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| **Table s1. Demographic and clinical characteristics in incident cases of ALS in FVG from 2010 to 2014. Comparison of patients excluded and included from the present study1.** |
|  | **Patients excluded****(n=34, 20.2%)****n (%)** | **Patients included****(n=134; 79.8%)****n (%)** | **p-value2** |
| **Demographic characteristics**  |  |  |  |  |
| *Sex* |  |  |  |  |
| Men | 17 (50.0%) | 65 (48.5%) |  |  |
| Women | 17 (50.0%) | 69 (51.5%) | 0.8764 |
| *Age at disease onset (years)*3 |  |  |  |  |
| <60 | 3 (13.0) | 27 (20.5) | 0.0567 |
| 60-70  | 5 (21.7) | 44 (33.3) |
| 70-80  | 10 (43.5) | 50 (37.9) |
| ≥80  | 5 (21.7) | 11 (8.3) |
|  Median age (IQR4) | 72.3 (64.8-79.4) | 68.8 (62.0-74.7) | - |
| Mean age (SD5) | 71.5 (9.7) | 67.5 (10.7) |  |  |
|  Range (min-max) | 49.4-85.1 | 22.6-89.4 | - |
| *Age at disease diagnosis (years)* |
| <60 | 3 (8.8) | 26 (19.4) | 0.2161 |
| 60-70  | 12 (35.3) | 40 (29.9) |
| 70-80  | 12 (35.3) | 52 (38.8) |
| ≥80  | 7 (20.6) | 16 (11.9) |
|  Median age (IQR4) | 72.62 (65.2 -78.5) | 70.4 (62.9-76.4) | - |
|  Mean age (SD5) | 71.9 (9.6) | 68.8 (10.8) |  |  |
|  Range (min-max) | 48.5-88.8 | 23.5-89.6 | - |
| **Clinical characteristics** |  |  |  |  |
| *Type of onset 6* |  |  |  |  |
|  Spinal | 15 (60.0) | 87 (64.9) | 0.4102 |
|  Bulbar  | 10 (40.0) | 47 (35.1) |
| 1 Percentages of patients with available data. 2 Chi-square test (or Fisher exact test) for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. 3 Information missing for 11 patients. 4 Interquartile range. 5 Standard deviation. 6 Information missing for 9 patients. |

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| **Table s2.**  **Type of physical/rehabilitation therapy or surgery.** |
| **Treatments** | **Number of patients** |
| Median nerve decompression surgery | 3 |
| Laminectomy | 3 |
| Speech therapy | 3 |
| Motor re-education | 2 |
| Discectomy | 1 |
| Muscular electrotherapy | 1 |
| Common popliteal nerve decompression surgery | 1 |
| Cervical medullary decompression surgery | 1 |
| Heel spur shock waves therapy | 1 |
| **Total** | **16** |

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| **Table s3. Number of instrumental evaluations performed between disease onset and ALS diagnosis according to kind of the first specialist consultation, onset type and misdiagnoses proposed.** |
| **N. of tests** |  | **First specialist referral** |  | **Type of onset** |  | **Misdiagnosis** |  | **Total patients****(%)** |
|  | **Neurologist**  | **Other than neurologist** | **p-value1** |  | **Bulbar or mixed** | **Spinal** | **p-value1** |  | **Yes**  | **No** | **p-value1** |  |
| 1 or 2 |  | 14 (22.6) | 16 (33.3) | **0.0071** |  | 14 (32.6) | 22 (28.6) | 0.8315 |  | 11(22.5) | 18 (33.3) | 0.4526 |  | 36 (30.0) |
| 3 or 4  |  | 29 (46.8) | 18(37.5) |  | 19 (44.2) | 31 (40.3) |  | 20(40.8) | 23 (42.6) |  | 50 (41.7) |
| 5 or 6 |  | 16 (25.8) | 4 (8.3) |  | 6 (14.0) | 15 (19.5) |  | 11(22.5) | 7 (13.0) |  | 21 (17.5) |
|  7 to 13 |  | 3 (4.8) | 10 (20.8) |  | 4 (9.3) | 9 (11.7) |  | 7(14.3) | 6(11.1) |  | 13 (10.8) |
| **Total**2 |  | **62** | **48**  |  | **43** | **77** |  | **49** | **54** |  | **120** |
| 1 Chi-square test. 2 Total of patients with information about first specialist referral, type of onset, misdiagnosis and number of instrumental evaluations.  |

