P029

The story of aggressive multiple sclerosis

F. Fneish[1*], K. Berger[2], P. Flachenecker[3], T. Friede[4], J. Haas[5], K. Hellwig[6], C. Kleinschnitz[7], F. Paul[8], D. Pöhlau[9], O. Rienhoff[10], P.S. Rommer[11], C. Warnke[12], A. Stahmann[1], U.K. Zettl[11], D. Ellenberger[1]

for the German Multiple Sclerosis Register of the German National MS Society

1: MS-Forschungs- und Projektentwicklungs-gGmbH, Hannover
2: Westfälische Wilhelms-Universität Münster, Institut für Epidemiologie und Sozialmedizin, Münster
3: Neurologisches Rehabilitationszentrum Quellenhof, Bad Wildbad
4: Universitätsmedizin Göttingen, Institut für Medizinische Statistik, Göttingen
5: Jüdisches Krankenhaus Berlin, MS-Zentrum, Berlin
6: St. Josef-Hospital - Katholisches Klinikum Bochum, Klinik für Neurologie, Bochum
7: Universitätsklinikum Essen, Essen
8: Charité – Universitätsmedizin Berlin, Berlin
9: DRK Kamillus Klinik, Asbach
10: Universitätsmedizin Göttingen, Institut für Medizinische Informatik, Göttingen
11: Universitätsmedizin Rostock, Rostock
12: Universitätsklinikum Köln, Köln

Background

Several studies have defined severe courses of MS, characterising those as ‘aggressive’ (agMS), also ‘malignant’, or ‘highly active’. The absence of standard criteria hinders the prompt and adequate treatment initiation of such patients. Recently it has been reported that the available definitions are limited, and their criteria fail to identify relevant subgroups. Moreover, limited knowledge about a reliable prediction of a highly active disease exists, whereas those patients may have specific needs in the management of the disease.

Objectives:

1. Identify and confirm the prevalence of agMS in Germany by implementing available definitions from the literature.
2. Extension of the existing criteria to allow better prediction of long-term disease outcomes.

Methods:

1. A total of 25,963 patients from the German MS register were included. Various available definitions of agMS patients were compared (see Figure 1).
2. Definitions are often based on composite criteria, of which (at least) one must be fulfilled. Those include EDSS progression, relapse history, MRI results, and type of diseased-modifying drugs (DMD) administered.
3. Early retirement was used as a competing additional criterium for agMS. We defined a subgroup of PwMS with early retirement due to MS within 5 years after disease onset and age less than 60 years.
4. Descriptive analyses were performed to compare agMS patient cohorts similarities and differences.

Results:

