

## Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

| eTable 1. Diagnoses among non-cases (where reports available)   |                                |                            |                                |                     |                           |                            |
|---|--------------------------------|----------------------------|--------------------------------|---------------------|---------------------------|----------------------------|
| Neurodegenerative   | Vascular                       | Cerebral insult            | Inflammation                   | Infection           | Miscellaneous             | Non-diagnostic examination |
| Total (n=41)  | Total (n=16)                   | Total (n=15)               | Total (n=8)                    | Total (n=2)         | Total (n=7)               | Total (n=8)                |
| AD (n=21)   | Cerebrovascular disease (n=12) | Anoxia (n=8)               | CD8+ encephalitis (n=3)        | Abscess (n=1)       | Metastatic RCC (n=1)      |                            |
| Dual pathology (n=12)   | Vasculitis (n=2)               | Metabolic (n=2)            | AIE (n=2)                      | Toxoplasmosis (n=1) | Fahr disease (n=1)        |                            |
| AD + DLB (n=10)   | APS (n=1)                      | Seizures (n=1)             | Influenza-associated ANE (n=1) |                     | Leukoencephalopathy (n=1) |                            |
| AD + tau (n=1)  | CAA (n=1)                      | Anoxia + seizures (n=1)    | Behcet's (n=1)                 |                     | Gliosis (n=1)             |                            |
| AD + MSA (n=1)  |                                | HE + seizures (n=1)        | Inflammation NOS (n=1)         |                     | Encephalopathy NOS (n=1)  |                            |
| DLB (n=3)   |                                | Hypoglycaemia (n=1)        |                                |                     | Other, NOS (n=2)          |                            |
| TDP43 (n=2)   |                                | Subcortical necrosis (n=1) |                                |                     |                           |                            |
| Tauopathy (n=2)   |                                |                            |                                |                     |                           |                            |
| CBD (n=1)   |                                |                            |                                |                     |                           |                            |
| Abbreviations. AD, Alzheimer's. AIE, autoimmune encephalitis. ANE, acute necrotizing encephalitis. APS, antiphospholipid syndrome. CAA, cerebral amyloid angiopathy. CBD, corticobasal degeneration. DLB, dementia with Lewy Bodies. HE, hepatic encephalopathy. MSA, multiple systems atrophy. NOS, not otherwise specified. RCC, renal cell carcinoma |                                |                            |                                |                     |                           |                            |

| <b>eTable 2. Neuropathological diagnoses in non-cases with positive investigations (where available)</b> |                                     |                                |                         |
|--|-------------------------------------|--------------------------------|-------------------------|
| <b>Cortical ribboning</b>  | <b>Basal ganglia hyperintensity</b> | <b>14-3-3</b>                  | <b>EEG</b>              |
| Total (n=10)   | Total (n=5)                         | Total (n=41)                   | Total (n=7)             |
| AD (n=3)   | AD + DLB (n=1)                      | AD (n=8)                       | AD (n=2)                |
| AD + DLB (n=1)   | AD + tau (n=1)                      | Anoxia (n=6)                   | APS (n=1)               |
| AD + tau (n=1)   | DLB (n=1)                           | Cerebrovascular disease (n=6)  | Hypoglycaemia (n=1)     |
| APS (n=1)  | Non-diagnostic (n=2)                | CD8+ encephalitis (n=3)        | Anoxia + seizures (n=1) |
| HE + seizures (n=1)  |                                     | AIE (n=2)                      | Tauopathy (n=1)         |
| AIE (n=1)  |                                     | AD + DLB (n=2)                 | Non-diagnostic (n=1)    |
| Encephalopathy NOS (n=1)   |                                     | TDP43 (n=1)                    |                         |
| Non-diagnostic (n=1)   |                                     | HE + seizures (n=1)            |                         |
|  |                                     | Anoxia + seizures (n=1)        |                         |
|  |                                     | Seizure (n=1)                  |                         |
|  |                                     | Hypoglycaemia (n=1)            |                         |
|  |                                     | Fahr disease (n=1)             |                         |
|  |                                     | Metastatic RCC (n=1)           |                         |
|  |                                     | Influenza-associated ANE (n=1) |                         |
|  |                                     | Abscess (n=1)                  |                         |
|  |                                     | Cerebral vasculitis (n=1)      |                         |
|  |                                     | Leukoencephalopathy (n=1)      |                         |
|  |                                     | Encephalopathy NOS (n=1)       |                         |
|  |                                     | Non-diagnostic (n=2)           |                         |