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| **Table s4. Time to diagnosis in incident cases of ALS in FVG from 2010 to 2014. Comparison of patients excluded and included from the present study.** |
|  | **Patients excluded (n=34, 20.2%)** | **Patients included (n= 134, 79.8%)** | **Wilcoxon-Mann-Whitney** **test p-value** |
|  | **Time to diagnosis****Median (IQR1)** | **Wilcoxon-Mann-Whitney** **test p-value** | **Time to diagnosis****Median (IQR1)** | **Wilcoxon-Mann-Whitney** **test p-value** |
| **Overall** | 7.8 (4.5-14.6) | **-** | 11.5 (7.1-18.3) | **-** | 0.1175 |
| **Demographic characteristics** |  |  |  |  |  |
| *Sex* |  |  |  |  |  |
|  Men  Women | 7.8 (5.5-12.3)6.6 (2.4-28.4) | 0.6869 | 13.2 (7.7-21.3)10.7 (6.1-15.2) | 0.0884 | - |
| *Age at disease onset* |  |  |  |  |  |
|  <60 years ≥60 years | 36.4 (12.0-60.9)6.8 (4.5-12.8) | 0.2096 | 8.1 (5.1-11.1)12.4 (7.4-21.5) | ***0.0064*** | - |
| **Clinical characteristics** |  |  |  |  |  |
| *Type of onset* |  |  |  |  |  |
|  Bulbar  Spinal  | 5.9 (4.5-12.3)8.3 (4.6-16.0) | 0.4994 | 10.3 (7.1-14.9)12.4 (7.1-22.0) | 0.1236 | - |
| 1 Interquartile range. |  |  |  |

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| **Table s5. Conclusions at first neurologic referral by type of ALS onset.** |
| **Conclusion** | **Bulbar or mixed onset patients** | **Spinal onset patients** | **p-value1** | **Total patients** |
| Other diseases different from ALS/MND | 9 (19.2%) | 24 (27.6%) | 0.2355 | 33(24.6%) |
| MND suspect | 9(19.2%) | 23 (26.4%) | 32(23.9%) |
| No hypothesis and prescription of instrumental ascertainments  | 15(31.9%) | 15 (17.2%) | 30(22.4%) |
| ALS considered in differential diagnosis | 3 (6.4%) | 6 (6.9%) | 9(6.7%) |
| Missing information | 11(23.4%) | 19(21.8%) | 30(22.4%)  |
| 1 Chi-square test. |

