**Table1 Comparisons of characteristics between our previous (<2015) and current (2015-2021) cohorts of pediatric multiple sclerosis patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Findings** | **Current cohort (2015-2021)**  **n=634** | **Previous cohort (<2015)1**  **n=193** | **p** |
| **Demographics and clinical characteristics** |  |  |  |
| Onset under 12 years of age | 89 (14.0) | 45 (23.3) | **0.002** |
| Sex ratio, F:M | 2.56 | 1.76 | **0.030** |
| Age at the first clinical attack, years | 14.1±2.51,  5 (3-17) | 13.5±2.88,  14 (4-17) | **0.005** |
| Interval between the first two attacks, months | 10.3±10.9,  7 (1-84) | 10.3±10.9,  6 (1-60) | 0.967 |
| Family history of MS | 48 (8.7) | 12 (6.5) | 0.345 |
| Infection/vaccination preceding initial episode | 23 (3.7) | 30 (15.7) | **<0.001** |
| Disease course, Relapsing remitting | 634 (100) | 191 (99.0) | 0.054 |
| Initial diagnosis of ADEM | 23 (3.6) | 21 (11.0) | **<0.001** |
| Presenting clinical phenotype, monofocal | 297 (46.8) | 86 (44.6) | 0.577 |
| Functional systems involved during initial attack |  |  |  |
| Optic neuritis | 194 (30.6) | 51 (26.4) | 0.266 |
| Motor | 228 (36.0) | 64 (33.2) | 0.476 |
| Sensory | 342 (53.9) | 85 (44.0) | **0.016** |
| Brainstem | 146 (23.0) | 71 (39.7) | **<0.001** |
| Cerebellar | 134 (21.1) | 57 (29.5) | **0.015** |
| Myelopathy | 33 (5.2) | 4 (2.1) | 0.065 |
| Sphyncteric dysfunction | 3 (0.5) | 8 (4.1) | **0.001** |
| Seizure | 9 (1.4) | 10 (5.2) | **0.005** |
| **MRI lesions at onset** |  | <0.001 |  |
| Cortical/ Juxtacortical | 549 (87.5) | 113 (64.2) | **<0.001** |
| Periventricular white matter | 603 (96.3) | 174 (96.1) | 0.904 |
| Infratentorial | 424 (67.7) | 135 (71.8) | 0.291 |
| Spinal cord | 321 (51.4) | 124 (67.0) | **<0.001** |
| **VEP latency abnormalities at the last follow up** | 236 (56.9) | 81 (51.9) | 0.289 |
| **Cerebrospinal fluid at the last follow up** |  |  |  |
| OCBs restricted to CSF | 478 (82.8) | 115 (68.0) | **<0.001** |
| Elevated IgG index | 374 (74.2) | 96 (62.3) | **0.004** |
| Data are number (%) or mean±SD,median (minimum-maximum), unless otherwise specified.  S.D: Standard deviation; ADEM: acute disseminated encephalomyelitis; VEP: visual evoked potentials; CSF: cerebrospinal fluid, F: female; M: male.  1. Yılmaz Ü, Anlar B, Gücüyener K; Turkish Pediatric Multiple Sclerosis Study Group. Characteristics of pediatric multiple sclerosis: The Turkish pediatric multiple sclerosis database. Eur J Paediatr Neurol. 2017;21(6):864-872 | | | |

**Table2 Comparisons of clinical and demographic characteristics between patients with earlier and later onset pediatric multiple sclerosis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **All patients** | **Onset <12 yrs** | **Onset 12-17 yrs** | **P** |
| Number, % | 634 | 89 (14.0) | 545 (86.0) |  |
| Sex ratio, F:M | 2.56 | 1.41 | 2.87 | **0.002** |
| Age at the first clinical attack, years | 14.1±2.51,  5 (3-17) | 9.22±2.00,  10 (3-11) | 14.9±1.49,  15 (12-17) | **<0.001** |