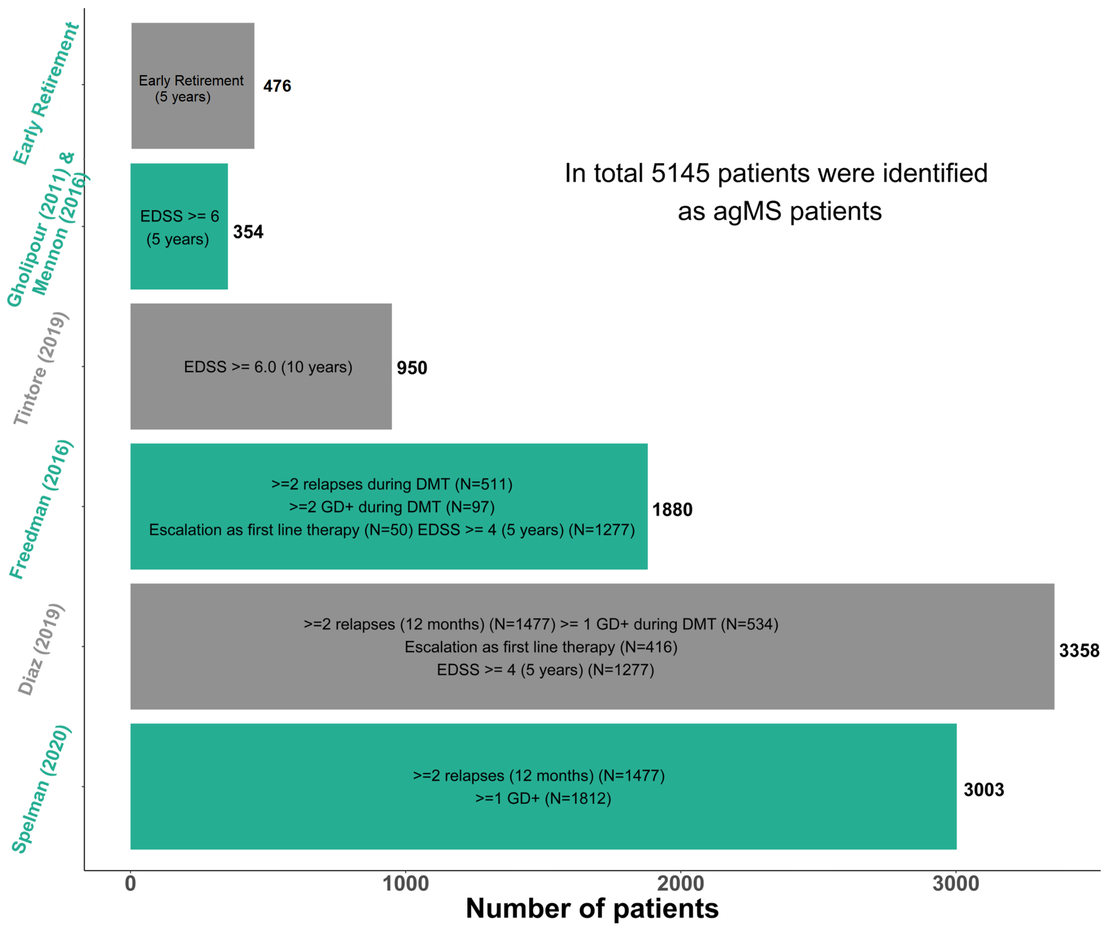

Figure 1: Definitions and patient counts by the different agMS criteria.

Criteria applied to German MS register data						
Mean (SD) / %	**Spelman (2020)**	**Diaz (2019)**	**Freedman (2016)**	**Tintore (2019)**	**Gholipour (2011) (& Menon 2016)**	**Criterium: Retirement (5 years)**
Age onset	31 (±10.3)	34.7 (±12.0)	38.1 (±12.3)	42.6 (±11.8)	44.2 (±11.8)	40.9 (±9.7)
Females (%)	73.0%	69.8%	66.7%	61.2%	62.2%	67.9%
Time to diagnosis (y)	1.86 (±3.82)	1.34 (±2.96)	1.14 (±2.44)	1.01 (±1.57)	0.67 (±0.94)	0.53 (±0.86)
Relapsing onset (%)	96%	91%	86%	74%	73%	87%
Progressive onset (%)	1.7%	7.7%	12.5%	24.4%	24.6%	10.9%
Disease Duration (y)	10.95 (±9.29)	9.16 (±8.13)	8.37 (±7.56)	8.01 (±4.03)	5.03 (±3.32)	5.52 (±3.36)
DMT (%)	77.7%	80.9%	78.7%	67.5%	66.7%	79.8%

Table 1: Characteristics of agMS patients within the population of the GMSR, stratified by criteria.

The definitions showed a high variation in progressive onset patients ranging from 1.7% to 24.6%.

The detailed classification of patients is shown in the Venn diagram (Figure 2).
The proposed new criteria of early retirement within 5 years after onset identified 476 patients. Interestingly, 185 possible agMS patients were uniquely identified by this criterion.

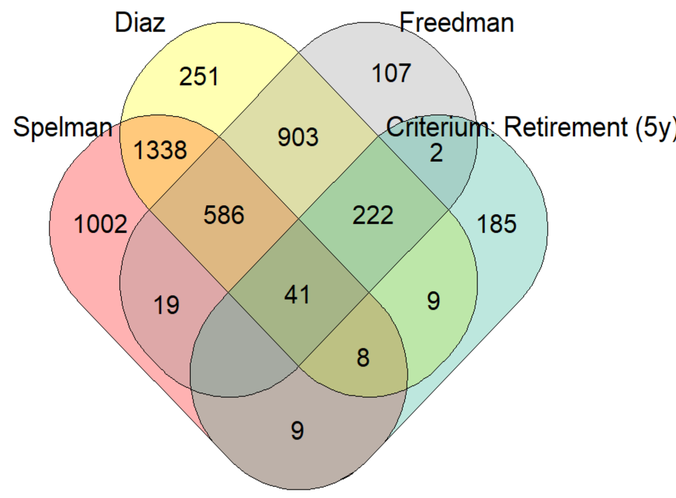

Figure 2: Overlap in patient groups defined by Spelman *et al.*, Diaz *et al.*, Freedman *et al.*, and the early retirement criteria.

Conclusion:

1. Our study shows that a single definition is so far neither rigid nor accurate enough to identify agMS. It might not be enough to focus on EDSS, relapses, and lesion counts alone.
2. Other known risk factors such as early retirement, impaired cognition, bladder problems, or brainstem function might be of importance to better predict the clinical course, besides advances in brain imaging.
3. Further investigations are needed to define and detect agMS. A scoring system including various of the above-mentioned parameters might be of help in clinical practice to predict agMS as early as possible and to allow evidence-based treatment decisions in the future.

