HLA-DRB1*15 association with multiple sclerosis is confirmed in a multigenerational Italian family

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† The Author passed away a few weeks before the final acceptance of this work. The co-Authors on her team were honored to collaborate with Dr. Penco, and recall her scientific expertise in genetic counseling, her clarity of mind, and her always positive and smiling attitude. Thank you Silvana.

Summary

Environmental and genetic factors seem to play a pathogenetic role in multiple sclerosis (MS). The genetic component is partly suggested by familial aggregation of cases; however, MS families with affected subjects over different generations have rarely been described.

The aim of this study was to report clinical and genetic features of a multigenerational MS family and to perform a review of the literature on this topic. We describe a multigenerational Italian family with six individuals affected by MS, showing different clinical and neuroradiological findings. HLA-DRB1* typing revealed the presence of the DRB1*15:01 allele in all the MS cases and in 4/5 non-affected subjects. Reports on six multigenerational MS families have previously been published, giving similar results. The HLA-DRB1*15:01 allele was confirmed to be linked to MS disease in this family; moreover, its presence in non-affected subjects suggests the involvement of other susceptibility factors in the development and expression of the disease, in accordance with the complex disease model now attributed to MS.

KEY WORDS: familial, human leukocyte antigen, multigenerational, multiple sclerosis, review

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS) (Compston and Coles, 2008). The heterogeneity of MS is well known, and this is seen in the clinical presentation, disease course, disease activity and disability progression (Lublin and Reingold, 1996; Lublin et al., 2014). The worldwide prevalence of MS is estimated to be 2.5 million cases, varying with latitude, with a lower prevalence found nearer the equator. MS is more common in women than in men, with a female-to-male ratio of 2.3 (Kamm et al., 2014).

The etiology of the disease is unknown and both environmental and genetic factors seem to play a key role in its development. Various environmental factors have been identified, to date season of birth, vitamin D levels, latitude, exposure to the Epstein-Barr virus, vascular comorbidities, smoking (Kamm et al., 2014; Files et al., 2015) and dietary salt intake (Hucke et al., 2015). Interestingly, studies performed on immigrant populations showed that people who migrated before adolescence acquire the risk profile of their new country, whereas those who migrated after adolescence retain that of their country of origin (Kamm et al., 2014).

Various evidence suggests the involvement of a genetic component. MS frequency differs between ethnicities (the highest incidence being found in individuals of northern European origin compared with African and Asian groups), regardless of geographic location (Haines et al., 1998; Stüve et Oksenberg, 2006). Familial aggregation occurs in MS and the estimated overall recurrence rate is 20–22.8% (Ebers et al., 2000; Kamm
The risk changes from 2.77% in first-degree relatives to 1.02% in second-degree relatives and 0.88% in third-degree relatives, compared with 0.3% in the general population (Robertson et al., 1996). Twin studies indicate about 50% concordance for monozygotic twins compared with about 3-5% for dizygotic twins (Haines et al., 1998; Kamm et al., 2014; Files et al., 2015). Furthermore, it has previously been shown that the maternal parent-of-origin effect increases the risk of the disease (Ebers et al., 2004).

All available genetic data suggest that the inheritance model of the pathology is complex; susceptibility is determined by multiple, possibly interacting genes, each exerting small to moderate risk effects (Haines et al., 1998; Vitale et al., 2002; Hafer et al., 2007). The human leukocyte antigen (HLA) complex on chromosome 6p21.3, was the first MS risk locus identified (Bertrams and Kuwert, 1972; Naito et al., 1972) and it remains the most important one by far (Lill, 2014); in particular, the HLA class II region has the largest influence, with HLA-DRB1*15:01 conferring a threefold increase in MS risk (Kamm et al., 2014; Lill, 2014).

Italy is a high risk area for MS, with Sardinia, in particular, showing the highest frequency (Rosati et al., 1996; Melcon et al., 2014); here, MS has been found to be associated with different HLA-DRB1 alleles, such as DRB1*03:01 and DRB1*04:05 (Marrosu et al., 1997; Cocco et al., 2013), since Sardinians are an ethnically homogeneous population with a genetic structure that is quite different from that of all other Italian and European populations.

Several genomewide association studies have been performed in MS, and they have revolutionized genetic analysis of the disease; more than 100 associated common variants have now been identified, implicating genes involved in immunological processes; many of them have already been associated with other autoimmune diseases (Sawcer et al., 2014). However, recent estimates suggest that the MS risk loci identified to date are able to explain only about a quarter of the reported heritability, most of which is attributable to the HLA locus (Svejgaard, 2008).

Familial MS aggregation is well known; multicase families with affected members found in more than one generation have been reported; it has been suggested that such families may represent an important resource for studying MS, since a higher aggregation of susceptibility loci in such families occurs as compared with the families of sporadic cases (Gourraud et al., 2011). Detailed clinical description of these families is a fundamental preliminary requirement to support such investigations. Here we describe an Italian family that has six members with MS (five females with a definite diagnosis and a male, possibly affected) spanning two, possibly three, generations. Affected and non-affected family members were typed for the HLA-DRB1* locus to test its association with the disease. Furthermore, we performed a review of literature data on MS multigenerational families.

Materials and methods

The proband was examined at MS Center of the Neurological Department at the ASST Grande Ospedale Metropolitano Niguarda (Milan, Italy); the other members were submitted to clinical and genetic assessment over time after spontaneously seeking and requesting advice. The proband and all family members who requested genetic testing were carefully counseled after signing an informed consent form approved by the local ethics committee. The controls in this study were family members with no symptoms, one belonging to the second generation (II:2, 86 years old), three belonging to the third generation (III:1; III:3; III:9: 68, 64 and 54 years old, respectively) and one belonging to the fourth generation (IV:10, 42 years old).