| Interval between the first two attacks, months | 10.3±10.9,  7 (1-84) | 13.8±16.2,  8 (1-84) | 9.70±9.55,  6 (1-53) | **0.006** |
| Total number of attacks | 2.09±1.33,  2 (1-12) | 2.26±1.28,  2 (1-6) | 2.06±1.34,  2 (1-12) | 0.199 |
| Duration of follow up, months | 28.4±22.3,  24 (1-96) | 34.6±27.6,  24 (1-96) | 27.4±21.2,  23 (1-84) | **0.005** |
| Coexistence of other autoimmune disorders, n=561 | 33 (5.9) | 2 (2.9) | 31 (6.3) | 0.412 |
| Family history of MS, n=553 | 48 (8.7) | 3 (4.4) | 45 (9.3) | 0.182 |
| Breastfeeding ≥6 months, n=414 | 321 (77.5) | 41 (75.9) | 280 (77.8) | 0.816 |
| Smoking at home, n=391 | 206 (52.7) | 29 (64.4) | 177 (51.2) | 0.093 |
| Infection/vaccination preceding initial episode, n=624 | 23 (3.7) | 8 (9.3) | 15 (2.8) | **0.008** |
| Disease course, relapsing remitting | 634 (100) | 89 (100) | 545 (100) |  |
| Initial diagnosis |  |  |  |  |
| RRMS | 452 (71.3) | 50 (56.2) | 402 (73.8) | **0.001** |
| CIS | 159 (25.1) | 26 (29.2) | 133 (24.4) | 0.332 |
| ADEM | 23 (3.6) | 13 (14.6) | 10 (1.8) | **<0.001** |
| Presenting clinical phenotype, monofocal | 297 (46.8) | 37 (41.6) | 260 (47.7) | 0.282 |
| Functional systems involved during initial attack |  |  |  |  |
| Optic neuritis | 194 (30.6) | 25 (28.1) | 169 (31.0) | 0.580 |
| Unilateral | 160 (25.2) | 20 (22.5) | 140 (25.7) |  |
| Bilateral | 34 (5.4) | 5 (5.6) | 29 (5.3) |  |
| Motor | 228 (36.0) | 33 (37.1) | 195 (35.8) | 0.813 |
| Sensory | 342 (53.9) | 37 (41.6) | 305 (56.0) | **0.012** |
| Brainstem | 146 (23.0) | 31 (34.8) | 115 (21.1) | **0.004** |
| Cerebellar | 134 (21.1) | 21 (23.6) | 113 (20.7) | 0.540 |
| Myelopathy | 33 (5.2) | 10 (11.2) | 23 (4.2) | **0.016** |
| Sphyncteric dysfunction | 3 (0.5) | 1 (1.1) | 2 (0.4) | 0.365 |
| Seizure | 9 (1.4) | 3 (3.4) | 6 (1.1) | 0.120 |
| Adequate/excellent academic performance | 472 (95.4) | 60 (93.8) | 412 (95.6) | 0.521 |
| Data are number (%) or mean±SD,median (minimum-maximum), unless otherwise specified.  S.D: Standard deviation; MS: multiple sclerosis; ADEM: acute disseminated encephalomyelitis; RRMS: relapsing remitting multiple sclerosis; CIS: clinically isolated syndrome; EDSS: Expanded Disability Status Scale; yrs: years; F: female; M: male.  “n” on the first column is the number of subjects who have data for the specific parameter on that line. | | | | |

**Table 3 Comparisons of paraclinical characteristics between patients with earlier and later onset pediatric multiple sclerosis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All patients** | **Onset <12 yrs** | **Onset 12-17 yrs** | **P** |
| **Anti-MOG-IgG** | 0/483 | 0/75 | 0/408 |  |
| **Anti-AQP4-IgG** | 0/437 | 0/65 | 0/372 |  |
| **MRI lesions at onset** |  |  |  |  |
| Cortical/ Juxtacortical, n=624 | 519 (83.2) | 76 (88.4) | 443 (82.3) | 0.165 |
| Periventricular white matter, n=624 | 594 (95.2) | 77 (89.5) | 517 (96.1) | **0.014** |
| Infratentorial, n=624 | 394 (63.1) | 60 (69.8) | 334 (62.1) | 0.170 |
| Spinal cord, n=624 | 288 (46.2) | 27 (31.4) | 261 (48.5) | **0.003** |