Abbreviations. AD, Alzheimer's. AIE, autoimmune encephalitis. ANE, acute necrotizing encephalitis. APS, antiphospholipid syndrome. CAA, cerebral amyloid angiopathy. CBD, corticobasal degeneration. DLB, dementia with Lewy Bodies. HE, hepatic encephalopathy. MSA, multiple systems atrophy. NOS, not otherwise specified. RCC, renal cell carcinoma

**eTable 3. sCJD subtypes defined by Codon 129 genotype and PrP glycoype combinations**

|                               | MM1             | MM2           | MM1+2        | MV1           | MV2                  | MV1+2             | VV1         | VV2           | VV1+2       |
|-------------------------------|-----------------|---------------|--------------|---------------|----------------------|-------------------|-------------|---------------|-------------|
| Demographics                  |                 |               |              |               |                      |                   |             |               |             |
| Total, n(%)                   | 130 (50.4)      | 15 (5.8)      | 24 (9.3)     | 19 (7.4)      | 22 (8.5)             | 7 (2.7)           | 1 (0.4)     | 38 (14.7)     | 2 (0.8)     |
| Sex, n (%)                    |                 |               |              |               |                      |                   |             |               |             |
| Male                          | 70 (53.8)       | 5 (33.3)      | 8 (33.3)     | 9 (47.4)      | 8 (36.4)             | 2 (28.6)          | 1 (100.0)   | 18 (47.4)     | 1 (50.0)    |
| Female                        | 60 (46.2)       | 10 (66.7)     | 16 (66.7)    | 10 (52.6)     | 14 (63.6)            | 5 (71.4)          | -           | 20 (52.6)     | 1 (50.0)    |
| Age, years (SD)               | 68.4 (10.3)     | 64.0 (12.2)   | 69.6 (9.4)   | 73.3 (5.5)    | 68.0 (9.0)           | 59.2 (14.1)       | 60.0 (-)    | 68.7 (9.0)    | 70.5 (5.0)  |
| Duration, days (IQR)          | 92.5 (67.8-150) | 451 (307-661) | 120 (88-223) | 173 (65-374)  | 411.5 (341.5-668.25) | 539 (309.5-649.5) | 320 (-)     | 170 (128-203) | 231 (-)     |
| Investigation sensitivity (%) |                 |               |              |               |                      |                   |             |               |             |
| EEG                           | 69/118 (58.5)   | 4/12 (33.3)   | 11/22 (50.0) | 11/19 (57.9)  | 4/18 (22.2)          | 3/6 (50.0)        | 0/1 (0.0)   | 4/34 (11.8)   | 0/2 (0.0)   |
| MRI (all)                     | 102/116 (87.9)  | 12/14 (85.7)  | 20/24 (83.3) | 14/17 (82.4)  | 21/22 (95.5)         | 7/7 (100.0)       | 1/1 (100.0) | 36/37 (97.3)  | 2/2 (100.0) |
| CR & BG                       | 53/116 (45.7)   | 3/14 (21.4)   | 8/24 (33.3)  | 10/17 (58.8)  | 7/22 (31.8)          | 6/7 (85.7)        | 1/1 (100.0) | 15/37 (40.5)  | 1/2(50.0)   |
| CR alone                      | 36/116 (31.0)   | 8/14 (57.1)   | 10/24 (41.7) | 2/17 (11.8)   | 4/22 (18.2)          | 1/7 (14.3)        | 0/1 (0.0)   | 1/37 (2.7)    | 0/2 (0.0)   |
| BG alone                      | 13/116 (11.2)   | 1/14 (7.1)    | 2/24 (8.3)   | 2/17 (11.8)   | 10/22 (45.5)         | 0/7 (0.0)         | 0/1 (0.0)   | 20/37 (54.1)  | 1/2 (50.0)  |
| CR (any)                      | 89/116 (76.7)   | 11/14 (78.6)  | 18/24 (75.0) | 12/17 (70.6)  | 11/22 (50.0)         | 7/7 (100.0)       | 1/1 (100.0) | 16/37 (43.2)  | 1/2 (50.0)  |
| BG (any)                      | 66/116 (56.9)   | 4/14 (28.6)   | 10/24 (41.7) | 12/17 (70.6)  | 17/22 (77.3)         | 7/7 (85.7)        | 1/1 (100.0) | 35/37 (94.6)  | 2/2 (100.0) |
| 14-3-3                        | 94/117 (80.3)   | 3/13 (23.1)   | 12/23 (52.2) | 11/16 (68.8)  | 6/19 (31.6)          | 2/6 (33.3)        | 1/1 (100.0) | 30/34 (88.2)  | 2/2 (100.0) |
| RT-QuIC                       | 79/83 (95.2)    | 4/6 (66.7)    | 16/17 (94.1) | 14/14 (100.0) | 14/14 (100.0)        | 2/2 (100.0)       | 0/1 (0.0)   | 22/23 (95.7)  | 2/2 (100.0) |

Age shown as mean, duration as median.