The family history was reconstructed through interviews and examination of the clinical records of each affected and non-affected member, to provide a family pedigree. MS diagnoses were based on the criteria applicable at the time of diagnosis, i.e., the Poser criteria for subject III:6 (Poser et al., 1983), the McDonald’s 2001 criteria for subject III:10 (McDonald et al., 2001), the McDonald’s 2005 criteria for subjects III:2 and III:4 (Polman et al., 2005) and the McDonald’s 2010 criteria for subject IV:1 (Polman et al., 2011). All MS diagnoses were confirmed using the 2010 revision of the McDonald’s criteria (Polman et al., 2011). The clinical course was defined according to the first consensus definition of MS clinical courses (Lublin and Reingold, 1996 oppure Lublin et al., 2014). A neuropsychological evaluation was performed in only three family subjects. In particular, the following tests were administered: phonemic fluency test, semantic fluency test, brief history, digit span, Corsi block-tapping test, Rey-Osterrieth complex figure test, attentional matrices, Trail Making tests A & B, Raven matrices test and Beck Depression Inventory test.

Blood samples were collected and DNA was extracted from peripheral blood leukocytes using standard procedures (Miller et al., 1988). HLA analysis was performed at low and high resolution; in particular, a commercial kit with sequence-specific primers designed to match single alleles was used for PCR-SSP (HLA-Ready Gene DRB Low, InnoTrain, Kronberg in Taunus, Germany) to determine the HLA class II (HLA-DRB1* locus). High-resolution 4-digit typing was carried out using a specific Olerup kit (Olerup, Stockholm, Sweden) (Cristallo et al., 2012). Alleles were assigned on the basis of analysis of the reaction profile, which was defined as the presence or absence of specific bands in addition to the internal control. This was done using the software SCORE which refers to the NCBI dbMHC database (http://www.ncbi.nlm.nih.gov/projects/gv/mhc/main.fcgi?cmd=init).

Alleles were named according to current official nomenclature (http://hla.alleles.org/). MS multigenerational families are defined as those in which there are at least two members affected occurring in different generations. The literature search was performed consulting the main online databases: EMBASE (www.elsevier.com/solutions/embase-biomedical-research), Pubmed (www.ncbi.nlm.nih.gov/pubmed), Scopus (www.scopus.com) and Web of Science (workinfo.com). The search criteria were “multiple sclerosis,” “family,” “multicausetic,” and “multi-generational,” with no limits of publication years. Each selected paper, together with its reference list, was carefully evaluated.

Results

Family overview

The family originated from a small town with about 8000 inhabitants located in southern Italy; the pedigree is
shown in figure 1. It consists of 46 members spanning four generations. No consanguineous marriages were reported.

Five females, belonging to generations III and IV, were affected by MS, defined as: progressive with relapse (PR) (III:2), secondary progressive (SP) (III:4; III:10) and relapsing remitting (RR) (III:8; IV:1). Moreover a possible diagnosis of primary progressive (PP) MS was made for a male family member, I:3 (Tab. I).

Six non-MS members were affected by various disorders (Fig. 1); no pathological conditions were reported in the other subjects.

All the members of the first two generations stayed in their place of birth all their lives, while six members of the third generation migrated to northern Italy: two MS (III:2, III:6) and three non-MS (III:3, III:7, III:9) subjects migrated after adolescence, while one healthy member (III:8) migrated at the age of 14 (Tab. I).

The index case is indicated by the arrow. Squares represent males; circles, females. Family members with MS diagnosis are shown in black; the grey symbol represents possible MS. A diagonal line through the symbol represents a deceased person. The asterisk indicates people analyzed for HLA-DRB1.

**Figure 1 - The Italian MS family pedigree.**

**Table I - Synopses of MS cases.**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age at onset (years)</th>
<th>Onset symptom</th>
<th>Time to 2nd relapse (years)</th>
<th>Clinical course</th>
<th>Disease Duration (years)</th>
<th>Brain MRI</th>
<th>Spinal MRI</th>
<th>Oligoclonal bands</th>
<th>Current EDSS score</th>
<th>Migration to northern Italy (age, years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I:3</td>
<td>M</td>
<td>20</td>
<td>Paraparesis</td>
<td>-</td>
<td>PP</td>
<td>30</td>
<td>NP</td>
<td>NP</td>
<td>-</td>
<td>6.5</td>
<td>no</td>
</tr>
<tr>
<td>III:2</td>
<td>F</td>
<td>47</td>
<td>Paraparesis</td>
<td>-</td>
<td>PR</td>
<td>15</td>
<td>&gt;20</td>
<td>&gt;3</td>
<td>extensive</td>
<td>6.5</td>
<td>yes (23)</td>
</tr>
<tr>
<td>III:4</td>
<td>F</td>
<td>42</td>
<td>Leg numbness</td>
<td>10</td>
<td>SP</td>
<td>17</td>
<td>&lt;9</td>
<td>extensive</td>
<td>-</td>
<td>6.5</td>
<td>no</td>
</tr>
<tr>
<td>III:6</td>
<td>F</td>
<td>19</td>
<td>Leg numbness</td>
<td>3</td>
<td>RR</td>
<td>40</td>
<td>&lt;10</td>
<td>extensive</td>
<td>-</td>
<td>2.5</td>
<td>yes (20)</td>
</tr>
<tr>
<td>III:10</td>
<td>F</td>
<td>24</td>
<td>Facial palsy</td>
<td>1</td>
<td>SP</td>
<td>23</td>
<td>confluent</td>
<td>extensive</td>
<td>-</td>
<td>6.5</td>
<td>no</td>
</tr>
<tr>
<td>IV:1</td>
<td>F</td>
<td>27</td>
<td>Leg paresis</td>
<td>1</td>
<td>RR</td>
<td>3</td>
<td>&lt;9</td>
<td>1</td>
<td>-</td>
<td>2.5</td>
<td>no</td>
</tr>
</tbody>
</table>

a F: female; M: male.

b PR: relapsing remitting; SP: secondary progressive; PR: progressive relapsing.

MRI findings are described; the focal lesion count is reported when possible; NP: not performed.

d Oligoclonal bands: (+) positive; (-) negative; NP: not performed.

e EDSS: Expanded Disability Status Scale (Kurtzke, 1983).

