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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. | | | | | | | | | | | | | | |