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DR. MARIA STEENHOF (Orcid ID: 0000-0001-6202-9595)

Article type: Original Article

Distribution of disease courses in familial versus sporadic multiple sclerosis

Short title: Course distribution in familial multiple sclerosis

Maria Steenhof¹,²,³,⁶ Nete Munk Nielsen⁵, Egon Stenager³,⁴,⁷, Kirsten Kyvik²,⁶, Sören Möller²,⁶, Jens Michael Hertz¹,²

¹Department of Clinical Genetics, Odense University Hospital, Denmark, 2. Department of Clinical Research, University of Southern Denmark, 3. Neurological Research Unit, Hospital of Southern Jutland, Denmark, 4. Department of Regional Health Research, University of Southern Denmark, 5. Department of Epidemiology Research, Statens Serum Institut, Copenhagen 6. Odense Patient Data Explorative Network, Odense University Hospital, Denmark 7. MS clinics of Southern Jutland (Sønderborg, Esbjerg, Kolding), Hospital of Southern Jutland, Sønderborg, Denmark.

Abstract

Objectives: The overall distribution of disease courses in multiple sclerosis (MS) is well established, but little is known about the distribution among familial MS cases. We examine the frequency of the different MS courses among familial and sporadic MS cases and determine whether MS cases within the same family had the same age at diagnosis and have experienced the same disease course.

Materials and methods: This is a nationwide register study, based on data from the Danish MS Registry, the Danish Civil Registration System and the Danish National Patient Registry. The main variables are MS diagnosis, MS course and 1st degree relatives with MS. The

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statistical analyses were carried out using logistic regression analysis, Kappa coefficient and intraclass correlations coefficient.

Results: In total 7,402 MS cases where included in the study, of which 531 have an affected first-degree relatives, and 6,871 are sporadic. We found that relapsing remitting MS including secondary progressive MS was more common among familial MS cases than among sporadic MS cases (Odds ratio=1.64, 95% CI: 1.20-2.24, p=0.002).

We subsequently analysed data on 133 MS families and found that MS courses correlate between the first and the second MS case diagnosed, while age at diagnosis does not.

Conclusion: Familial MS cases are more likely to have relapsing remitting MS than a progressive course compared to sporadic MS cases. Secondly, we find that within MS families, first-degree relatives are likely to have the same MS course, but we do not find that they are diagnosed at the same age.

Keywords: familial MS, multiple sclerosis, MS courses, progressive MS, relapse-remitting MS,

Corresponding author

Maria Steenhof, MD, Department of Clinical Genetics, Odense University Hospital, Odense, Denmark, Department of Neurology, Hospital of Southern Jutland, Sønderborg, Denmark, Department of Clinical Research, University of Southern Denmark, Denmark

Odense Patient data Explorative Network, Odense University Hospital, Denmark

E-mail: maria.steenhof@rsyd.dk Telephone: +45 6541 3550

Introduction

Multiple sclerosis (MS) is one of the most common neurological disorders diagnosed among young adults. The diagnosis is based on international diagnostic criteria, and MS patients are categorised into one of three courses: relapsing remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS).

RRMS patients account for approximately 80% of all cases and they usually have disease onset between 20 and 40 years of age. Within the first 10 years of onset of disease around half of the RRMS cases will enter a SPMS course, which means they will experience a progressive loss of...
function over time without relapses. The third group are PPMS patients. They have a progressive course with gradual loss of function from disease onset. They are typically diagnosed among patients aging 40+ and represent 10-20% of all cases.

MS aetiology is in general unknown, but based on genetic studies it is established that a genetic component is included. Based on twin studies concordance rate for monozygotic twins is reported to be 25-30% as compared to 3-5% for dizygotic twins. This is further supported by the fact that familial MS account for 12.5% of all MS cases. The highest appearance of familial cases in a MS cohort is reported to be nearly 20%, but in these studies familial are defined as 1st to 3rd degree relatives with MS. The general population has an approximate risk of MS of 0.2%. First degree relatives have an approximate risk on 3-5%, and 15-25 times higher relative risk of MS compared to the background population. Several genetic MS studies have been conducted, among them genome-wide association studies (GWAS). GWAS have found an association between MS and more than 200 genes, single nucleotid polymorphisms (SNP) and loci, but each variant only accounts for a small part of the genetic aetiology leaving many questions unanswered.

