Transient focal neurological episodes due to Cerebral Amyloid Angiopathy: a 25-month follow-up population study

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Background: Sporadic **cerebral amyloid angiopathy** (CAA) is a common age-related cerebral small vessel disease characterized by progressive deposition of beta-amyloid in the wall of cortical and leptomeningeal small arteries.

Transient focal neurological episodes (**TFNE**) are recurrent, stereotyped and brief episodes with a wide spectrum of clinical features ranging from TIAs to "aura-like" symptoms.
TFNE are increasingly recognized as common clinical presentation of CAA, apart from spontaneous lobar intracerebral haemorrhages (ICH).

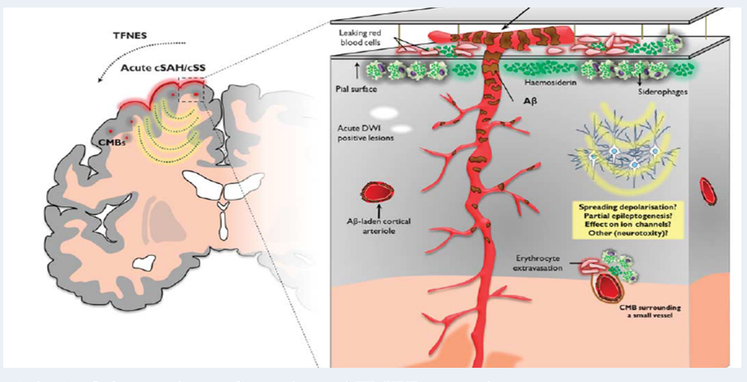

Fig 1. *Schematic explanation of TNFE genesis*

Aim:

1. to describe **demographic and clinical features** of patients with CAA presenting with TFNE
2. to assess which are the most frequent **diagnosis** and **therapeutic** work-up at first event
3. to define **risk factors for lobar ICH or TFNE relapses**

Methods: 33 patients with a final diagnosis of probable CAA according to Boston criteria (modified by Linn, Tab 1) recruited from 2010 to 2015 were studied. Clinical data and neuroimaging CAA features (TC scan and MRI with GRE or SWI sequences) were collected at onset and for each new CAA-related episode during 25-month follow-up. MRI sequences were reviewed with an expert neuroradiologist to confirm imaging evidences of CAA (lobar cerebral microbleeds, superficial cortical siderosis (cSS) or acute focal convexity sub-arachnoid haemorrhage (cSAH).

Results: 21 (63%) CAA patients presented with TFNE, 9 (27%) with lobar ICH and 3 (10%) with CAA-related inflammation (Fig 2). Demographic features and systemic risk factors were not different among groups (Tab 2).
TFNE group presented more frequently negative TIA-like episodes (52%), whereas positive aura-like (28%) symptoms were less reported (Fig 3).

CAA Diagnosis	Modified Boston Criteria (by Linn 2010)
Definite CAA	Full postmortem examination demonstrating: - Lobar, cortical, or cortico-subcortical hemorrhage - Severe CAA with vasculopathy - Absence of other diagnostic lesion
Probable CAA with supporting pathology	Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating: - Lobar, cortical, or cortico-subcortical hemorrhage - Some degree of CAA in specimen - Absence of other diagnostic lesion
Probable CAA	Clinical data and MRI or CT demonstrating: - **Multiple hemorrhages** restricted to lobar, cortical, or cortico-subcortical regions (cerebellar hemorrhage allowed) **or** - **Single** lobar, cortical, or cortico-subcortical hemorrhage and **focal or disseminated superficial siderosis** - Age 55 y - Absence of other cause of hemorrhage or superficial siderosis
Possible CAA	Clinical data and MRI or CT demonstrating: - **Single** lobar, cortical, or cortico-subcortical hemorrhage **or** - **Focal or disseminated superficial siderosis** - Age 55 y - Absence of other cause of hemorrhage or superficial siderosis

Tab 1. *Modified Boston criteria for CAA-related hemorrhage (Linn et al. Neurology 2010)*