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| **Table s6. Patients subjected to instrumental investigations during the diagnostic process1.** |
| **Instrumental investigations** | **During the whole diagnostic process2** | **As first test** |
| **Total**  | **Type of onset** | **First referral: neurologic** | **Misdiagnosis** | **Total**  | **Type of onset** | **First referral: neurologic** | **Misdiagnosis** |
| **Bulbar/****mixed** | **Spinal**  | **Yes** | **No** | **Yes** | **No** | **Bulbar/****mixed** | **Spinal**  | **Yes** | **No** | **Yes** | **No** |
| EMG and NC | 116 (86.6) | 39 (83.0) | 77 (88.5) | 62(95.4) | 44(89.8) | 47(95.9) | 52(88.1) | 50 (37.3) | 13 (27.7) | 37 (42.5) | 24(36.9) | 18(36.7) | 21(42.9) | 22(37.3) |
| Head, brain and brainstem and/or spine CT scan  | 80 (59.7) | 25 (53.2) | 55 (63.2) | 43(66.2) | 33(67.3) | 34(69.4) | 38(64.4) | 25 (18.7) | 16 (34.0) | 9 (10.3) | 13(20.0) | 11(22.4) | 7(14.3) | 16(27.1) |
| Brain and brainstem and/or spine MRI  | 72 (53.7) | 24 (51.1) | 48 (55.2) | 42(64.5) | 28(57.1) | 34(69.4) | 31(52.5) | 26 (19.4) | 6 (12.8) | 20 (23.0) | 17(26.2) | 9(18.4) | 12(24.5) | 9(15.3) |
| Motor, somatosensorial or visual evoked potentials | 41 (30.6) | 12 (25.5) | 29 (33.3) | 23(35.4) | 17(34.7) | 14(28.6) | 22(37.3) | 6(4.5) | 1 (2.1) | 5 (5.7) | 3(4.5) | 2(4.1) | 1(2.0) | 3(5.1) |
| Exams of upper digestive system or larynx | 12 (9.0) | 12(25.5) | 0(0.0) | 5(7.7) | 7(14.3) | 6(12.2) | 6(10.2) | 6 (4.5) | 5 (10.6) | 1 (1.1) | 2(3.1) | 4(8.2) | 3(6.1) | 2(3.4) |
| Head blood vessels or carotid imaging | 9 (6.7) | 5(10.6) | 4(4.6) | 3(4.6) | 0(0.0) | 6(12.2) | 3(5.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| Lumbar puncture | 8 (6.0) | 2 (4.3) | 6 (6.9) | 4(6.2) | 3(6.1) | 3(6.1) | 4(6.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| Spine, shoulders or temporo-mandibular joint radiograph | 7 (5.2) | 2 (4.3) | 5 (5.7) | 2(3.1) | 5(10.2) | 4(8.2) | 2(3.4) | 3 (2.2) | 0 (0.0) | 3 (3.4) | 1(1.5) | 2(4.1) | 2(0.0) | 1(1.7) |
| Abdomen ultrasonography or CT scan  | 4 (3.0) | 2 (4.3) | 2 (2.3) | 1(1.5) | 3(6.1) | 3(6.1) | 1(1.7) | 1 (0.7) | 1 (2.1) | 0 (0.0) | 1(1.5) | 0(0.0) | 0(0.0) | 1(1.7) |
| Repetitive nerve stimulation or neostigmine test | 4 (3.0) | 4 (8.5) | 0 (0.0) | 1(1.5) | 3(6.1) | 2(4.1) | 2(3.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| Neck or salivary glands ultrasonography | 3(2.2) | 3 (6.4) | 0(0.0) | 0(0.0) | 1(2.0) | 2(4.1) | 1(1.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| Thorax CT scan  | 2 (1.5) | 1(2.1) | 1 (1.1) | 0(0.0) | 2(4.1) | 1(2.0) | 1(1.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| Blood tests (tumour markers or thyroid hormones) | 2 (1.5) | 0 (0.0) | 2 (2.3) | 0(0.0) | 2(4.1) | 2(4.1) | 0(0.0) | 1 (0.7) | 0 (0.0) | 1 (1.1) | 0(0.0) | 1(2.0) | 1(2.0) | 0(0.0) |
| Brain SPECT or scintigraphy | 2 (1.5) | 1 (2.1) | 1 (1.1) | 1(1.5) | 1(2.0) | 2(4.1) | 0(0.0) | 1 (0.7) | 0 (0.0) | 1 (1.1) | 1(1.5) | 0(0.0) | 1(2.0) | 0(0.0) |
| ECG | 1 (0.7) | 1 (2.1) | 0 (0.0) | 0(0.0) | 1(2.0) | 1(2.0) | 0(0.0) | 1 (0.7) | 1 (2.1)  | 0 (0.0) | 0(0.0) | 1(2.0) | 1(2.0) | 0(0.0) |
| Muscular biopsy | 1 (0.7) | 0 (0.0) | 1 (1.1) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) |
| Missing data | 14 (10.4) | 4 (8.5) | 10 (11.5) | 3(4.6) | 1(2.0) | 0(0.0) | 5(8.5) | 14 (10.4) | 4 (8.5) | 10 (11.5) | 3(4.6) | 1(2.0) | 0(0.0) | 5(8.5) |
| **Total**3 | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **134** | **47** | **87** | **65** | **49** | **49** | **59** |
| 1 The numbers reported on the table are expressed in number and percentage of patients who underwent to different instrumental investigations. 2 It also includes the first instrumental examination carried out after ALS onset. 3 The column totals exceed 134 (100%) because several patients underwent more than one instrumental examination. |