Clinical and neuroradiological features of patients are described; information on migration from birth country to northern Italy is also provided.

All patients had MRI findings compatible with MS; brain and spinal lesion load varied.
The clinical data of the MS cases are summarized in Table I and briefly described below.

- **Subject I:3** He died aged 50 years in 1940. He had presented a progressive gait disorder since he was 20 years and was confined to a wheelchair by the age of 33 years. No investigations were performed and a diagnosis of possible PP MS was made on the basis of a review of the medical records recovered.

- **Subject II:2** She was born in June 1949. She presented progressive spasticity, painful dysesthesias and urinary disorders by the age of 47 years. Ten years later she was admitted to our hospital for transient diplopia. Brain and spinal MRI showed T2-weighted hyperintense lesions and few T1-weighted enhancing lesions after gadolinium infusion. Cerebrospinal fluid (CSF) oligoclonal bands (OBs) were detected. Visual evoked potentials were within normal limits. A diagnosis of PR MS was made. Interferon beta-1b was started without benefit. In 2012, she scored 6.5 points on the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983); at this time a breast carcinoma was removed.

- **Subject III:4** She was born in January 1953. At the age of 42 years she developed abdominal and leg hypoesthesia, with spontaneous remission within three months. Two years later a diagnosis of seronegative spondyloarthitis and fibromyalgia was made. A further eight years later she reported dizziness and bladder dysfunction. Brain and spinal MRI showed T2-hyperintense lesions and CSF OBs were detected; evoked potentials were not performed. She was treated with immunosuppressive agents for three years. She had further relapses and a progressive worsening of deambulation from the age 55 years. At the last examination her disability score was 6.5 EDSS; some visible cognitive dysfunctions were present, but no specific neuropsychological assessment was performed.

- **Subject III:6 (proband)** She was born in July 1955. At the age of 19 years she developed transient leg numbness, followed by episodes of paresthesia and diplopia. She was admitted to our hospital in 1999. Brain and spinal MRI showed T2-hyperintense lesions compatible with MS and CSF OBs were found. Visual evoked potentials were within normal limits. Interferon beta-1a therapy was started. In 2009 a diagnosis of spondyloarthitis was made. At the last examination spastic paraparesis was present; multimodal evoked potentials were within normal limits. Pingolimod therapy was started after Interferon beta-1a. At the last examination, her EDSS score was 2.5. At the time of diagnosis, no neuropsychological dysfunctions were detected. Migraine with aura was also reported.

### HLA genotypes

Ten subjects were analyzed for the HLA-DRB1* locus, five with MS and five not affected.

In the MS subjects, the HLA genotypes were found to be DRB1*15:01,*11 in II:2, II:4, III:6 and III:10 and DRB1*15:01,*16 in IV:1.

In the non-MS individuals, the HLA genotypes were found to be DRB1*15:01,*11 in III:1, III:3, and III:9; DRB1*15:01,*07:01 in II:2 subject, and DRB1*1,*04 in IV:10.

### Literature review

To the best of our knowledge, six MS multigenerational families have been reported prior to the one reported herein. Table II summarizes the relative descriptions of pedigree, clinical and genetic findings (Bird, 1975; Vitale et al., 2002; Dyment et al., 2002; Haghighi et al., 2006; Dyment et al., 2008; Binzer et al., 2010).

Three of the families came from North America (Bird, 1975; Vitale et al., 2002; Dyment et al., 2002; Dyment et al., 2008), two from Sweden (Haghighi et al., 2006) and one from the Faroe Islands (Binzer et al., 2010).

Overall, 52 MS subjects and three possible MS cases over three or four generations were studied. All the patients were adults except for two adolescents, aged 15 and 17 years (Bird, 1975; Dyment et al., 2002). The prevalence of female gender was confirmed in all but two of the families (Bird, 1975; Haghighi et al., 2006). The subjects’ clinical conditions were heterogeneous in terms of MS type and mean age at onset. With regard to MRI, detailed reports were not available.

The HLA pattern was analyzed in the MS cases in all the families and the HLA-DRB1*15 allele was detected in most of them; however, in those reports in which HLA analysis was extended to all the family (Vitale et al., 2002; Haghighi et al., 2006; Binzer et al., 2010), the same allele was found also in some family members not affected by MS.

### Discussion

We have here described clinical, MRI and HLA-DRB1 findings in an Italian family in which six out of 46 members were found to be affected by MS (five definite and one possible). Their clinical presentation was heterogeneous in terms of type of MS, age and symptoms at onset and disability, as well as MRI lesion load. All the definite cases were females while the individual with a possible diagnosis of MS was male. The five analyzed cases all carried the HLA-DRB1*15:01 allele.

All MS cases shared the same environmental risk factors, since the only two who migrated did so after adolescence. No correlation between the occurrence of MS and the season of birth was found in our family, although previous data suggested that the highest rate of MS occurred in people born in May and the lowest in those born dur-
MS families with more than three affected individuals have rarely been described. In the data set described by Haines et al. (1998), referring to 98 Caucasian multiplex families, 14% had four or more affected individuals. Moreover, among 28,000 MS cases collected in the Canadian population, 10% of families had two or three affected cases, 0.2% four or five and five families had seven–nine cases (Dyment et al., 2008).

Pedigrees with more than two consecutive generations are even more rarely described. Our review of the literature disclosed reports on clinical and HLA findings in six MS multigenerational families, published prior to the present one (Tab. II) (Bird, 1975; Vitale et al., 2002; Dyment et al., 2002; Haghighi et al., 2006; Dyment et al., 2008; Binzer et al., 2010). These families showed similar clinical heterogeneity to that found in our family; it is also to be noted that, with the exception of two studies, the gender distribution showed a female predominance (Tab. II).