MS courses distribution is well established and it is also generally accepted that genes are involved in the aetiology contributing to a subpopulation of familial MS patients. But little is known on distribution of courses among familial MS cases.

The objectives of this study are to analyze the distribution of courses in familial versus sporadic MS and to analyze the course distribution and age of diagnosis within MS families. Differences in these clinical characteristics can contribute to differentiate familial cases from the total population.

**Material:**

This is a nationwide register study based on data from the Danish Multiple Sclerosis Registry, the Danish Civil Registration System and the Danish National Patient Registry.

*The Danish Civil Registration System* was established in 1968 (Greenland 1972) and is the basis for all individualized public registration in Denmark. All Danish residents born after or alive April 1st 1968 are assigned with a unique identification number. This makes it possible to link individual information from different Danish registries. Variables used from the registry are gender, date and place of birth and familial information on first-degree relatives.
Information on parent/child relations are found to be nearly complete for all individuals born in Denmark since 1960, but the relation is based on a legal relationship, meaning that biological and adoptive cases cannot be differentiated \(^{23}\).

*The Danish Multiple Sclerosis Registry* is established in 1956 and holds data on all Danes diagnosed with MS who were alive in 1949 and on all Danes diagnosed with MS since then. The patients in the registry fulfil the diagnostic criteria of Poser and/or MacDonald\(^{21,22}\). Since 1994 the registry has also collected clinical information on relapses, progression and remission. The register receives data from all the departments of neurology at Danish hospitals, from private Danish neurologists and from MS hospitals in Denmark\(^{22}\). It is updated regularly based on information from the neurologist, who reports to the registry in relation to consultation with the MS patients. The registry is found to be more than 90% complete\(^{21}\). We received data from the registry in September 2016 and included the following variables: MS diagnosis, year of MS diagnosis, validity of diagnosis and clinical information on relapses, remission and progression making it possible to establish MS courses.

*The Danish National Patient Registry* is a nationwide registry which since 1977 has registered information on all diagnoses, including the MS diagnoses and in some cases MS courses, from hospitalization in the Danish hospitals. Since 1995 it has also been possible to retrieve information on diagnoses in relation to outpatient contacts\(^{24}\). From this registry we have used information on MS diagnoses.

Using the unique identification numbers as linkage\(^{23}\) we combined information from the three registries allowing us to generate a nationwide cohort of Danish MS patients including the following variables: Year of birth, gender, place of birth, year of MS diagnosis, certainty of the MS diagnosis, information on first degree relatives and clinical information on relapses, progression and remission.

From these variables we defined the MS courses as well as familial status.

MS courses: Cases registered as having relapses and remission but without progression are categorized as RRMS, cases with relapses, remission, and progression as SPMS and finally MS cases with progression, but without relapses and remission, are categorized as PPMS. Since clinical information is regularly updated in the MS registry, we expect that the information concerning MS courses is updated at the time we received the data.
Familial MS are defined as MS cases having one or more first-degree relatives with MS, whereas sporadic MS cases don’t have first-degree relative with MS. Due to the risk of having adoptive relations in the familial group, we have excluded families if a child/sibling in a MS family is born outside Denmark.

Methods:

From The Danish MS Registry we have information on 25,471 Danish MS patients (including Greenland). From this population the MS cohort and secondly the MS family cohort were defined. The MS cohort includes sporadic and familial MS cases. In some of the families only one family member remain in the MS cohort due to other inclusion and exclusions criteria. The MS family cohort includes MS families with at least two family members from each family.

MS cohort: Inclusion criteria: a definite MS diagnosis and diagnosed between 1994 and 2014. Clinical information used to determine MS courses has not been included regularly in the MS registry until after 1994, we therefore have a restricted time period.

Exclusion criteria: possible adoptive relations and missing information on MS courses.