| Total T2-lesion number, n=607 |  |  |  | 0.815 |
| 1-3 | 61 (10.0) | 7 (8.3) | 54 (10.3) |  |
| 4-9 | 271 (44.6) | 37 (44.0) | 234 (44.7) |  |
| ≥10 | 275 (45.3) | 40 (47.6) | 235 (44.9) |  |
| Gd-enhancing lesion number, n=562 |  |  |  | 0.931 |
| None | 115 (20.5) | 14 (19.2) | 101 (20.7) |  |
| 1-3 | 288 (51.2) | 36 (49.3) | 252 (51.5) |  |
| 4-9 | 112 (19.9) | 16 (21.9) | 96 (19.6) |  |
| ≥10 | 47 (8.4) | 7 (9.6) | 40 (8.2) |  |
| **VEP latency abnormalities** |  |  |  |  |
| **At onset**, n=400 | 211 (52.8) | 29 (65.9) | 182 (51.1) | 0.064 |
| Patients with a history of ON, n=133 | 114 (85.7) | 12 (100) | 102 (84.3) | 0.138 |
| Patients without a history of ON, n=267 | 97 (36.3) | 17 (53.1) | 80 (34.0) | **0.035** |
| **At the last follow up, n=415** | 236 (56.9) | 33 (66.0) | 203 (55.6) | 0.164 |
| Patients with a history of ON, n=169 | 142 (84.0) | 17 (94.4) | 125 (82.8) | 0.202 |
| Patients without a history of ON, n=246 | 94 (38.2) | 16 (50.0) | 78 (36.4) | 0.141 |
| **Cerebrospinal fluid** |  |  |  |  |
| OCB-restricted to CSF, at onset, n=577 | 468 (81.1) | 51 (63.8) | 417 (83.9) | **<0.001** |
| OCB-restricted to CSF, at the last visit, n=577 | 478 (82.8) | 56 (70.0) | 422 (84.9) | **0.001** |
| Conversion of CSF-restricted OCBs from negative to positive, n=17 | 10 (58.8) | 5 (71.4) | 5 (50.0) | 0.622 |
| Conversion duration of CSF-restricted OCBs from negative to positive, months, n=10 | 11.3±9.5,  8 (3-30) | 12.6±11.3,  10 (3-30) | 10.0±8.3,  6 (3-24) |  |
| Elevated IgG index, at onset, n=502 | 365 (72.7) | 33 (55.9) | 332 (74.9) | **0.002** |
| Elevated IgG index, at the last visit, n=504 | 374 (74.2) | 38 (62.3) | 336 (75.8) | **0.023** |
| Presence of lymphocytes in CSF (>5/ml), n=489 | 68 (13.9) | 14 (21.9) | 54 (12.7) | **0.048** |
| Protein in CSF, mg/dl, n=541 | 34.1±15.2,  31 (5-91) | 29.5±12.1,  27 (10-78) | 34.8±15.5,  31 (5-91) | **0.006** |
| High protein levels in CSF | 68 (13.9) | 6 (8.6) | 85 (18.0) | **0.048** |
| **25-hydroxyvitaminD** |  |  |  |  |
| Serum levels at onset, n=549 | 16.3±9.47,  14 (3-88) | 18.2±9.1,  15.5 (4-48) | 16.0±9.5,  14 (3-88) | 0.087 |
| Patients with low serum levels at onset, n=549 | 401 (73.0) | 45 (68.2) | 356 (73.7) | 0.343 |
| Serum levels at the last visit, n=368 | 25.1±12.2,  22 (4-86) | 25.0±11.7,  21 (9-68) | 25.1±12.3,  23 (4-86) | 0.966 |
| Patients with low serum levels at the last visit, n=368 | 154 (41.8) | 20 (42.6) | 134 (41.7) | 0.916 |
| Data are number (%) or mean±SD,median (minimum-maximum), unless otherwise specified.  S.D: Standard deviation; MRI: magnetic resonance imaging; yrs: years; MOG: myelin oligodendrocyte glycoprotein; AQP4: aquaporin 4; VEP: visual evoked potentials; ON: optic neuritis; CSF: cerebrospinal fluid, OCB: oligoclonal band  “n” on the first column is the number of subjects who have data for the specific parameter on that line. | | | | |

**Table 4 Treatment in patients with pediatric multiple sclerosis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All patients** | **Onset <12 yrs** | **Onset 12-17 yrs** | **P** |
| **Initial Disease-Modifying Therapies, n=634** |  |  |  | 0.460 |