Only Dyment et al. (2002) and Vitale et al. (2002) reported MRI findings, without providing detailed descriptions. In our cases, MRI lesion load was found to be consistent with clinical phenotype and disease duration. An association between MS and the HLA-DRB1*15 allele was found in all reports, except for the family described by Bird (1975), supporting its role as strong susceptibility factor. The frequency of this allele within the family reported by Dyment et al. (2008) was 79% in MS cases and 38% in the unaffected subjects (Dyment et al., 2008). On the contrary, we detected the HLA-DRB1*15 allele in four out of five non-affected subjects, including the proband’s mother (II:2) and three adult sisters, who are currently healthy.

It is conceivable that a high genetic burden may be operating within families with co-affected relatives (Gourraud et al., 2012), while it is probable that, according to the complex disease model, other factors (genetic and non-genetic) play a role in determining the expression of the disease (Dyment et al., 2012; Sawcer et al., 2014; Barizzone et al., 2015; Hollenbach and Oksenberg 2015). A more extensive molecular analysis has been planned in our multigenerational MS family in order to identify genes/genetic variants with a possible modifier role in this disease.

Table II - Multigenerational MS families: review of the literature.

<table>
<thead>
<tr>
<th>First Author, year</th>
<th>Country</th>
<th>Families (N)</th>
<th>Members (N)</th>
<th>MS patients (N)</th>
<th>Generations (N)</th>
<th>MS type&lt;sup&gt;b&lt;/sup&gt; (N&lt;sub&gt;a&lt;/sub&gt; patients)</th>
<th>MS F-MS M&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Mean age at onset (Range)</th>
<th>HLA findings (MS n/T&lt;sup&gt;d&lt;/sup&gt; (not-MS n/T&lt;sup&gt;d&lt;/sup))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bird, 1975</td>
<td>North America</td>
<td>1</td>
<td>80</td>
<td>3 (+1 possible)</td>
<td>3</td>
<td>RR (3) (+1 PP)</td>
<td>1-3</td>
<td>20 (15-26)</td>
<td>Haplotype 11, W16&lt;sup&gt;e&lt;/sup&gt; (3/3)</td>
</tr>
<tr>
<td>Vitale, 2002</td>
<td>North America</td>
<td>1</td>
<td>21</td>
<td>7 (+1 possible)</td>
<td>3</td>
<td>SP (2) RR (4) UK (1) (+ 1 PP)</td>
<td>6-2</td>
<td>30 (24-37)</td>
<td>DRB1*15&lt;sup&gt;f&lt;/sup&gt; (77/4) (4/11)</td>
</tr>
<tr>
<td>Dyment, 2002</td>
<td>North America</td>
<td>1</td>
<td>96</td>
<td>15 (+1 possible)</td>
<td>3 (possibly 4)</td>
<td>PP (2) SP RR (7) (+ 1 PP)</td>
<td>10-6</td>
<td>27 (17-49)</td>
<td>DRB1*15&lt;sup&gt;g&lt;/sup&gt; (11/14)</td>
</tr>
<tr>
<td>Dyment, 2008</td>
<td>North America</td>
<td>1</td>
<td>96</td>
<td>15 (+1 possible)</td>
<td>3 (possibly 4)</td>
<td>PP (2) SP RR (7) (+ 1 PP)</td>
<td>10-6</td>
<td>27 (17-49)</td>
<td>DRB1*15&lt;sup&gt;g&lt;/sup&gt; (11/14)</td>
</tr>
<tr>
<td>Haghighi, 2006</td>
<td>Western Sweden</td>
<td>2</td>
<td>Family A</td>
<td>88</td>
<td>7</td>
<td>UK</td>
<td>7-0</td>
<td>42 (18-78)</td>
<td>DRB1*15&lt;sup&gt;g&lt;/sup&gt; (17/41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Family B</td>
<td>15</td>
<td>6</td>
<td>UK</td>
<td>2-4</td>
<td>41 (19-61)</td>
<td>DRB1*15&lt;sup&gt;g&lt;/sup&gt; (5/6)</td>
</tr>
<tr>
<td>Binzer, 2010</td>
<td>Faroe Islands</td>
<td>1</td>
<td>67</td>
<td>14</td>
<td>4</td>
<td>PP (7) RR (5) UK (2) SP (1) RR (1) (+ 1 PP)</td>
<td>9-5</td>
<td>34 (19-51)</td>
<td>DRB1*15&lt;sup&gt;g&lt;/sup&gt; (3/6)</td>
</tr>
<tr>
<td>Present report</td>
<td>Italy</td>
<td>1</td>
<td>46</td>
<td>5 (+1 possible)</td>
<td>2 (possibly 3)</td>
<td>PP (7) RR (5) UK (2) SP (1) RR (1) (+ 1 PP)</td>
<td>5-1</td>
<td>32 (19-48)</td>
<td>DRB1*15 (5/5) (4/5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> N: number.  
<sup>b</sup> RR: relapsing remitting; SP: secondary progressive; PR: progressive relapsing; PP: primary progressive; UK: unknown.  
<sup>c</sup> MS F: MS female; MS M: MS male.  
<sup>d</sup> n/T: number of subjects with the reported allele out of the total number of analyzed patients; no information are reported on heterozygous or homozygous state of the allele.  
<sup>e</sup> This paper does not allow to compare with the actual HLA classification  
<sup>f</sup> The HLA allele is reported according to the current official nomenclature although different names were reported in the original articles (Vitale et al., 2002: DR15; Haghighi et al., 2006: DRB1*02(15); Binzer et al., 2010: DR15).  
<sup>g</sup> No data on HLA typing are available for non-affected family members.
Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References


The Italian real-life post-stroke spasticity survey: unmet needs in the management of spasticity with botulinum toxin type A

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Summary

The present national survey seeking to identify unmet needs in the management of spasticity with botulinum toxin type A focused on the use of OnabotulinumtoxinA, since this is the brand with the widest range of licensed indications in Italy. Physicians from twenty-four Italian neurorehabilitation units compiled a questionnaire about “real-life” post-stroke spasticity management. OnabotulinumtoxinA was reported to be used in the following average doses: upper limb 316.7 ± 79.1 units; lower limb 327.8 ± 152.3; upper and lower limb 543.7 ± 123.7 units. Of the physicians surveyed, 37.5% felt that increasing the frequency of OnabotulinumtoxinA injection would improve its efficacy; 70.8% use electrical stimulation/electromyography guidance (one fourth of injections with no instrumental guidance). Instrumental evaluation was used by 41.7% of the physicians.