We excluded 4,753 cases because they did not have a definite MS diagnosis or were possible adoptive cases. Another 10,049 cases were excluded since they were not diagnosed from 1994-2014 and 3,267 cases were excluded because they were lacking information on MS courses. After having excluded cases due to the criteria’s listed, there are now MS families represented by at least one of the MS cases. In total we ended up with a cohort of 7,402 MS cases (figure 1).

MS family cohort: Analysing the distribution of MS courses and age at diagnosis within families, we selected a group of familial cases from the MS cohort study. We now only included familial MS cases, meaning that sporadic cases were excluded (6,871 cases). We have further excluded familial cases, if just one case from a family is included in the MS cohort. At least two cases from each family are required to be able to analyze course distribution within families; 261 MS cases were excluded due to this criterion. We ended up with 133 MS families, 129 of them including 2 first-degree relatives and 4 families including 3 first-degree relatives (figure 1).

We define the proband as the first case in a family diagnosed with MS. The numbering of family members is based on time for diagnosis.
The Regional Committees in Health Research for Southern Denmark (S-20150175) and the Danish Data Protection Agency (j.nr: 15/52395) have approved the study. This is in accordance with national rules and regulations on registry studies and does not require accept from the patients.

Statistics:

In the MS cohort we have analyzed the distribution of MS courses in familial MS versus sporadic MS. We have used logistic regression with MS courses as the independent variable and familial indicator variable as the dependent variable. Covariates included in the analysis were: gender, age, and age at diagnosis. Since SPMS cases have progressed from RRMS, these two groups are likely to overlap. We therefore analyzed MS courses divided into PPMS, RRMS and SPMS, but also RRMS+SPMS as one group compared to PPMS.

In the MS family cohort we analyzed the distribution of MS courses and age at diagnosis within families. We analyzed courses within each family using Kappa coefficient. Values =<0.60 is inadequate, 0.61–0.80 is substantial, and 0.81–1.00 is almost perfect agreement. Age at diagnoses within families was analyzed using intraclss correlation coefficient (ICC). Values less than 0.5 are indicative of poor reliability and values greater than 0.90 indicate excellent reliability. For the families with 3 first-degree relatives we used kappa coefficient for courses, and ICC with bootstrapped standard error for age at diagnosis.

Concordance rate is calculated using the formula: number of first degree relations with the same MS courses divided by the total number of first-degree relations.

Results

MS cohort study: In total 7,402 MS cases were included in the study. Demographic information is shown in table 1. We found a significant difference in age at diagnosis, year of birth and MS courses in the two groups, but no differences in the distribution of sex (table 1a). We compared demographic data on included cases and cases excluded due to missing information on MS courses, and we did not find significant differences between the two groups (table 1b).

In the logistic regression analysis, we found a 1.64 odds ratio (OR) (95% CI: 1.20-2.24, p=0.002) for having RRMS+SPMS in the familial group compared to the sporadic MS group (table 2). We included gender, age and age at diagnosis, in the logistic regression analyses and in the fully adjusted model the OR was lowered to 1.43 (95% CI: 1.01-2.02). Moreover, we repeated the analysis for the three MS courses separately (table 2).
MS family study: The analysis is based on 133 MS families (first-degree relatives), in total 270 individuals. One-hundred-twenty-nine families consist of two first-degree relatives, and 4 families include 3 first-degree relatives. The familial relation is mother/child in 44 cases (including one family with three MS cases), father/child in 23 cases and siblings in 66 cases (including 3 families with 3 MS cases). The group of siblings include two twin pairs with unknown zygosity. The MS course distribution of the 1st and 2nd family-member respectively, is listed in table 3. The numbers are based on the first two cases diagnosed in each family, excluding the third family members. Since SPMS cases progress from RRMS, we have analyzed course distribution separately but also with RRMS+SPMS combined as a group. Combining SPMS+RRMS, we find that the 1st and the 2nd family-member have the same MS course in 118 (in table3) out of the 133 families. Based on these numbers we calculate the concordance rate and find it to be 0.89 (118/ 133= 0.89). Meaning that in 89% of the families the 1st and 2nd family-member have the same course, the majority of these are RRMS+SPMS cases. We have further calculated the kappa coefficient and found a high level of agreement (88.7%), but a low kappa coefficient 0.059 (table 4).

