and 4 cases, respectively)</td>
<td>mRS 4–6 not provided</td>
<td>8/35 vs 16/34 vs 24/125</td>
</tr>
</tbody>
</table>

NR: not reported/retrievable.
PICO 15: In adults with probable/definite PACNS does long-term immunosuppression versus no long term immunosuppression improve the outcomes?

- The extracted data derived from two retrospective case series providing 293 PACNS patients, including 82 patients receiving maintenance therapy after induction and 211 patients without maintenance therapy after induction.
- French cohort: among the 106 patients, who achieved remission, 52 (46%) received maintenance therapy with an immunosuppressant (41 pts azathioprine 2 mg/kg per day, 7 pts methotrexate 0.3–0.5 mg/kg per week, 4 pts MMF 2 g/day) and 45/52 continued glucocorticoids in addition to the maintenance therapy.
- Mayo Clinic cohort: among the 185 patients, who achieved remission, 35 (19%) received maintenance therapy (19 pts azathioprine 100–200 mg/die, 8 pts MMF 2–3 g/die, 5 pts methotrexate 7.5–20 mg/kg/week, 2 pts oral CYC, 1 pt infliximab 5 mg/kg after oral).
- Observational data consistently show that long term immunosuppression improves outcomes.
- The best evidence exists for azathioprine.
- The available data do not allow an evidence-based recommendation regarding the duration of the maintenance treatment (in the cohorts under investigation, the median duration of maintenance therapies was 24 and 17 months).
Conclusion

- This is the first international multidisciplinary guideline on PACNS
- The current diagnostic criteria have several limitations and this issue was addressed in detail
- The quality of the evidence is very low
- No dedicated neurovascular approach emerges in analyzing the data
- Neuroimaging information on acquisition, findings and reporting for different techniques is rarely reported and it makes the data not comparable
- New techniques (e.g. HRVWI-MRI) are promising, but they needs to be validated and standardized
- DSA is still the gold standard for large and medium-sized vessel imaging
- The outcomes are largely underreported
Areas of future research

Primary/secondary prevention of Stroke
• Indications and benefit for antithrombotic treatment
• Role of the control of ‘classical’ vascular risk factors
• SV-PACNS vs LV-PACNS

Diagnosis
• Updated criteria according to technological improvement (but DSA remains the gold standard techniques for large and medium-sized vessels)
• Updated criteria according to a wide range of differential diagnosis
• Search for new CSF markers (diagnosis, pathogenesis, prognosis)
• Medium-sized vessel involvement as a distinct category
• Definition of an updated and standardized diagnostic pathway

Treatment
• RCTs for induction and maintenance therapy (SV-PACNS vs LV-PACNS)
• Treatment of vascular risk factors

Prognosis
• Consistent information on long-term prognosis
• Consistent information on the cerebrovascular outcome

Patients often have several diseases simultaneously and diagnostic criteria have to consider it. Rare and frequent diseases may cohabit, but also more than one rare disease may be present in the same individual.
ESO Guideline on Primary Central Nervous System Angiitis (PACNS)

Rosario Pascarella, Katerina Antonenko, Grégoire Boulouis, Hubert De Boysson, Caterina Giannini, Mirjam R. Heldner, Odysseas Kargiotis, Thanh N. Nguyen, Claire M. Rice, Carlo Salvarani, Antje Schmidt-Pogoda, Daniel Strbian, Salman Hussain, Marialuisa Zedde

Thanks for your attention