The participants expressed the view that early identification of post-stroke spasticity would be facilitated by the availability of a post-stroke checklist, and that this should be used by physiotherapists (91.7%), physiatrists (58.3%), family doctors (50%), stroke unit physicians (25%), patients and caregivers (79.2%).

According to our findings, the management of post-stroke spasticity has several unmet needs that, we re they addressed, might improve these patients’ clinical outcomes and quality of life. These needs concern patient follow-up, where a clearly defined pathway is lacking; furthermore, there is a need to use maximum doses per treatment and to ensure early intervention on post-stroke spasticity.

KEY WORDS: botulinum toxins, disease management, muscle spasticity, rehabilitation

Introduction

Stroke is the fourth cause of death worldwide (in-hospital mortality rates for ischemic stroke have been estimated to stand at between 11% and 15%) and the second leading cause of disability in Europe (about half of stroke survivors are left with some degree of physical or cognitive impairment) (Bustamante et al., 2016). Spasticity, defined as a disorder of the sensorimotor system characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks (Lance, 1980), is a common complication of stroke. It is considered a “positive” sign of upper motor neuron syndrome, since it represents excessive muscle tone and stretch reflexes (other so-called positive consequences include clonus and spasms) (Li and Francisco, 2015). The prevalence of post-stroke spasticity ranges widely (from 19% to 92%), as does the timing of its onset after stroke (Ward, 2012; Wissel et al., 2013; Li and Francisco, 2015); in most cases, however, it emerges between 1 and 6 weeks after the initial damage (Balakrishnan and Ward, 2013). It has been suggested that early recognition of post-stroke spasticity could result in earlier treatment and possibly better outcomes (Wissel et al., 2015). Botulinum toxin type A (BoNT-A) has been proven to be effective and safe in the treatment of focal post-stroke spasticity (Simpson et al., 2008). It acts in the cytosol of nerve endings and inhibits acetylcholine release by cleaving the synaptosomal-associated 25 kDa protein, which is required for vesicle docking; consequently, it also inhibits neurotransmitter release (Aoki, 2003). Currently, three brands of BoNT-A are marketed in Italy: OnabotulinumoxinA (Allergan, Botox®, Irvine, CA, USA), AbobotulinumtoxinA (Ipsen, Dysport®, Boulogne-Billancourt, France) and IncobotulinumoxinA (Merz, Xeomin®, Frankfurt am Main, Germany) (Albanese, 2011). These products are not considered interchangeable, as they differ significantly in terms of their biological manufacturing processes (i.e. isolation and purification techniques), molecular structures and formulations, which may affect local migration from the injection site, and also in terms of their potency characteristics, which may influence their efficacy, safety profile and antigenic potential (Albanese, 2011; US Food and Drug Administration, 2010; Caputi and Rossi, 2013).
In daily clinical practice, a number of organizational and methodological aspects have to be taken into account when planning a treatment strategy that includes the administration of BoNT-A. These include the treatment goals and methods, the method of assessment of clinical improvement, the injection schedule (e.g., the muscles to be injected, injection technique, number of injection sites per muscle, dose and dilution) and other treatment modalities (e.g., rehabilitation procedures) to be integrated into the treatment plan (Franceschini et al., 2014; Smania et al., 2013; Carda et al., 2011; Smania et al., 2010). Taking these aspects into account, a post-stroke checklist has been proposed in order to identify persistent long-term problems and improve long-term care for stroke survivors (Paolucci and Smania, 2015; Philp et al., 2013).

Although a growing number of physicians use BoNT-A to treat a range of clinical conditions, there are still some open practical problems and conjectures concerning BoNT-A injection-based therapeutic strategies (Smania et al., 2013). For this reason, we decided to conduct a national survey aimed at identifying the unmet needs in the management, with BoNT-A, of patients suffering from post-stroke spasticity. Specifically, the survey focused on the use of OnabotulinumtoxinA, since this is the brand with the widest range of licensed indications in Italy (upper and lower limb spasticity associated with stroke in adults, focal spasticity associated with pediatric cerebral palsy, cervical dystonia, blepharospasm and hemifacial spasm, primary axillary hyperhidrosis, chronic migraine, overactive bladder and neurogenic detrusor overactivity).

The present paper reports the main findings of the Italian Real-Life Post-Stroke Spasticity Survey.

Methods

Thirty-eight Italian neurorehabilitation units selected from the Italian Society of Neurological Rehabilitation (SIRN) database qualified for inclusion in this survey. Each unit involved was required to compile a self-administered two-part questionnaire. Tables I and II show the full questionnaire.

Statistical analysis

Descriptive statistics were used for all the items investigated. Statistical analysis was carried out using the Statistical Package for Social Science for Macintosh, version 20.0 (SPSS Inc, Chicago, IL).

