**WEB APPENDICES**

## Appendix 1: MRI definitions used

**MRI Lesion definitions:**

- periventricular lesions: lesions in direct contact with the ventricular system (lateral or third);
- juxtacortical lesions: lesions in direct contact with the cortical gray matter with no intervening white matter;
- Infratentorial locations: brainstem and cerebellar lesions;
- cortical lesions: located within the cortical grey matter;
- corpus callosum: lesions perpendicular to the corpus callosum long axis;
- deep white matter: lesions in the supratentorial white matter which is not juxtacortical, corpus callosal or periventricular;
- large lesions: lesions in the white matter with a diameter larger than 2cm;
- deep grey nuclei lesions: thalamic and basal ganglia lesions which are located predominantly within grey matter;
- gadolinium enhancing lesion: enhancing signal on T1-weighted contrast-enhanced imaging and corresponding to a T2 lesion;
- well defined and discrete lesions: clear lesions borders with an abrupt decrease in intensity of T2-weighted signal at the borderline between lesion and surrounding brain tissue;
- black hole: hypointense lesion(at least to grey matter) on T1-weighted image and is concordant with a hyperintense lesion on a T2-weighted image;
- spinal cord: lesion within the grey or white matter of the spinal cord; subclassified as whether equal or greater than 3 segments.

**International Paediatric MS Study Group (IPMSSG) recommended McDonald 2001 criteria for dissemination in space (DIS):**

Three out of four features are satisfied:
(1) nine or more T2 white matter lesions or one gadolinium-enhanced lesion;
(2) one juxtacortical lesion;
(3) three periventricular lesions;
(4) one infratentorial lesion.

**McDonald 2010 DIS criteria are fulfilled if:**

One or moreT2 lesion is present in two out of four areas:
(1) juxtacortical;
(2) periventricular;
(3) infratentorial;
(4) spinal cord (if the patient has a brainstem or spinal cord syndrome, symptomatic lesions are excluded from the criteria and do not contribute to the count).

**McDonald 2010 dissemination in time (DIT) criteria can be fulfilled if:**

a new T2 and or gadolinium-enhanced lesion is present on follow-up MRI irrespective of the timing of a baseline MRI, or if there is simultaneous presence of gadolinium-enhanced and non-enhanced lesions at any time (including at time of first scan).

**Clinically Isolated Syndrome (CIS) Classifications:**

Type 1 CIS: clinically monofocal, at least one asymptomatic MRI lesion
Type 2 CIS: clinically multifocal, at least one asymptomatic MRI lesion
Type 3 CIS: clinically monofocal, MRI may appear normal; no asymptomatic MRI lesions
Type 4 CIS: clinically multifocal, MRI may appear normal; no asymptomatic MRI lesions
Type 5 CIS: no clinical presentation to suggest demyelinating disease, but MRI is suggestive.

## Appendix 2:

**Table showing Comparison of MRI features in Clinically Isolated Syndrome (CIS) cases with abnormal MRI scans (n=41) and Acute Disseminated Encephalomyelitis (ADEM) cases (n=40)**

| | Lesions (n) | CIS | ADEM |
|---|---|---|---|
| T2 total lesions | 1-4 lesions | 12 | 17 (43%) |
| | 5-10 lesions | 8 | 7 |
| P=0.084 | >10 lesions | 21 (51%) | 16 |
| Gadolinium enhancing lesions | 0 lesions | 12 (52%) | 13 (72%) |
| p=0.385 | 1-2 lesions | 7 | 2 |
| | >2 lesions | 4 | 3 |
| Periventricular lesions | 0 lesions | 13 | 31 (78%) |
| | 1-4 lesions | 11 | 5 |
| p<0.001 | >4 lesions | 17 (41%) | 4 |
| Juxtacortical lesions | 0 lesions | 14 | 16 (40%) |
| | 1-4 lesions | 9 | 10 |
| P=0.42 | >4 lesions | 18 (44%) | 14 |
| Deep white matter lesions | 0 lesions | 11 | 20 (40%) |
| | 1-4 lesions | 7 | 11 |
| p=0.003 | >4 lesions | 23 (56%) | 9 |
| Cerebellar lesions | 0 lesions | 27 (66%) | 23 (58%) |
| | 1-2 lesions | 10 | 15 |
| p=0.053 | >2 lesions | 4 | 2 |
| Brainstem lesions | 0 lesions | 20 (49%) | 18 (45%) |
| | 1-2 lesions | 16 | 19 |
| p=0.931 | >2 lesions | 5 | 3 |
| Corpus Callosum lesions | 0 lesions | 24 (59%) | 37 (93%) |
| | 1-2 lesions | 12 | 1 |
| p=0.001 | >2 lesions | 5 | 2 |
| Thalamic/ basal ganglia | 0 lesions | 39 | 16 |
| p<0.001 | 1-2 lesions | 1 | 18 |
| | >2 lesions | 1 | 6 |
| Black Holes p=0.008 | | 11/41(27%) | 2/40 (5%) |
| Well Demarcated (p<0.001) | | 30/41(73%) | 11/40 (28%) |
| Large lesions present (p<0.001) | | 26/41(63%) | 8/40 (20%) |
| Cortical grey lesions | 0 lesions | 39 (95%) | 26 |
| p=0.001 | ≥1 lesion | 2 | 14 (35%) |
| Spinal lesions (p=0.851) | | 13/20 (65%) | 8/12 (67%) |
| Spinal >3segments (p=0.13) | | 9/13 (69%) | 8/8 (100%) |