For age at diagnosis within families, we calculated ICC and found ICC= 0.008 (95% CI: -0.16-0.18) in families with two first-degree relatives (n=129) and for concordant pairs of first-degree relative (n=118) ICC were -0.031 (95% CI: -0.21-0.15). To examine the families with three first-degree relatives, ICC bootstrap with standard error were used, this did not affect the results significantly. We find a low ICC value, which is interpreted as no relationship on age at diagnosis between the 1st and 2nd MS family member. The result was consistent regardless of whether we analyzed the total 133 MS relations or only the 118 relations who had concordant MS courses (figure 2).

Discussion:

Overall, we have found that familial MS has a higher risk of having a relapsing course than progressive compared to sporadic cases. Analyzing only the familial MS cases, we further found in 89% of the families the 1st and 2nd family-member have the same MS course.

MS cohort study: We found a 1.64 time higher risk of having RRMS+SPMS in the familial MS group compared to the sporadic group. The results are slightly influenced when covariates are included in the analysis. Since age at diagnosis differs according to MS courses, PPMS cases being diagnosed at a later age than RRMS, we do expect to see a difference in age. Hence, interpretation of the results with adjustment for age at diagnosis should be taken with caution.

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We have not found previous studies analyzing the exact same issues, but the literature includes a study looking into genetic differences between the different MS courses. Sorosina et al calculated the weighted genetic risk score in a MS cohort and found that a higher weighted genetic risk score was associated with earlier age at onset in RRMS. This would support that genetic factors are important in the RRMS, which in turn reinforces our findings of a higher OR for RRMS in familial cases compared to sporadic one. Robertson et al calculated recurrence rates based on 674 probands and their relatives from MS families. They found that the relative risk of MS is reduced with genetic distance from the proband, which supports that a close genetic relation equals a higher relative risk of MS compared to more distant relatives.

The mentioned studies differ from our study in several aspects and since they are not raising the same questions, comparisons of results are not feasible.

The majority of studies within this area are analyzed based on a general MS population and not a distinct familial cohort. If familial information is included, they often have different definitions of familial MS, low numbers of familial cases, different methodological approaches and most lack information on courses.

**MS family study:** We analyzed 270 MS cases from 133 MS families and found a high concordance rate for MS courses within MS families. In the Kappa analysis we found a high agreement, but a low kappa coefficient, which is expected due to the low number of PPMS cases. We overall found a high concordance rate but with low statistical agreement. Secondly, we found a weak correlation for age at diagnosis between the 1st and 2nd MS family-members. Our findings are in line with some of the previous studies, and adds information to the speculations on whether genetic aetiology could differentiate depending on the MS course.

The study that is methodologically closest to ours is Heinsiek et al, since they included first-degree relatives from 1083 MS families and report that clinical MS courses are similar between MS siblings. Robertson et al, Chataway et al and Oturai et al all support that conclusion, since they found significant concordance for MS courses in MS sibling pairs.

Brassat et al also studied MS sibling pairs, but found no correlation for MS courses between siblings with MS, the study is of smaller scale, and based on non-nationwide registry data.

Brassat et al and Robertson et al further examined whether there were concordance for age at diagnosis in MS relatives, which neither of them found. The same was analyzed by Oturai et al, who found significant concordance of age of disease onset in coaffected sib pairs. Overall the results on this subject are divergent, which could be due to methodological differences. The main differences are
the definition of familial MS (first-degree relatives or sibling-pairs), the selection methods and the final number of cases. Especially the numbers of familial PPMS cases tend to be low, influencing the strength of the studies. These differences could explain why the results differ and they also highlight why comparison and making final conclusions are difficult.

**Strength’s and limitations:**

We used nation-wide registers to identify our study cohort and classified MS courses according to information from registries. We have a different approach compared to most former familial studies on MS since we focused on MS courses and familial cases. In general these elements are adding strengths to our study, but there are also limitations. One being, that information is missing on MS course for a proportion of cases. Comparison of demographic data on included and excluded cases, show no significant differences, excluded cases are randomly distributed between familial and sporadic MS cases.