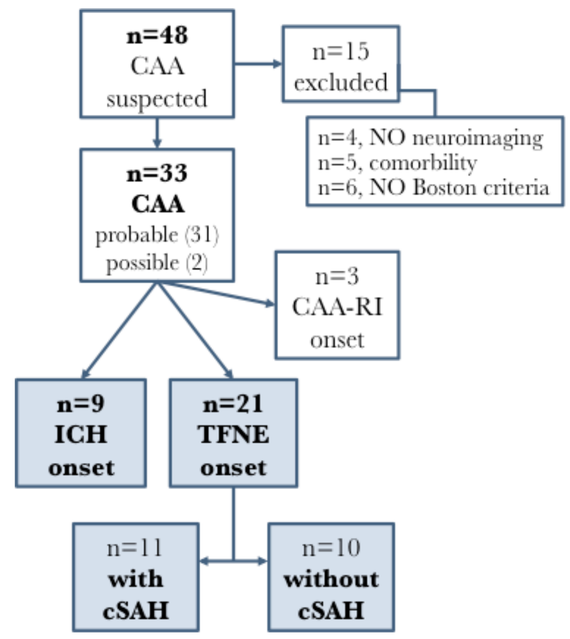

Fig 2. *Flow chart of the study population*

Clinical features	TNFE n=21	ICH n=9	p value
age mean+-SD	74 +-8.6	73 +-9.6	0.8
gender female n (%)	18 (85)	5 (55)	0.09
hypertension n (%)	22 (87.5)	7 (90)	0.9
cognitive deficits n (%)	8 (33)	2 (22)	0.5
cardiovascular risk factors n (%)	21 (75)	5 (55)	0.3

Tab 2. *Demographic features of the study population*

The most frequent diagnosis of TFNE at baseline was stroke or TIA (43%), following CAA in 4 (19%) and cortical venous thrombosis in 3 patients (12.5%) (Fig 4). At first visit 70% of patients with TFNE was treated with antithrombotics (antiplatelet drugs or vitamin K-antagonists) (Fig 5).

Symptoms Frequency

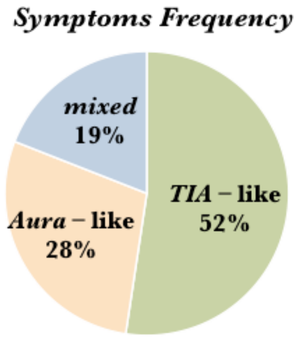

Fig 3. *Pie chart of each clinical classes in which the first TFNE was categorized regarding the presence of positive (aura like), negative (TIA like) or both symptomatology*

Symptoms Phenomenology

Clinical Aspects	n (%)
speech impairment	12 (57)
limb paresthesias	10 (52)
mouth deviation	4 (36)
perioral paresthesias	3 (14)
limb numbness	2 (9)
limb weakness	1 (5)

Tab 3. *Frequencies for each presenting symptoms. Dysphasia and paresthesias were the most common (red circle)*

Symptoms Duration

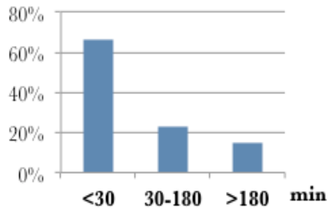

Fig 4. *Symptoms lasting time (minutes). In the majority TNFE lasted less than 30 minutes*

Discharge Diagnosis after 1° TFNE

Diagnosis	n (%)
TIA	8 (30)
acute ischaemic stroke	3 (12.5)
seizures due to cortical venous thrombosis	3 (12.5)
seizures due to ESA	3 (12.5)
CAA	4 (19)

Tab 4. *Diagnosis at discharge after the first TFNE. The most common were diagnosis of cerebrovascular event (TIA and ischaemic stroke, red circle)*

Therapy at Discharge after 1° TFNE

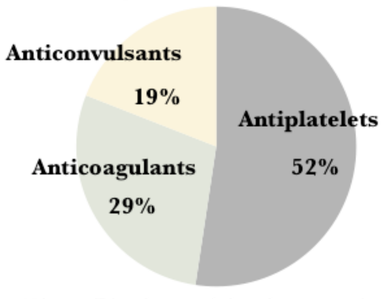

Fig 5. *Pie chart of the therapy given after the first TFNE, note in the majority (81%) an antithrombotic therapy was started*

MRI Findings	n (%)
Lobar microbleeds	16 (89)
cSAH	11 (61)
cSS (focal and disseminated)	14 (78)
Posterior leukoaraiosis	15 (83)
Acute ischaemic lesion	3 (17)

Tab 5. *MRI typical features of CAA identified after the first TFNE (MRI imaging was performed within 14+-2 days)*

On MRI, microbleeds were detected in 88% and cSAH in 52% of TFNE cases.