Abbreviations: BG, basal ganglia. CR, cortical ribboning. EEG, electroencephalography. IQR, interquartile range. MRI, magnetic resonance imaging. RT-QuIC, real-time quaking-induced conversion assay. SD, standard deviation.

| <b>eTable 4. Comparison of CJD subjects according to disease duration</b>   |                                |                                 |                                    |                 |
|---|--------------------------------|---------------------------------|------------------------------------|-----------------|
|   | <b>Disease duration (days)</b> |                                 |                                    |                 |
|   | <b>Short (&lt;75) (n=121)</b>  | <b>Typical (75-222) (n=242)</b> | <b>Prolonged (&gt;222) (n=121)</b> | <b>P value</b>  |
| Sensitivity (%) [95% CI]  |                                |                                 |                                    |                 |
| Diagnostic criteria   |                                |                                 |                                    |                 |
| Clinical features   | 102/120 (85.0) [77.3-90.7]     | 213/239 (89.1) [84.5-92.8]      | 98/119 (82.4) [74.3-88.7]          | .19             |
| Probable sCJD   |                                |                                 |                                    |                 |
| Revised criteria  | 51/52 (98.1) [89.8-100]        | 109/110 (99.1) [95.0-100]       | 53/56 (94.6) [85.1-98.9]           | .19             |
| Prior criteria  | 43/52 (82.7) [69.7-91.8]       | 91/110 (82.7) [74.4-89.3]       | 32/56 (57.1) [43.2-70.3]           | <b>.001</b>     |
| Investigations  |                                |                                 |                                    |                 |
| EEG   | 68/109 (62.4) [52.6-71.5]      | 105/225 (46.7) [44.2-58.2]      | 28/105 (26.7) [18.5-36.2]          | <b>&lt;.001</b> |
| MRI   | 92/106 (86.8) [78.8-92.6]      | 190/223 (85.3) [79.9-89.6]      | 104/115 (90.4) [83.5-95.1]         | .41             |
| CR & BG   | 48/106 (45.3) [35.6-55.3]      | 86/223 (38.6) [32.1-45.3]       | 43/115 (37.4) [28.6-46.9]          | .42             |
| CR alone  | 33/106 (31.1) [22.5-40.9]      | 59/223 (26.5) [20.8-32.8]       | 33/115 (28.7) [20.7-37.9]          | .67             |
| BG alone  | 11/106 (10.4) [5.3-17.8]       | 45/223 (20.2) [15.1-26.1]       | 28/115 (24.4) [16.8-33.2]          | <b>.02</b>      |
| CR (any)  | 81/106 (76.4) [67.2-84.1]      | 145/223 (65.0) [58.4-71.3]      | 76/115 (66.1) [56.7-74.7]          | .94             |
| BG (any)  | 59/106 (55.7) [45.7-65.3]      | 131/223 (58.7) [52.0-65.3]      | 71/115 (61.7) [52.2-70.7]          | .66             |
| 14-3-3  | 90/107 (84.1) [75.8-90.5]      | 175/226 (77.4) [71.4-82.7]      | 53/108 (49.1) [39.3-58.9]          | <b>&lt;.001</b> |
| RT-QuIC   | 59/68 (86.8) [76.4-93.8]       | 126/131 (96.2) [91.3-98.7]      | 59/67 (88.1) [77.8-94.7]           | <b>.03</b>      |
| Sensitivity defined the percentage of cases with a positive outcome on an investigation or for overall classification as probable sCJD. P values from X <sup>2</sup> test |                                |                                 |                                    |                 |
| Groups defined by quartiles: short, 1st quartile; typical, quartiles 2-3; prolonged, 4 <sup>th</sup> quartile   |                                |                                 |                                    |                 |
| Abbreviations: BG, basal ganglia. CR, cortical ribboning. EEG, electroencephalography. MRI, magnetic resonance imaging. RT-quIC, real-time quaking induced conversion.    |                                |                                 |                                    |                 |