Results

Twenty-four of the selected units compiled the question-
Post-Stroke Spasticity Survey

Eighteen (75%) units had a dedicated outpatient service for the treatment of patients with BoNT-A (on average, each center had 3.4 ± 2.4 clinicians specialized in and responsible for performing BoNT-A injections). The physicians included in this survey reported that they used OnabotulinumtoxinA for the following licensed indications: spasticity 56.6% ± 30.9%; dystonia 1.4% ± 11.1%; blepharospasm 13.5% ± 13.8%; chronic migraine 6.4% ± 7.8%; overactive bladder 0%; others 7.3% ± 12.3%. On average, each center treated 334.6 ± 327.2 patients per year, corresponding to a mean of 461.7 ± 322.8 BoNT-A treatments performed in each center per year. In 66.7% of cases, the clinicians reported that, at least in part, the patients they treated were under their own clinical care; in 91.7% of cases, the choice both of target muscles (injection sites) and of the injection doses were reported to be based on the independent clinical evaluation of the injector. With regard to the timing of BoNT-A treatment, the decision was made by the injector in 87.5% of cases, and by the referring physician in the remaining 12.5% of cases (in 20.8% of cases, the BoNT-A treatment has been requested beforehand by the patient). With regard to the assessment procedures used to select the BoNT-A injection sites, instrumental evaluation (e.g. EMG analysis of gait) was used by 41.7% of the physicians included in this survey. As for the use of instrumental support in performing BoNT-A injections, 70.8% of clinicians reported using electrical stimulation/electromyography guidance, and 50% ultrasonography guidance; the clinicians used no instrumental guidance for 25% of the treatments administered. For evaluation of the treatment, the surveyed clinicians mainly evaluated BoNT-A treatment efficacy by means of clinical evaluation (87.5%) and scales (70.5%).

With regard to post-stroke spasticity, according to 83.3% of the clinicians, caregivers play a key role in the early identification of muscle hypertonia after stroke onset, while 91.7% considered the post-stroke spasticity checklist a useful tool, indicating that it should be used by physical therapists (91.7%), physiatrists (58.3%), family doctors (50%), stroke unit physicians (25%), and others.

### Table II - Survey questionnaire – Part B.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 What are the clinical conditions related to the development of spasticity that are usually treated in your center?</td>
<td></td>
</tr>
<tr>
<td>2 How long have the patients currently treated with OnabotulinumtoxinA suffered from spasticity?</td>
<td></td>
</tr>
<tr>
<td>3 How long is the follow-up of patients OnabotulinumtoxinA-treated patients in your center?</td>
<td></td>
</tr>
<tr>
<td>4 What muscles do you usually treat with OnabotulinumtoxinA in patients with upper limb spasticity?</td>
<td></td>
</tr>
<tr>
<td>5 What muscles do you usually treat with OnabotulinumtoxinA in patients with lower limb spasticity?</td>
<td></td>
</tr>
<tr>
<td>6 What dose of OnabotulinumtoxinA do you usually inject for the treatment of spasticity?</td>
<td></td>
</tr>
<tr>
<td>7 What is the incidence of the different patterns of spasticity in your center?</td>
<td></td>
</tr>
<tr>
<td>8 What is the interval between two consecutive OnabotulinumtoxinA injections in your series?</td>
<td></td>
</tr>
<tr>
<td>9 Could increasing the frequency of OnabotulinumtoxinA injection help to improve its efficacy? (If yes) What, in your opinion, is the ideal interval between two consecutive OnabotulinumtoxinA injections?</td>
<td></td>
</tr>
<tr>
<td>10 What proportion of patients do not come back for the planned treatment?</td>
<td></td>
</tr>
<tr>
<td>11 What are the main reasons for this?</td>
<td></td>
</tr>
<tr>
<td>12 What, in your opinion, is the level of satisfaction with OnabotulinumtoxinA treatment among patients?</td>
<td></td>
</tr>
<tr>
<td>13 What, in your opinion, is the level of satisfaction with OnabotulinumtoxinA treatment among physicians?</td>
<td></td>
</tr>
<tr>
<td>14 What, in your opinion, are the main reasons for patients’ satisfaction after treatment with OnabotulinumtoxinA?</td>
<td></td>
</tr>
<tr>
<td>15 What, in your opinion, are the main reasons for dissatisfaction after treatment with OnabotulinumtoxinA?</td>
<td></td>
</tr>
<tr>
<td>16 What, in your opinion, are the main reasons for delayed treatment of spasticity with OnabotulinumtoxinA?</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: U=Units; mo=months; ys=years; wk=weeks.

Functional Neurology 2017; 32(2): 89-96
The physicians included in this survey used OnabotulinumtoxinA to treat spasticity resulting from the following clinical conditions: stroke 55.4% ± 23.0%; acquired brain injury 10.5% ± 16.7%; cerebral palsy 10.1% ± 12.7%; multiple sclerosis 9.9% ± 11.9%; spinal cord injury 4.8% ± 7.6%; myelopathy 2.3% ± 0.9%; others 5.5% ± 11.9%. Figure 1 details the duration of spasticity prior to the first treatment. On average, the duration of spasticity follow-up was 4.9 ± 1.9 years (with a mean maximum of 10.9 ± 4.0 years).

The muscles usually treated with OnabotulinumtoxinA in patients with upper limb spasticity were the following: pectoralis major, biceps brachii, brachioradialis, pronator teres, flexor carpi radialis, flexor carpi ulnaris, flexor digitorum superficialis, flexor digitorum profundus, flexor pollicis longus. The muscles usually treated with OnabotulinumtoxinA in patients with lower limb spasticity were as follows: rectus femoris, medial and lateral hamstrings, adductor longus, medial and lateral gastrocnemius, soleus, tibialis posterior, flexor digitorum longus. Table 3 provides data on the OnabotulinumtoxinA dose per muscle.

The mean OnabotulinumtoxinA doses used to treat spasticity were as follows: upper limb spasticity 316.7 ± 79.1 units; lower limb spasticity 327.8 ± 152.3 units; upper and lower limb spasticity 543.7 ± 123.7 units. Figure 2 shows the different distribution patterns of the spasticity.

The surveyed physicians reported that they allowed the following intervals between two consecutive OnabotulinumtoxinA injections: ≤ 10 weeks (2.2% ± 3.9%); 11–12 weeks (28.9% ± 34.7%); 13–14 weeks (14.4% ± 13.8%); 14–15 weeks (10.8% ± 11.8%); 15–16 weeks (16.0% ± 16.1%); ≥ 17 weeks (28.0% ± 34.7%). Meanwhile, 37.5% believed that increasing the frequency of OnabotulinumtoxinA injection would help to improve its efficacy (ideal interval between two consecutive injections: ≤ 7 weeks 4.2%; 7–8 weeks 12.5%; 11–12 weeks 12.5%; 13–14 weeks 8.3%). The proportion of patients who fail to return for the second treatment was reported to be 8.9% ± 9.2%, and the survey participants attributed this phenomenon mainly to: unsatisfactory results 20.8%; difficulty reaching the hospital 29.2%; the lack of a standardized pathway 29.2%; other reasons 12.5%.

