The INTERnational Study on Primary Angiitis of the CEntral nervous system (INTERSPACE)

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Primary (isolated) angiitis of the CNS (PACNS) = real diagnostic and therapeutic challenges

Diagnostic challenges
- Rarer than several other potential mimickers
- No individual clinical manifestation or non-invasive test result is specific
- Diagnosis often presumed from a combination of manifestations and test results otherwise unexplained
- CNS biopsy can confirm PACNS, but invasive and ≥30% false-negatives
- Several patients remain with a presumptive diagnosis of PACNS
Therapeutic challenges
• Optimal therapeutic regimen and duration are unknown for PACNS in general and for specific subgroups

- Risk of adverse effects of immunosuppressant agents
- Risk of treatment failure due to insufficient treatment

• Monitoring of therapeutic response can be difficult
• Predictors of treatment failure and recurrent PACNS are unknown
Design: Observational prospective multicentre study on PACNS

Funding: Unrestricted grant from *La Fondation des Gouverneurs de l’Espoir*
Primary objective: Predictors of death or dependence (mRS 3 to 6) at the end of follow-up

Sample size calculation: Assuming death or dependence in 30% of the study population, 200 participants are necessary to identify and integrate 6 predictors to a multivariate model
1) Predictors of death or dependence 1 year following initiation of immunosuppressive therapy

2) Predictors of neurological deterioration due to treatment failure (>14 days after initiation of immunosuppressive therapy) or recurrent PACNS (following discontinuation of immunosuppressive therapy), defined by the combination of:
   • Clinical manifestations of active vasculitis
   • Investigation results consistent with active vasculitis

3) Long-term outcome (>1 year following initiation of immunosuppressive therapy)

4) Recognizable subsets of PACNS with specific clinical manifestations, investigation results, or outcomes
Optional sub-studies with separate protocols:

1) Innovative brain and vascular imaging techniques (R Swartz, Toronto)
2) CSF biomarkers (R Geraldes, Lisbon)
3) Genetics (D Hunt, Edinburgh)
4) Incidence study (S Lanthier, Montreal)
5) Sensitivity of non-invasive investigations
6) Differential diagnosis of PACNS
7) PACNS revealed only at autopsy
Inclusion criteria

• Age ≥16 years
• Acquired neurological dysfunction (headaches, cognitive decline, seizures and focal deficits) consistent with PACNS and unexplained by a long list of other causes
• A “high-probability" imaging study of the CNS vessels OR CNS histopathology confirming PACNS
• Exclusion of diseases that can mimic PACNS

Exclusion criteria:

• Immunosuppressive therapy initiated before obtaining brain or spinal cord MRI
• Immunosuppressive therapy initiated >30 days before study enrolment
• Consent form not obtained
INTERSPACE: Enrolment process

Participant enrolment process

- PACNS patient
  - INTERSPACE investigator reviews inclusion criteria
    - Inclusion criteria met = potential participant
      - INTERSPACE investigator reviews exclusion criteria and submits CRF-1
        - No exclusion criteria = study participant
          - INTERSPACE investigator submits CRF-2
            - Presence of ≥1 exclusion criteria = patient is excluded (CRF-1 baseline data will be analyzed for internal validation)
              - Adjudication process (see next page)
## INTERSPACE: Data collection

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Potential triggering factors</th>
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<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>Lifestyle</td>
<td>Clinical manifestations</td>
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<td>Past medical history</td>
<td>Neurological scales (mRS, MoCA, NIHSS)</td>
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### Investigation

<table>
<thead>
<tr>
<th>Blood tests</th>
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<td>CSF analysis</td>
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<td>Brain and spinal cord imaging (T1, T2, FLAIR, GRE, DWI, ADC and gado.); Vascular imaging from the aortic arch to the brain (catheter angio., CTA and MRA)</td>
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<td>Histopathology</td>
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<td>Centralized review by blind NRad at the CHUM, using standard criteria</td>
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<td>Treatment</td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Antithrombotics</td>
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<td>Corticosteroids and cytotoxic agents</td>
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<td>Other therapies</td>
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Predefined clinical visits:

- Baseline: ≤14 days following initiation of immunosuppressant drugs
- Follow-up at 3 months, 6 months, 12 months, and at the end of each additional year
- When neurological decline (recurrence or treatment failure) is diagnosed

Data transmission:

- e-CRF available at www.youngstrokenetwork.org → Web-based database in Helsinki, Finland
- Brain, spinal cord and vascular imaging: Selected images downloaded on e-CRF for adjudication and complete set of images recorded on a CD and sent at the CHUM for analysis
- CNS histopathology: Selected images downloaded on e-CRF for adjudication and glass slides sent at the MGH for analysis
INTERSPACE: Current status

- Study launched in Lisbon, 2017-05 with 2 active sites
- Targeted invitations sent on 2012-11-14 → positive responses

Canada: n=22
USA: n=6
Europe: n=36
Russia: n=1
M.East: n=2
India: n=2
S.Am.: n=5
INTERSPACE: Study projections

- 100 participating centres x 0.5 study subjects per year per centre x 4 years = 200 participants
- Follow-up $\geq$ 1 year
- Study completion in 2018
• Get REB approval and contracts signed from participating centres to start recruiting study subjects
• Increase the number of study sites with:
  o More sites from Asia, Africa, and Australia
  o More Rheumatology, other medical disciplines
CONCLUSION

- INTERSPACE possible through the collaboration of a large number of study centres
- Minimal individual effort but a huge collective effort
- Many thanks to:

  **Worldwide INTERSPACE investigators**
  **Study subjects**
  **Steering Committee:** S Lanthier, LH Calabrese, JM Ferro
  **Database Committee (Helsinki, Finland):** J Putaala, D Strbian
  **Histopathology Committee (Boston, USA):** Matthew Frosch
  **Radiology Committee (CHUM, Canada):** J Raymond, F Guilbert, L Létourneau

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