**Appendix 3: Table showing summary of studies investigating the incidence of first onset childhood Central Nervous System Inflammatory Demyelinating Diseases (CNS-IDs)**

| Author (Year) | Study period & sample size | Study Design and setting | Conditions Studied | Incidence of CNS-ID | Demographics | i.Surveillance unit used/ ii. Expert panel used | Sources of ascertainment | IPMSSG consensus definitions used | Additional/ other criteria or definitions used | MRI scan review & reported | Methodology considering impact of missed cases |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Absoud et al (present manuscript) | 09/2009 – 09/2010 (13 months); n=125 | Prospective, surveillance; British Isles (latitudes 50-59°N) | ADEM, ON, TM, other CIS, NMO | 9·83 per million children <16 yrs/ year | 51·2% female; median age 10·0 yrs (range: 1·3 – 15.9 yrs). M=8·9 yrs, F=11·4 yrs (p=0·046). 81 % white. 34% cases in England lived in 20% most deprived districts. | i. Two independent units used (94% & 78% card return rates)<br>ii. Yes | Paediatricians, paediatric neurologists (BPSU) and ophthalmologists (BOSU) | Yes | McDonald 2010 MRI criteria[1], Verhey criteria[2] | Yes 124/125 | Sensitivity analysis and two source capture recapture method |
| Langer-Gould et al[3] 2011 | 01/2004 – 12/2009; n= 81 | Retrospective; Southern California, USA (latitudes 33-34°N). | ADEM, ON, TM, other CIS, NMO | 15·6 per million children ≤18 yrs/ year | 56·8% female; 49% Hispanic, 19% white, 20% black; mean age= 12·6 yrs (range 0·7-18·0). | i. No<br>ii. No | electronic database searches using ICD-9 codes, Kaiser Permanente members, medical records review. | Yes | No | No | No |
| Parvone et al[4] 2010 | 1992 – 2009; n=17 | Prospective, one institution; Catania, Italy (latitudes 37-38°N), | ADEM | 11 per million children (<10 years)/ year | 41·2% female; median age= 3·1 yrs (range 1·5-8·0 yrs). | i. No<br>ii. No | One paediatric neurology department | Yes (after 2007) | No | Yes 10/17 | No |
| Toriso et al[5] 2010 | 09/1998 – 08/2003; n=30 | Retrospective multicentre; Fukuoka, Japan (latitudes 33-34°N). | ADEM, TM | 7·4 per million children <15 yrs/ year | 36·.7% female; mean age= 5.8 yrs (range 0-15.0). | i. No<br>ii. No | Five major medical centres, questionnaire based. | No | Own criteria | Yes | No |
| Banwell et al[6] 2009 | 04/ 2004 – 03/2007; n=219 | Prospective, surveillance; Canada (latitudes 42-80°N). | ADEM, ON, TM, other CIS. | 9·0 per million children <18 yrs/ year | 52·1% female; mean age= 10·5 yrs (range 0·66–18·0 years); sex ratio consistent when evaluated as a function of age. | i. One unit used (80% card return rate)<br>ii. No | Paediatricians, paediatric neurologists and paediatric ophthalmologists | No | Own criteria likely to not have changed classification as per IPMSSG | No | No |
| Pohl et al[7] 2007 | 01/ 1997 – 12/1999; n= 160 | Prospective, surveillance; Germany (latitudes 47-55°N). | ADEM (n=28), MS (n=132) | 3.7 per million children <16 yrs/ year | ADEM: 42.8% female; median age= 6.0 yrs (range 1-14 yrs).<br>Cohort: 53% female, median age 13 years. | i. One Unit used (94% card return rate)<br>ii. No | Paediatric departments in Germany | No | No | No | No |

ADEM = acute disseminated encephalomyeltis; BOSU = British Ophthalmological Surveillance Unit; BSPU= British Paediatric Surveillance Unit; CNS-ID; F= female; M= male; MRI= magnetic resonance imaging; MS= multiple sclerosis; NMO = Neuromyelitis optica; ON= optic neuritis; TM= transverse myelitis; yrs= years

**Systematic review**

We searched PubMed for articles published between 1st January 1980, and 1st December 2011. The search terms for the childhood central nervous system inflammatory demyelinating diseases (CNS-IDs) were "incidence or epidemiology" and "childhood or paediatric or pediatric or children" and "demyelination or demyelinating or acute disseminated encephalomyelitis or transverse myelitis or optic neuritis or neuromyelitis or multiple sclerosis." Only original reports reporting the incidence of any or all of the CNS-IDs were included. Review articles were not included, but their references screened for any relevant articles. For each study included, we summarised the design, incidence rates and demographic characteristics in the table in appendix 3.

**References**


1. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011; 69: 292-302.
2. Verhey LH, Branson HM, Shroff MM, et al. MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: a prospective national cohort study. *Lancet Neurol*. 2011.
3. Langer-Gould A, Zhang JL, Chung J, Yeung Y, Waubant E and Yao J. Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children. *Neurology*. 2011; 77: 1143-8.
4. Pavone P, Pettoello-Mantovano M, Le Pira A, et al. Acute disseminated encephalomyelitis: a long-term prospective study and meta-analysis. *Neuropediatrics*. 2010; 41: 246-55.
5. Torisu H, Kira R, Ishizaki Y, et al. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. *Brain Dev*. 2010; 32: 454-62.
6. Banwell B, Kennedy J, Sadovnick D, et al. Incidence of acquired demyelination of the CNS in Canadian children. *Neurology*. 2009; 72: 232-9.
7. Pohl D, Hennemuth I, von Kries R and Hanefeld F. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. *Eur J Pediatr*. 2007; 166: 405-12.