Figure 3 shows the participants’ opinions on the levels of patient satisfaction with the treatment. In their view, patient satisfaction after treatment with OnabotulinumtoxinA could be attributed mainly to the following factors: for treatment of the upper limb, improvements in activities of daily living (29.2%), improvements in personal hygiene management (45.8%), pain reduction (62.5%), other reasons, such as improvements in esthetics, posture, body image and muscle stiffness (20.8%); for treatment of the lower limb: improved gait (79.2%), improved posture (29.8%), reduced clonus (50.0%), reduced pain (45.8%) and other reasons, such as improvements in social life (8.3%). The main reasons for dissatisfaction after treatment with BoNT-A were considered to be: low doses, physical weakness, a short or weak antispastic effect, unavailability of specific (integrated and innovative) post-injection management protocols, insufficient awareness of the benefits of the treatments, muscle tone improve-ments that are not reflected in an improved functional profile or better quality of life, goals that are not made clear or agreed with the physician, and delayed post-injection rehabilitation treatment. The participants gave the following main reasons for delayed treatment of spasticity with OnabotulinumtoxinA: delayed diagnosis of spasticity; difficulty in reaching the treatment centers; lack of a hub and spoke organizational model; lack of information about BoNT-A among family doctors and physical therapists; shortage of dedicated hospital staff.
<table>
<thead>
<tr>
<th>Muscle</th>
<th>Average dose (mean)</th>
<th>Minimum dose (mean)</th>
<th>Maximum dose (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pectoralis</td>
<td>76 U</td>
<td>37 U</td>
<td>123 U</td>
</tr>
<tr>
<td>Latissimus dorsi</td>
<td>73 U</td>
<td>36 U</td>
<td>103 U</td>
</tr>
<tr>
<td>Subscapularis</td>
<td>51 U</td>
<td>32 U</td>
<td>81 U</td>
</tr>
<tr>
<td>Teres major</td>
<td>35 U</td>
<td>21 U</td>
<td>57 U</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>73 U</td>
<td>41 U</td>
<td>121 U</td>
</tr>
<tr>
<td>Brachioradialis</td>
<td>55 U</td>
<td>32 U</td>
<td>82 U</td>
</tr>
<tr>
<td>Brachialis</td>
<td>58 U</td>
<td>36 U</td>
<td>92 U</td>
</tr>
<tr>
<td>Triceps brachii</td>
<td>66 U</td>
<td>40 U</td>
<td>120 U</td>
</tr>
<tr>
<td>Ext. carpi radialis</td>
<td>36 U</td>
<td>21 U</td>
<td>62 U</td>
</tr>
<tr>
<td>Ext. carpi ulnaris</td>
<td>36 U</td>
<td>20 U</td>
<td>62 U</td>
</tr>
<tr>
<td>Flex. carpi radialis</td>
<td>53 U</td>
<td>34 U</td>
<td>95 U</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Average dose (mean)</th>
<th>Minimum dose (mean)</th>
<th>Maximum dose (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flex. carpi ulnaris</td>
<td>48 U</td>
<td>28 U</td>
<td>87 U</td>
</tr>
<tr>
<td>Pronator teres</td>
<td>43 U</td>
<td>23 U</td>
<td>74 U</td>
</tr>
<tr>
<td>Pronator quadratus</td>
<td>31 U</td>
<td>19 U</td>
<td>51 U</td>
</tr>
<tr>
<td>Ext. dig. communis</td>
<td>27 U</td>
<td>19 U</td>
<td>42 U</td>
</tr>
<tr>
<td>Flex. dig. superficialis</td>
<td>57 U</td>
<td>28 U</td>
<td>102 U</td>
</tr>
<tr>
<td>Flex. dig. profundus</td>
<td>56 U</td>
<td>30 U</td>
<td>105 U</td>
</tr>
<tr>
<td>Flex. pollicis longus</td>
<td>30 U</td>
<td>16 U</td>
<td>53 U</td>
</tr>
<tr>
<td>Adductor pollicis</td>
<td>21 U</td>
<td>13 U</td>
<td>39 U</td>
</tr>
<tr>
<td>Thenar</td>
<td>21 U</td>
<td>14 U</td>
<td>36 U</td>
</tr>
<tr>
<td>Lumbrical</td>
<td>33 U</td>
<td>19 U</td>
<td>47 U</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Average dose (mean)</th>
<th>Minimum dose (mean)</th>
<th>Maximum dose (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adductor longus</td>
<td>75 U</td>
<td>44 U</td>
<td>105 U</td>
</tr>
<tr>
<td>Adductor magnus</td>
<td>89 U</td>
<td>49 U</td>
<td>142 U</td>
</tr>
<tr>
<td>Gracilis</td>
<td>69 U</td>
<td>49 U</td>
<td>92 U</td>
</tr>
<tr>
<td>Iliopsoas</td>
<td>73 U</td>
<td>46 U</td>
<td>109 U</td>
</tr>
<tr>
<td>Rectus femoris</td>
<td>72 U</td>
<td>41 U</td>
<td>110 U</td>
</tr>
<tr>
<td>Medial hamstrings</td>
<td>78 U</td>
<td>42 U</td>
<td>105 U</td>
</tr>
<tr>
<td>Biceps femoris</td>
<td>82 U</td>
<td>48 U</td>
<td>125 U</td>
</tr>
<tr>
<td>Quadriceps femoris</td>
<td>101 U</td>
<td>62 U</td>
<td>185 U</td>
</tr>
<tr>
<td>Gastrocnemius medialis</td>
<td>72 U</td>
<td>37 U</td>
<td>108 U</td>
</tr>
<tr>
<td>Gastrocnemius lateralis</td>
<td>66 U</td>
<td>34 U</td>
<td>105 U</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Average dose (mean)</th>
<th>Minimum dose (mean)</th>
<th>Maximum dose (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibialis posterior</td>
<td>71 U</td>
<td>39 U</td>
<td>112 U</td>
</tr>
<tr>
<td>Tibialis anterior</td>
<td>63 U</td>
<td>36 U</td>
<td>95 U</td>
</tr>
<tr>
<td>Ext. hallucis longus</td>
<td>41 U</td>
<td>25 U</td>
<td>62 U</td>
</tr>
<tr>
<td>Flex. hallucis longus</td>
<td>44 U</td>
<td>28 U</td>
<td>68 U</td>
</tr>
<tr>
<td>Flex. dig. longus</td>
<td>55 U</td>
<td>33 U</td>
<td>85 U</td>
</tr>
</tbody>
</table>