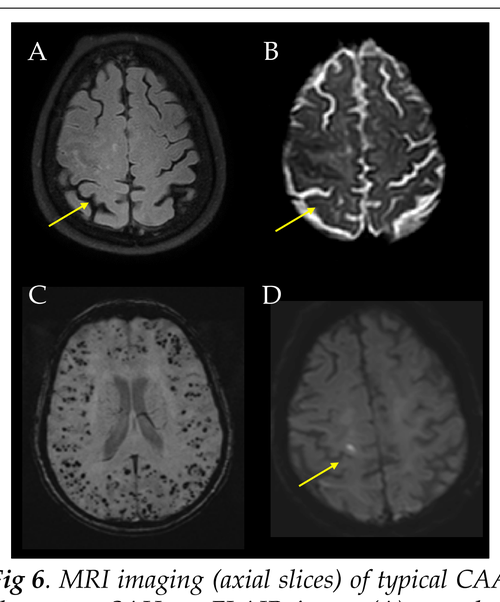

Fig 6. *MRI imaging (axial slices) of typical CAA elements. cSAH on FLAIR image (A) as sulcal hypeintensity (arrow); focal cSS on SWI image (B) visible as curvilinear low signal intensity (**bilinear 'track-like' appearance**) on cortical sulci (arrow). SWI image (C) reveals multiple lobar microbleeds as round low signal spots. Small cortical acyute ischaemic lesion on DWI (D, arrow)*

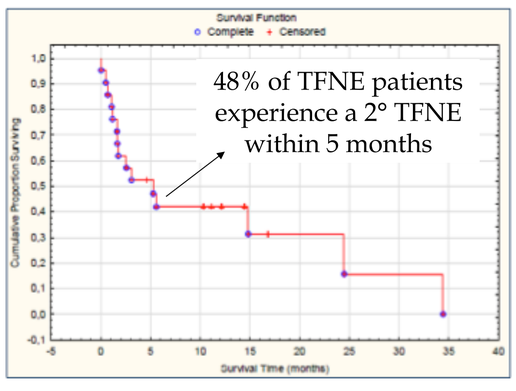

Fig 7. *Kaplan Meier curves showing the cumulative risk of a second CAA event after a first TFNE*

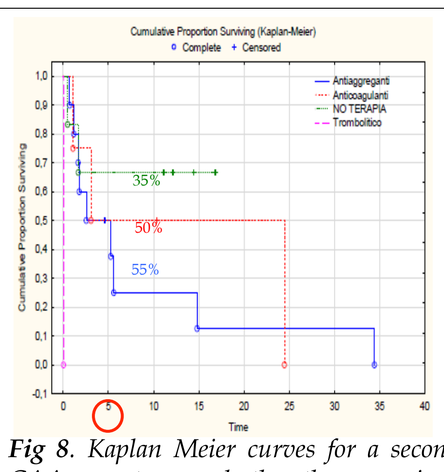

Fig 8. *Kaplan Meier curves for a second CAA event regard the therapy given between first and second event. The frequencies of patients with a second event at 5 months are reported, see that around 50% of patients in antithrombotic therapy had a second CAA episode at 5 months*

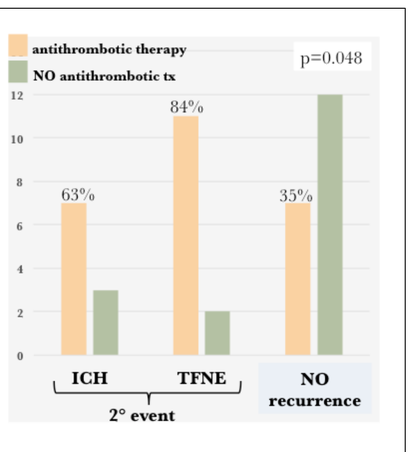

Fig 9. *A second event (both ICH and TFNE) was significantly more common among patients taking antithrombotic drugs (63% and 84%) than in people without this therapy (35%)*

During follow-up, the total risk of ICH after a first TFNE was 42%, being 14% in the first two months after the first TFNE. A significant association between TFNE/ ICH relapse and antithrombotic drugs use was found (p=0.04) (Figg 7-9).

Misdiagnosis of CAA-related TFNE is frequent given the heterogeneous clinical manifestations (often hardly distinguishable from TIAs), and because differential diagnosis of neuroimaging findings may be challenging (e.g. cortical venous thrombosis vs cSAH/ superficial cortical siderosis). CAA-related TFNE are associated with high early risk of lobar ICH, hence avoiding antiplatelet drugs or anticoagulants in CAA patients is recommended.