Adoptive and biological relations can’t be differentiated based on Danish registry data. If we compare the total annual number of adoptions to the number of newborns, we find that potential adoptive cases will only represent a very limited number. We have further tried to minimize the risk of including adoptive cases, since we excluded familial cases in which children/siblings were born outside Denmark. Finally, we have not included 2nd or 3rd degree relatives in the study. This means that families with distant relatives with MS are assigned to the sporadic group. This could explain why we find a lower percentage of familial cases compared to previous studies.

**Conclusion:**

We found that familial MS cases (first degree relatives) have a significantly higher risk of having RRMS compared to sporadic MS cases. Secondly, we found a weak concordance for MS courses in MS relatives, but we did not find that age at diagnosis correlate between first-degree relatives with MS. Familial MS cases more frequently had RRMS+SPMS courses compared to sporadic MS cases. Further studies on differences between familial and sporadic MS cases are warranted before making final conclusions.
Future directions:
A limited number of studies have analyzed differences between familial and sporadic MS cases. We find that there are differences supporting that some of the answers to MS genetics are likely to be found among familial MS cases, thus further studies with this approach are warranted.

Disclosure
The authors declare no conflicts of interest.

Acknowledgement and funding
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19. Canto E, Oksenberg JR. Multiple sclerosis genetics. (1477-0970 (Electronic)).

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Table 1a: Description of the study cohort according to familial MS status, N=7402

<table>
<thead>
<tr>
<th></th>
<th>MS cases</th>
<th></th>
<th>Test for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Familial (n)</td>
<td>Sporadic (n)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>531</td>
<td>6871</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>170 (32%)</td>
<td>2199 (32%)</td>
<td>Pearson's chi² test</td>
</tr>
<tr>
<td>Female</td>
<td>361 (68%)</td>
<td>4672 (68%)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>62</td>
<td>624</td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td>74</td>
<td>806</td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td>79</td>
<td>935</td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td>92</td>
<td>1,064</td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td>68</td>
<td>1,012</td>
<td>T-test</td>
</tr>
<tr>
<td>&gt;45</td>
<td>156</td>
<td>2,410</td>
<td>P=0.0002</td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1950</td>
<td>55</td>
<td>903</td>
<td></td>
</tr>
<tr>
<td>1950-1969</td>
<td>265</td>
<td>3,578</td>
<td>T-test</td>
</tr>
<tr>
<td>≥1970</td>
<td>211</td>
<td>2,390</td>
<td>P=0.0002</td>
</tr>
<tr>
<td>MS course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRMS</td>
<td>363 (68.4%)</td>
<td>4,505 (65.5%)</td>
<td>Pearson's chi² test</td>
</tr>
<tr>
<td>SPMS</td>
<td>123 (23.2%)</td>
<td>1,462 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>PPMS</td>
<td>45 (8.5%)</td>
<td>904 (13.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1b: Test for differences between in- and excluded case due to missing information on MS courses, N=10,669

<table>
<thead>
<tr>
<th></th>
<th>MS cases</th>
<th></th>
<th>Test for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Included (n)</td>
<td>Excluded (n)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7,402</td>
<td>3,267</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2,369 (32%)</td>
<td>1,071 (33%)</td>
<td>Pearson's chi² test</td>
</tr>
<tr>
<td>Female</td>
<td>5,033 (68%)</td>
<td>2,196 (67%)</td>
<td></td>
</tr>
<tr>
<td>Family information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial</td>
<td>531 (7.2%)</td>
<td>214 (6.6%)</td>
<td>Pearson's chi² test</td>
</tr>
<tr>
<td>Sporadic</td>
<td>6,871 (92.8%)</td>
<td>3,053 (93.5%)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (years)</td>
<td>39.8</td>
<td>40.3</td>
<td>T-test</td>
</tr>
<tr>
<td>95% CI</td>
<td>39.56-40.09</td>
<td>39.86-40.60</td>
<td></td>
</tr>
</tbody>
</table>

