SUPPLEMENTAL MATERIAL

Table S1 - Baseline characteristics, vascular risk factors and other relevant past medical history and family history (by group age)

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| --- | --- | --- | --- |
|  | Age < 45(n=16) | Age ≥45(n=61) | p-value |
| Female sex | 13 (81.2) | 43 (70.5) | 0.534 |
| Caucasian | 14 (87.5) | 60 (98.4) | 0.108 |
| Risk factors |  |  |  |
|  Hypertension | 6 (37.5) | 35 (57.4) | 0.173 |
|  Diabetes Mellitus\* | 0 (0) | 7 (11.5) | 0.334 |
|  Dyslipidemia | 6 (37.5) | 35 (57.4) | 0.173 |
|  Smoking# | 4 (25.0) | 28 (45.9) | 0.162 |
|  Alcohol consumption# | 6 (37.5) | 26 (42.6) | 0.782 |
|  Coronary artery disease | 0 (0) | 2 (3.3) | 1.000 |
|  Atrial fibrillation | 0 (0) | 1 (1.6) | 1.000 |
|  Previous stroke/TIA | 8 (50.0) | 31 (50.8) | 1.000 |
|  |  |  |
| Number of risk factors 0 1 2 ≥3 | 3 (18.8)7 (43.8)3 (18.8)3 (18.8) | 6 (9.8)10 (16.4)15 (24.6)30 (49.2) | 0.093 |
|  |  |  |
| MigraineMigraine With aura | 7 (43.8)3 (18.8) | 23 (37.7)13 (21.3) | 0.7751.000 |
| Depression | 6 (37.5) | 30 (49.2) | 0.575 |
| Head trauma | 3 (18.8) | 14 (24.1) | 0.750 |
| Syncope | 5 (31.2) | 9 (15.3) | 0.161 |
| Seizures | 0 (0) | 3 (4.9) | 1.000 |
| Family history  Stroke Dementia Psychiatry disease | 5 (31.2)3 (18.8)5 (31.2) | 17 (27.9)6 (9.8)15 (24.6) | 0.7650.3830.749 |
|  |  |  |
|  |  |  |

Table S2 – Reasons for referral and patients’ symptoms (by age group)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Age < 45(n=16) | Age ≥45(n=61) | p-value |
| Reasons for referral to Neurology Outpatient Clinic |
|  Focal sign | 6 (37.5) | 17 (27.9) | 0.542 |
|  Headache | 3 (18.8) | 13 (21.3) | 1.000 |
|  Cognitive complaints | 1 (6.2) | 2 (3.3) | 0.508 |
|  Seizure | 0 (0) | 2 (3.3) | 1.000 |
|  Vertigo  | 1 (6.2) | 4 (6.6) | 1.000 |
|  Syncope | 0 (0) | 1 (1.6) | 1.000 |
|  Other | 5 (31.2) | 22 (36.1) | 0.778 |
| Patients’ symptoms in the Neurology Outpatient Clinic |
|  Depressive symptoms | 6 (37.5) | 27 (44.3) | 0.778 |
|  Memory impairment | 4 (25.0) | 27 (44.3) | 0.252 |
|  Other cognitive complaints | 3 (18.8) | 13 (21.3) | 1.000 |
|  Gait disturbance | 2 (12.5) | 13 (21.3) | 0.723 |
|  Vertigo | 3 (18.8) | 11 (18.0) | 1.000 |
|  Urinary complaints | 2 (12.5) | 3 (4.9) | 0.276 |
| Neurological findings in the Neurology Outpatient Clinic |
|  Pyramidal signs | 4 (25.0) | 19 (31.1) | 0.764 |
|  Gait impairment | 2 (12.5) | 14 (23.0) | 0.499 |
|  Dysarthria | 1 (6.2) | 9 (14.8) | 0.678 |
|  Cerebellar signs | 1 (6.2) | 7 (11.5) | 1.000 |
|  Sensitive signs | 3 (18.8) | 14 (23.0) | 1.000 |
|  Primitive reflexes | 0 (0) | 14 (23) | 0.034 |
|  MMSE, median (IQR)\* | 30 (29–30) | 29 (27–30) | 0.197 |
|  Positive screening test with MMSE\* | 1 (7.7) | 3 (6.1) | 1.000 |
|  MoCA, median (IQR)# | 28 (26–28) | 24 (21–26) | 0.059 |
|  Positive screening test with MoCA# | 1 (6.2) | 9 (14.8) | 0.678 |
| \*65 patients |  |  |  |
| #56 patients |  |  |  |

Table S3 – Imaging characteristics (by age group)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Age < 45(n=16) | Age ≥45(n=61) | p-value |
| Fazekas II | 12 (75.0) | 37 (60.7) | 0.384 |
| Fazekas III | 4 (25.0) | 24 (39.3) |
| ARWMC (rated 2-3) Frontal Parieto-occipital Temporal Basal ganglia Infratentorial | 13 (81.2)14 (87.5)3 (18.8)4 (25.0)2 (12.5) | 54 (88.5)51 (83.6)23 (37.7)24 (39.3)11 (18.0) | 0.4251.0000.2360.3840.725 |
| Cerebral microbleeds\* | 3 (23.1) | 20 (37.7) | 0.517 |
|  Deep | 1 (33.3) | 10 (50) | 0.303 |
|  Cortical | 2 (66.6) | 5 (25) |
|  Both | 0 (0) | 5 (25) |
| \* Cerebral microbleeds evaluation in 66 of 77 patients |

Table S4 – Investigations performed in order to screen genetic disorders associated with vascular white matter lesions

|  |  |
| --- | --- |
|  | Patients with one or more diagnostic test for a monogenic disease(N=58) |
| Fabry disease Alfagalactosidase Dried blood spot\* Alfagalactosidase Whole blood test\* Complete *GLA* gene sequence# | 40 (68.9)33 (56.9)5 (8.6)15 (25.9) |
| CADASIL*NOTCH3* exons 3, 4, 11, 18/19 ¥ Complete *NOTCH3* gene sequence Skin biopsy | 33 (56.9)33 (56.9)6 (10.3)1 (1.7) |
| MELAS (MT-TL1transfer RNA gene) | 2 (3.4) |
| COL4A1 (complete *COL4A1* gene sequence) | 1 (1.7) |
| Krabbe Disease, Metacromatic Leucodistrophy, Mucopolissacaridosis (type IVb) | 1 (1.7) |
| \* Alfagalactosidase enzyme activity# All 7 *GLA* gene exons and respective exon/intron boundaries were studied¥ According to the laboratorial protocol only exons 3, 4, 11, 18/19 were studied |