

Movement disorders in systemic autoimmune diseases: clinical spectrum, ancillary investigations, pathophysiological considerations

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Abstract

With the advances in neuroimmunology especially due to the discovery of new neuronal antibodies, the recognition of treatable antibody-related movement disorders has recently received much attention. In contrast, the identification and characterisation of movement disorders associated with systemic autoimmune diseases remains a substantially unexplored area. Beyond the classic few associations such as chorea and antiphospholipid syndrome, or ataxia and coeliac disease, movement disorders have been reported in association with several systemic autoimmune diseases, however a clear image of clinical phenotypes, investigations, and treatment outcomes in these conditions has never been drawn. In this review, we analyse data from approximately 300 cases and summarise the epidemiological, clinical and diagnostic features of movement disorders associated with systemic autoimmune diseases, and the available knowledge about treatment and outcomes. We highlight that movement disorders in systemic autoimmune conditions are frequently the only or among a few presenting manifestations and are mostly treatable disorders responding to immunotherapy or dietary modifications. We point out the pertinent combination of clinical features and investigations which can suggest the underlying autoimmune nature of these movement disorders, and thus address the most appropriate treatment.

INTRODUCTION

Systemic autoimmune diseases (SADs) comprise a broad group of heterogeneous disorders characterized pathophysiologically by immune dysregulation. The resulting loss of self-tolerance induces pathological changes in many different organ systems, including the central nervous system (CNS). In recent years, numerous CNS-predominant immune-mediated disorders associated with novel neuronal antibodies have been described [1]. The phenotypic spectrum of these conditions is well characterised, and frequently comprises prominent movement abnormalities. In contrast, little is known about the presence and/or nature of movement disorders resulting from CNS involvement as part of SADs.

Herein, we review the literature regarding movement disorders associated with SADs. Data from nearly 300 cases were analysed for all diseases. While many of the described associations reflect data only from limited numbers of cases, and should therefore be interpreted with caution, the often-distinct disease-specific phenotypes and response to immunotherapy do suggest causative associations. Table 1 provides an overview of the spectrum of movement disorders in SADs.

METHODS

Search strategy, inclusion and exclusion criteria

The Pubmed database was searched with the following search terms: [systemic lupus erythematosus] OR [antiphospholipid syndrome] OR [Behcet] OR [Sjögren] OR [rheumatoid arthritis] OR [celiac] OR [coeliac] OR [gluten] OR [sarcoidosis] OR [systemic sclerosis] AND [movement disorders] OR [neurological disease] OR [chorea] OR [ataxia] OR [parkinsonism] OR [dystonia] OR [tics] OR [paroxysmal dyskinesia] OR [tremor] OR [myoclonus]. Articles published between January 1990 and April 2020 were considered. Articles not in English or with too little information were excluded, as were articles where established criteria for SADs were not met, or where movement disorders were plausibly caused by disorders other than SADs.

THE CLINICAL SPECTRUM OF MOVEMENT DISORDERS IN SADs

Chorea

Within SADs, chorea is almost invariably associated with positive antiphospholipid (aPL) antibodies, either as part of a primary antiphospholipid syndrome (PAPS), or alongside systemic lupus erythematosus (SLE). Other than presenting with positive aPL, patients with SLE can either have secondary anti-phospholipid syndrome (SLE-APS) or not (SLE-aPL).

SLE-aPL, SLE-APS and PAPS chorea

Three large case series [2-4] and multiple single case reports of chorea occurring in SLE and APS [5-26] were reviewed. In line with previous literature, we included cases of SLE or APS not fulfilling all the diagnostic criteria, called 'incomplete SLE/APS'. A summary of the collected data is presented in Table 2.

Epidemiology

SLE-aPL chorea, SLE-APS chorea and PAPS chorea are all primarily diseases of young women (median age at onset ~20 years), and in roughly 50%, chorea appears concomitantly with systemic manifestations.

Chorea is the third commonest neurological symptom (after headache and seizures) in SLE, with estimated prevalence of 0-7% [17, 27]. However, one prospective study of adult SLE patients followed for 3 years (n=370, median age: 32 years) reported no new diagnoses of chorea [28]. Additional longitudinal studies are therefore required to define the incidence and prevalence of chorea in SLE.

In PAPS, chorea is the commonest movement disorder [29], with prevalence of 1.3-4.5% [29, 30]. Traditionally considered as an 'extra-clinical criterion' of PAPS [31], it has been suggested that chorea should become a core APS criterion, given its relevance to patient outcomes and clinical decision-making [32].