* RRMS / SPMS / PPMS
** RRMS + SPMS / PPMS

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| Table 2: OR for types of MS among familiar versus sporadic MS cases. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | Familial (%)    | Sporadic (%)    | OR (95% CI, p-value) | OR (95% CI, p-value)* | OR (95% CI, p-value)** | OR (95% CI, p-value)*** |
| **MS courses**                  |                 |                 |                  |                  |                  |                  |
| RR/MS/SPMS                     | 485            | 5967            | 1.64 (1.20-2.24, p=0.002) | 1.41 (1.01-1.99, p=0.047) | 1.45 (1.04-2.06, p=0.031) | 1.43 (1.03-2.02, p=0.044) |
| PPMS                            | 45             | 904             | 1                 | 1                 | 1                 | 1                 |
| SPMS                            | 123            | 1,462           | 1.69 (1.29-2.24, p=0.003) | 1.54 (1.08-2.23, p=0.038) | 1.52 (1.06-2.18, p=0.022) | 1.55 (1.07-2.24, p=0.020) |
| PPMS                            | 45             | 904             | 1                 | 1                 | 1                 | 1                 |
| **MS courses**                  |                 |                 |                  |                  |                  |                  |
| RR/MS/SPMS                     | 485            | 5967            | 1.64 (1.20-2.24, p=0.002) | 1.41 (1.01-1.99, p=0.047) | 1.45 (1.04-2.06, p=0.031) | 1.43 (1.03-2.02, p=0.044) |
| PPMS                            | 45             | 904             | 1                 | 1                 | 1                 | 1                 |
| **logistic regression including the covariates: sex and age.** |
| **logistic regression including the covariates: age at diagnosis and sex.** |
| **logistic regression including the covariates: age at diagnosis, sex, and age.** |

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<table>
<thead>
<tr>
<th>2nd family member</th>
<th>1st family member</th>
<th>PPMS</th>
<th>RRMS</th>
<th>SPMS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPMS</td>
<td></td>
<td>1* (14%)</td>
<td>4 (57%)</td>
<td>2 (29%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>RRMS</td>
<td></td>
<td>8 (9%)</td>
<td>71* (79%)</td>
<td>11* (12%)</td>
<td>90 (100%)</td>
</tr>
<tr>
<td>SPMS</td>
<td></td>
<td>1 (3%)</td>
<td>32* (89%)</td>
<td>3* (8%)</td>
<td>36 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>10 (8%)</td>
<td>107 (80%)</td>
<td>16 (12%)</td>
<td>133 (100%)</td>
</tr>
</tbody>
</table>

The table shows the distribution of MS courses within MS families for PPMS, RRMS and SPMS as separate groups.

* Concordant pairs if RRMS + SPMS are grouped together. In total 110 MS relatives.

PPMS: primary progressive multiple sclerosis, RRMS: relapse-remitting multiple sclerosis
<table>
<thead>
<tr>
<th>Agreement</th>
<th>Expected Agreement</th>
<th>Kappa</th>
<th>Standard Error</th>
<th>P-value</th>
<th>MS courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>88.72%</td>
<td>88.01%</td>
<td>0.0594</td>
<td>0.6852</td>
<td>0.2427</td>
<td>RRMS+SPMS / PPMS*</td>
</tr>
<tr>
<td>56.39%</td>
<td>58.09%</td>
<td>-0.0406</td>
<td>0.0650</td>
<td>0.7338</td>
<td>RRMS / SPMS / PPMS**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Observed Kappa Coefficient</th>
<th>Bias</th>
<th>Bootstrapped</th>
<th>95% CI</th>
<th>MS course</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.051</td>
<td>-0.007</td>
<td>0.114</td>
<td>-0.17-0.27</td>
<td>RRMS+SPMS / PPMS*</td>
</tr>
<tr>
<td>-0.064</td>
<td>-0.003</td>
<td>0.0661</td>
<td>-0.18-0.08</td>
<td>RRMS / SPMS / PPMS**</td>
</tr>
</tbody>
</table>

The analysis is calculated for PPMS compared to RRMS+SPMS* as one group and with RRMS, SPMS and PPMS* as separate groups.
We find a high agreement, but a low Kappa coefficient, which is believed to be due to the lower number of, especially PPMS, cases.

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Figure 2: The graph shows the intrafamilial relation between age at MS diagnosis in MS families. Families with concordant and discordant MS courses are shown.