References:

1. Spelman et al. 2020. Patients with high disease activity relapsing remitting multiple sclerosis in real world clinical practice: A population-based study in Sweden. Clinical Therapeutics. DOI:10.1016/j.clinthera.2019.11.018
2. Menon et al. 2016. Disability progression in aggressive multiple sclerosis. Multiple Sclerosis Journal. DOI: 10.1177/ 1352458516653273
3. Gholipour et al. 2011. Demographic and clinical characteristics of malignant multiple sclerosis. Neurology. DOI: 10.1212/WNL.0b013e31821e559d
4. Freedman & Rush 2016. Severe, highly active, or aggressive multiple sclerosis. CONTINUUM: Lifelong Learning in Neurology. DOI: 10.1212/CON.0000000000000331
5. Diaz et al. 2019. Highly active multiple sclerosis: An update. MSRD 2019. DOI: 10.1016/j.msard.2019.01.039
6. Tintore et al. 2019. The long-term outcomes of CIS patients in the Barcelona inception cohort: Looking back to recognize aggressive MS. Multiple Sclerosis. DOI: 10.1177/1352458519877810

Disclosure – Declaration of Interest

FF, JH, OR, DE nothing to disclose. KB received a grant from the German Ministry of Education and Research (within the German Competence Net Multiple Sclerosis) plus additional funds from Biogen, all to the University of Muenster for an investigator initiated adverse events register for patients with multiple sclerosis. None resulted in a conflict of interest. PF has received speaker’s fees and honoraria for advisory boards from Almirall, Bayer, Biogen Idec, Celgene, Genzyme, Novartis, Merck-Serono, Roche and Teva. He has participated in pharmaceutical company sponsored trials by Roche. None resulted in a conflict of interest. TF has received personal fees for consultancies from Bayer, BiosenseWebster, Boehringer Ingelheim, Cardialysis, CSL Behring, DaiichiSankyo, Enanta, Feldmann Patent Attorneys, Fresenius Kabi, Galapagos, IQVIA, Janssen, Mediconomics, Novartis, Penumbra, Roche, SGS, Vifor. None resulted in a conflict of interest. KH has received speaking fees, travel support, and research honoraria from Biogen, Teva, Sanofi-Genzyme, Novartis, Bayer Healthcare, Merck Serono, and Roche. None resulted in a conflict of interest. CK has received institutional support from Alexion, Almirall, Amgen, Amicus, Bayer, Biogen, Biotronik, Boehringer Ingelheim, Bristol Myers-Squibb, Celgene, CSL Behring, Daiichi Sankyo, Desitin, Eisai, Ever Pharma, GE Healthcare, MedDay Pharmaceuticals, Merck Serono, Mylan, Novartis, Pfizer, Roche, Sanofi-Genzyme, Siemens, Stago, Teva. None resulted in a conflict of interest. FP has received speaking fees, travel support, honoraria from advisory boards, and/or financial support for research activities from Bayer, Novartis, Biogen, Teva, SanofiAventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, Shire, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis of the USA. He serves as academic editor for PLoS ONE and associate editor for Neurology, Neuroimmunology and Neuroinflammation. None resulted in a conflict of interest. DP received research grants from Sandoz, Schering, Biogen; speaker fees from Almirall, Bayer, Biogen, Merck, Novartis, Roche, Sanofi Genzyme and Teva. None resulted in a conflict of interest. PSR has received speaking fees, honoraria from advisory boards, and/or financial support for research activities from AbbVie, Amicus, Biogen, Daiichi-Sankyo, Merck Serono, Novartis, Roche, Sandoz, Sanofi Genzyme, and Teva. None resulted in a conflict of interest. CW has received institutional support from Novartis, Alexion, Sanofi-Genzyme, Biogen, and Roche. None resulted in a conflict of interest. AS has no personal pecuniary interests to disclose, other than being the lead of the German MS Registry, which receives funding from a range of public and corporate sponsors, recently including The German Innovation Fund (G-BA), The German MS Trust, The German MS Society, Biogen, Celgene (BMS), Merck and Novartis. None resulted in a conflict of interest. UKZ has received speaking fees, travel support and/or financial support for research activities from Alexion, Almirall, Bayer, Biogen, Merck, Novartis, Roche, Sanofi Genzyme, Teva as well as EU, BMBF, BMWi and DFG. None resulted in a conflict of interest.