Clinical manifestations

In SLE-aPL and SLE-APS, isolated limb chorea was the commonest phenotype described, whereas symmetric generalized chorea (involving head, face, and mouth) was commonest in PAPS. Additional neurological signs including ataxia, dysarthria, migraine, epilepsy, dystonia, and cognitive deficits were more frequent in PAPS (58%) than in SLE-aPL (39%) and SLE-APS (34%), while psychiatric features were described in roughly 30% of all conditions.

Investigations

Brain MRI was generally normal (75% of PAPS, 58% of SLE-APS and 50% of SLE-aPL). Reported abnormalities included ischemic basal ganglia (BG) lesions (sometimes ipsilateral to hemichorea and thus of uncertain relevance), and non-specific T2-hyperintensities involving the subcortical white matter (WM) or cerebral hemispheres. In only two cases of SLE-aPL were imaging findings suggestive of vasculitis [13].

Little data regarding cerebrospinal fluid (CSF) was available. In SLE-aPL, CSF was normal in 3/5 cases [6, 8, 10], and either non-specific or inflammatory in the others [9]. In SLE-APS, CSF was either normal [2] or demonstrated paired oligoclonal (OCB) bands in serum and CSF [26]. CSF was normal in the one PAPS case with reported findings [20]. Normal CSF examination is therefore common in all these disorders.

Thrombocytopenia was the commonest blood count abnormality in all conditions (most prevalent in SLE-APS-49%). Antinuclear (ANA) and anti-double stranded DNA (anti-dsDNA) antibodies were positive in the majority of SLE-aPL and SLE-APS cases, but only in a minority of PAPS (36% and 7% respectively).

Lupus anticoagulant (LA) was the commonest aPL antibody reported in both SLE-aPL and SLE-APS, whereas anti- β 2glycoprotein I (β 2GPI) and anti-cardiolipin (aCL) were more common in PAPS.

Treatment

Most patients with SLE made a full recovery following immunotherapy; recurrence was reported in 30%. Most patients with PAPS also recovered after treatment with either anticoagulant, aspirin, or immunotherapy. No clear pattern predicting incomplete recovery emerged in either disease.

In summary, the data show that chorea in SLE-aPL and SLE-APS represents a similar entity. It generally presents with isolated limb involvement, with 1/3 of cases comprising additional neurological features. Imaging is normal in up to 50%, and ANA, LA and aCL antibody positivity is common (rarely β 2GPI). Response to immunotherapy is generally good. Chorea in PAPS seems slightly different. It is more generalised, and over 50% of cases have cerebellar features, migraine or epilepsy. Imaging is normal in up to 75% of cases, and all of LA, β 2GPI and aCL antibodies are generally positive. Outcomes appear less dependent on immunotherapy than in SLE-chorea.

Chorea in other SADs

Sydenham chorea (one of the major criteria for the diagnosis of rheumatic fever) is an immune-mediated para-infectious disorder generally occurring 4-8 weeks following group A beta-haemolytic streptococcal pharyngitis [33]. It remains the most common cause of chorea in children worldwide, though it is now rare outside developing countries, principally due to early antibiotic treatment of streptococcal infections [33]. Age of onset is usually 8-9 years, with female predominance, and chorea generally presents with other systemic features of rheumatic fever (carditis, arthritis), though it can occur alone [33, 34]. Generalised chorea accompanied by hypotonia, motor impersistence, tics and behavioural abnormalities are typical [33]. Though typically monophasic, recurrences may occur in about 1/3 patients, generally as a consequence of re-infection or hormonal changes in the setting of oral contraceptive use or pregnancy (chorea gravidarum) [34].

Chorea in other SADs is rarely reported. Generalised chorea was reported in four cases of Behcet's disease (BD), three cases of Primary Sjögren syndrome (PSS) and five cases of Coeliac disease (CD). In BD, it formed part of a broader neuropsychiatric syndrome alongside typical systemic signs of BD, with periventricular/subcortical T2-hyperintensities on MRI, and an inflammatory CSF (elevated IgG-albumin index or OCB). Response to immunotherapy was good [35-38]. In PSS, onset was subacute, sometimes as the first manifestation of disease, and responded well to immunotherapy [39-41]. In CD, chorea was frequently associated with ataxia. All patients were female (median age at onset 54 years, range 24 – 77). Symptoms sometimes pre-dated other disease manifestations and improved with gluten-free diet, together with reductions in antibodies titres [42, 43]. Other purported associations of chorea with CD were excluded because more

plausible causes were present, e.g. tardive dyskinesia [44], or because a clear association between the two conditions was difficult to draw [45, 46].

