SUPPLEMENTAL MATERIAL

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

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | | 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 |
|  |  |  | | | | | |
| Migraine  Migraine With aura | | | 7 (43.8)  3 (18.8) | | 23 (37.7)  13 (21.3) | 0.775  1.000 |
| 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) | 0.765  0.383  0.749 |
|  |  |  | |
|  |  |  | |

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) | 0.425  1.000  0.236  0.384  0.725 |
| 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 | |