| eTable 5. Criteria and investigation sensitivity, sCJD cases stratified by age   |                            |                          |                            |                            |                          |
|--|----------------------------|--------------------------|----------------------------|----------------------------|--------------------------|
|  | Age (years)                |                          |                            |                            |                          |
|  | <50 (n=19)                 | 50-59.9 (n=70)           | 60-69.9 (n=170)            | 70-79.9 (n=168)            | ≥80 (n=70)               |
| Sensitivity (%) [95% CI]   |                            |                          |                            |                            |                          |
| Diagnostic criteria  |                            |                          |                            |                            |                          |
| Probable sCJD  |                            |                          |                            |                            |                          |
| Any investigation  |                            |                          |                            |                            |                          |
| Revised  | 18/19 (94.7) [74.0-99.9]   | 62/69 (89.9) [80.2-95.8] | 152/164 (92.7) [87.6-96.2] | 155/164 (94.5) [89.8-97.5] | 60/68 (88.2) [78.1-94.8] |
| Prior  | 16/19 (84.2) [60.4-96.6]   | 58/69 (84.1) [73.3-91.8] | 122/164 (74.4) [67.0-80.9] | 131/164 (79.9) [72.8-85.7] | 49/68 (72.1) [59.9-82.3] |
| All investigations   |                            |                          |                            |                            |                          |
| Revised  | 11/11 (100.0) [71.5-100.0] | 29/31 (93.6) [78.6-99.2] | 74/74 (100.0) [95.1-100.0] | 74/75 (98.7) [92.8-100.0]  | 28/30 (93.3) [77.9-99.2] |
| Prior  | 9/11 (81.8) [48.2-97.7]    | 26/31 (83.9) [66.3-94.6] | 55/74 (74.3) [62.8-83.8]   | 59/75 (78.6) [67.7-87.3]   | 20/30 (66.6) [47.2-82.7] |
| Investigations   |                            |                          |                            |                            |                          |
| EEG  | 6/17 (35.3) [14.2-61.7]    | 24/62 (38.7) [26.6-51.9] | 77/156 (49.4) [41.3-56.5]  | 69/147 (46.9) [38.7-55.3]  | 30/63 (47.6) [34.9-60.6] |
| MRI (all)  | 18/19 (94.7) [74.0-99.9]   | 63/67 (94.0) [85.4-98.3] | 134/152 (88.2) [81.9-92.8] | 129/150 (86.0) [79.4-91.1] | 48/63 (76.2) [63.8-86.0] |
| CR & BG  | 8/19 (42.1) [20.3-66.5]    | 37/67 (55.2) [42.6-67.4] | 64/152 (42.1) [34.2-50.4]  | 58/150 (38.7) [30.8-47.0]  | 13/63 (20.6) [11.5-32.7] |
| CR alone   | 2/19 (10.5) [1.3-33.1]     | 9/67 (13.4) [6.3-24.0]   | 44/152 (29.0) [21.9-36.9]  | 50/150 (33.3) [25.9-41.5]  | 22/63 (34.9) [23.3-48.0] |
| BG alone   | 8/19 (42.1) [20.3-66.5]    | 17/67 (25.4) [15.5-37.5] | 26/152 (17.1) [11.5-24.1]  | 21/150 (14.0) [8.9-20.6]   | 13/63 (20.6) [11.5-32.7] |
| CR (any)   | 10/19 (52.6) [28.9-75.6]   | 46/67 (68.7) [56.2-79.4] | 108/152 (71.1) [63.2-78.1] | 108/150 (72.0) [64.1-79.1] | 35/63 (55.6) [42.5-68.1] |
| BG (any)   | 16/19 (84.2) [60.4-96.6]   | 54/67 (80.6) [69.1-89.2] | 90/152 (59.2) [51.0-67.1]  | 79/150 (52.7) [44.4-60.9]  | 26/63 (41.3) [29.0-43.4] |
| 14-3-3   | 15/19 (79.0) [54.4-94.0]   | 47/67 (70.2) [57.7-80.7] | 108/158 (68.4) [60.5-75.5] | 107/148 (72.3) [64.4-79.3] | 46/57 (80.7) [68.1-90.0] |
| RT-QuIC  | 11/13 (84.6) [54.6-98.1]   | 33/36 (91.7) [77.5-98.3] | 82/90 (91.1) [83.2-96.1]   | 90/96 (93.8) [86.9-97.7]   | 33/36 (91.7) [77.5-98.3] |
| Sensitivity defined as positive outcome/total for investigations or for criteria definition as <i>probable</i> sCJD.   |                            |                          |                            |                            |                          |
| Abbreviations. BG, basal ganglia. CR, cortical ribboning. EEG, electroencephalography. MRI, magnetic resonance imaging. RT-QuIC, real-time quaking-induced conversion. |                            |                          |                            |                            |                          |