Abbreviations: U=units; Ext=extensor; Flex=flexor; dig=digitorum.
Discussion

The main aim of this survey was to provide an overview of some important issues concerning the use of BoNT-A to treat patients with post-stroke spasticity, and to highlight related unmet needs. We surveyed a representative sample of Italian physicians from 24 neurorehabilitation units that use BoNT-A (corresponding to more than 80 clinicians). They provided feedback based on their current practice, and reported spasticity as the main licensed indication treated with OnabotulinumtoxinA (56.6%) in their centers.

The first unmet need in the management of post-stroke spasticity with BoNT-A, identified from present survey findings, is the need to define a consistent pathway able to ensure that patients will be diagnosed and assisted promptly after the onset of stroke and then regularly followed up. In particular, it was striking, in a negative sense, that 25% of the clinical units surveyed do not have a dedicated outpatient service delivering BoNT-A treatments. Along the same lines, we observed that 25% of BoNT-A treatments were delivered with no instrumental guidance, despite the growing evidence of the usefulness of electrical stimulation/electromyography and ultrasonography guidance (Picelli et al., 2012 a, b; Picelli et al., 2014 a, b). Furthermore, a considerable proportion of patients with post-stroke spasticity are treated late (over 2 or 3 years after the onset of stroke).

The second unmet need concerns the OnabotulinumtoxinA doses used to treat post-stroke spasticity and the limbs treated. Our personal observations of real-life practice suggest that there is a need to re-consider the maximum dose administered per single treatment of both the upper and the lower limb (also when the two are treated together), since the use of high doses of OnabotulinumtoxinA is an established practice that, moreover, addresses the very real need to improve the quality of life of patients with post-stroke spasticity (Barich et al., 2015). In line with these findings, our results showed a high percentage of patients (up to about 62%) who need a combined BoNT-A treatment of upper and lower limb, while only a very low proportion (< 25% on average) require treatment in the upper or lower limb alone in a single session. In addition, there is a lack of long-term follow-up studies on the use of BoNT-A in post-stroke spasticity, with scant data supporting the sustained efficacy of the BoNT-A treatment. Our anecdotal, unpublished, 10-year follow-up observations showed that a tendency to increase BoNT-A doses over time was paralleled by a tendency of patients to be more satisfied.

The third unmet need regards early intervention on post-stroke spasticity, which should be understood as early detection as well as early treatment. With regard to the early development of spasticity after stroke, several possible predictors have been identified, including development of increased muscle tone, initial paresis, hemihypesthesia, a low Barthel Index score, a low Fugl-Meyer Assessment score, and lesion location (Wissel et al., 2015; Opheim et al., 2015; Picelli et al., 2014 c, d; Urban et al., 2010). Predictors of spasticity development have proved useful; indeed, accurate prediction of outcome after stroke not only leads to early treatment, but also assists in rehabilitation planning and supports realistic goal setting by clinicians and patients (Fietzek et al., 2014; Hesse et al., 2012; Rosales et al., 2012; Sti-

near, 2010). Along these lines, our findings support the need for a post-stroke checklist designed to identify treatable post-stroke problems, facilitate referral for treatment, and improve the standard of long-term management of stroke survivors (Paolucci and Smania, 2015; Philip et al., 2013). According to our survey observations, this checklist should be used not only by hospital medical doctors (e.g. physiatrists and neurologists), but also by physical therapists and family doctors. Furthermore, the involvement of patients and caregivers could be crucial for promptly identifying the development of muscle hypertonia after stroke.

This survey has several limitations. First, even though our sample is representative of the most important neurorehabilitation units in Italy (corresponding to about 80 Italian specialists with expertise in the field of botulinum toxin), it is possible that the small population size may have limited our evaluation of some aspects of the management of post-stroke spasticity with BoNT-A. Second, we focused only on the use of OnabotulinumtoxinA, because it is the product with the widest range of licensed indications in Italy. Thus, we cannot draw any conclusions about the use of AbobotulinumtoxinA and IncobotulinumtoxinA in patients with post-stroke spasticity. Future studies should take the above issues into account, also comparing the observations of this survey with those available across Europe.

In conclusion, our findings show that Italy lacks a consistent clinical care model for the treatment of post-stroke spasticity with BoNT-A. This is mainly due to the lack of an established clinical pathway, but also to the existence of different regional laws. Furthermore, our results highlighted the need for combined treatment of the upper and lower limbs, and also the need for doses higher than the licensed ones in order to improve our patients’ clinical outcomes and quality of life. Thus, as shown by our observations of current daily practice, there is a practical need to optimize our treatment paradigms in terms of muscles/limbs/doses, taking into account published clinical evidence and consensus, clinical experience showing a good safety profile both with short- and long-term use, and that the fact that the optimal OnabotulinumtoxinA dose is determined by the patient’s characteristics and specific treatment goals (Ghasemi et al., 2013; Naumann et al., 2006; Naumann and Jankovic, 2004). The present survey set out to highlight unmet needs of patients suffering from post-stroke spasticity, and it is hoped that its findings may help to improve the use of BoNT-A in their clinical and rehabilitation management.

Acknowledgment

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A. Picelli et al.

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