| **Moderate efficacy** | 505 (79.7) | 70 (78.7) | 435 (79.8) |  |
| Interferon beta 1-a | 412 (65.0) | 60 (67.4) | 352 (64.6) |  |
| Interferon beta 1-b | 47 (7.4) | 6 (6.7) | 41 (7.5) |  |
| Glatiramer acetate | 15 (2.4) | - | 15 (2.8) |  |
| Teriflunomide | 31 (4.9) | 4 (4.5) | 27 (5.0) |  |
| **High efficacy** | 41 (6.5) | 4 (4.5) | 37 (7.8) |  |
| Dimethyl fumarate | 16 (2.5) | - | 16 (2.9) |  |
| Fingolimod | 15 (2.4) | - | 15 (2.8) |  |
| Ocrelizumab | 5 (0.8) | 1 (1.1) | 4 (0.7) |  |
| Rituximab | 3 (0.5) | 3 (3.4) | - |  |
| Natalizumab | 2 (0.3) | - | 2 (0.4) |  |
| IVIG (monthly) | 4 (0.6) | 4 (4.5) | - |  |
| Unknown | 23 (3.6) | 4 (4.5) | 19 (3.5) |  |
| No medication | 61 (9.6) | 7 (7.9) | 54 (9.9) |  |
| Reason for not starting DMTs, n=58 |  |  |  |  |
| Planned but not started yet | 17 (27.9) | 1 (14.3) | 16 (29.6) |  |
| Parents' refusal | 6 (9.8) | - | 6 (11.1) |  |
| Low MRI lesion load | 2 (3.3) | - | 2 (3.7) |  |
| Unknown | 36 (59.0) | 6 (85.7) | 30 (55.6) |  |
| Number of clinical attacks at which treatment was started, n=550 |  |  |  |  |
| 1 | 312 (56.7) | 35 (44.9) | 277 (58.7) |  |
| 2 | 204 (37.1) | 34 (43.6) | 170 (36.0) |  |
| 3 | 27 (4.9) | 7 (9.0) | 20 (4.2) |  |
| ≥4 | 6 (1.1) | 2 (2.6) | 4 (0.8) |  |
| Increase in MRI activity | 1 (0.2) | - | 1 (0.2) |  |
| Time from the first attack to start of treatment, months, n=550 | 6.07±11.0,  2 (0-84) | 10.9±17.3,  4.5 (0-84) | 5.27±9.36,  2 (0-58) | **<0.001** |
| Duration of treatments with DMTs, months |  |  |  |  |
| 1st DMT, n= 549 | 18.0±16.3,  12 (1-84) | 18.0±19.0,  10 (1-78) | 18.0±15.8,  12 (1-84) | 0.993 |
| 2nd DMT, n=158 | 15.4±13.7,  12 (1-66) | 17.6±14.5,  11 (1-48) | 15.1±13.6,  12 (1-66) | 0.477 |
| 3rd DMT, n= 32 | 14.6±13.0,  12 (1-66) | 16.3±14.4,  12 (1-36) | 14.2±13.0,  11.5 (3-66) | 0.743 |
| 4th DMT, n=6 | 22.0±7.77,  22.5 (12-30) | - | 22.0±7.77,  22.5 (12-30) |  |
| Effectiveness of DMTs |  |  |  |  |
| 1st DMT, n= 383 |  |  |  |  |
| Effective | 166 (43.3) | 14 (28.6) | 152 (45.5) | **0.025** |
| Non-effective | 217 (56.7) | 35 (71.4) | 182 (54.5) |  |
| Relapses | 197 (51.4) | 32 (65.3) | 165 (49.4) |  |
| Increased / active MRI lesions | 11 (2.9) | 2 (4.1) | 9 (2.7) |  |
| Adverse events | 6 (1.6) | 1 (2.0) | 5 (1.5) |  |
| Nonadherence / patients’ choice | 3 (0.8) | - | 3 (0.9) |  |
| 2nd DMT, n=102 | 59 (57.8) | 4 (30.8) | 55 (61.8) | **0.034** |
| 3rd DMT, n= 20 | 14 (70.0) | 4 (100) | 10 (62.5) |  |
| 4th DMT, n= 6 | 3 (50.0) | - | 3 (50.0) |  |
| Data are number (%) or mean±SD,median (minimum-maximum), unless otherwise specified.  S.D: Standard deviation; MRI: magnetic resonance imaging; yrs: years; DMTs: Disease-Modifying Therapies.  “n” on the first column is the number of subjects who have data for the specific parameter on that line. | | | | |

Figure: Pediatric multiple sclerosis is rare in children younger than 12 years of age. The female-male ratio shows an increasing trend with age.