Parkinsonism

Parkinsonism can be associated with a variety of SADs. However, its phenotypic manifestations appear relatively uniform within distinct diseases.

PSS-parkinsonism

Between 2017 and 2020, four Taiwanese nationwide, population-based studies evaluated the incidence of idiopathic Parkinson's disease (IPD) in patients with PSS [47-50]. Despite differing methodologies, all found PSS to be associated with increased risk of PD, with adjusted hazard ratios (aHR) ranging from 1.23 to 1.56 [48]. Despite this, reports of parkinsonism in patients with PSS are limited – only ten met our criteria for analysis [51-58].

Epidemiology

Median age at onset was 62.5 years (range, 40 – 74 years); 90% were female. Parkinsonism preceded other PSS manifestations in 70% of cases [51, 53, 54, 56, 57].

Clinical manifestations

In 50% of cases, clinical features resembled IPD (asymmetric akinetic-rigid syndrome, with or without rest tremor) [52-54, 57]. In 30% of cases, there was additional early and prominent gait impairment and cognitive dysfunction, resembling progressive supranuclear palsy-parkinsonism (PSP-P) [51, 55, 58]. One case (10%) presented with asymmetric parkinsonism and visual hallucinations [54], and one other (10%) with symmetric parkinsonism, tremor, balance impairment, psychosis (auditory and visual hallucinations) and sensory ganglionopathy [56].

Investigations

Brain MRI was generally abnormal, showing either diffuse periventricular/subcortical T2-hyperintense lesions (50%) [51, 54, 55], or ischemic lesions in the BG contralateral to the maximally involved side (20%) [51, 57]. Normal scans [53, 58], or mild diffuse cortical atrophy [56], were documented in the other cases. In one patient, ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed bilateral striatal hypometabolism (DAT scan was not performed) [58].

Where performed, CSF showed intrathecal IgG synthesis in 57% of cases [53, 54], but was normal (29%) [51, 58], or non-specific (14%) in the remainder [56].

All reported blood counts were normal. ANA was positive in 67% of patients [51, 53, 55, 58]. Anti-Ro/SSA and anti-La/SSB antibodies, generally positive in 60-70% of PSS patients [59], were both negative in 71% of PSS-parkinsonism cases [51, 52, 56-58], while the remaining cases showed both or only anti-Ro/SSA positivity [53, 55].

Treatment

Six cases received immunotherapy (predominantly steroids), which led to improvement in clinical (and sometimes radiological) features in half [53, 55, 56]. The remainder had null, or very mild improvement [51, 57, 58]. Response to levodopa varied. Some experienced significant benefit, with later motor complications (wearing off) [52], while others reported partial [53], or no response (mostly PSP-P-like cases) [51, 53-55, 58]. One case improved with selegiline and amantadine [57]. Response to dopaminergic therapies supports the idea that at least a subgroup of PSS-parkinsonism patients has co-occurring IPD (see also below).

Parkinsonism in SLE

Parkinsonism in SLE is uncommon, but if present, generally manifests with a young-onset, atypical phenotype. Conversely, the risk of ‘classic’ late-onset IPD seems to be reduced in SLE [60]. Below, we summarise data from 24 cases of SLE-parkinsonism, including one case secondary to probable CNS lupus vasculitis [61].

Epidemiology

Median age at parkinsonism onset was 32 years (range 9 – 74): 58% of cases had onset < 40 years, and most of these had juvenile onset (< 20 years). Females accounted for 88% of cases. In 57% of cases, parkinsonism post-dated the diagnosis of SLE, by anywhere from one week to 18 years [62-71]. In the remainder, parkinsonism preceded the diagnosis of SLE up to 5 years (13%) [72-74], or presented together with findings suggestive of SLE (30%) [61, 75-80]. Neither age of onset nor the interval between the diagnosis of SLE and parkinsonism associated with clinical phenotype or rate of progression.

Clinical manifestations

Onset was generally subacute (77%), or more rarely acute. Two main clinical phenotypes were observed. Parkinsonism was most often isolated, tremulous (81%) and frequently symmetrical (43%) [61, 63-68, 70-72, 74, 78, 80], though classic ‘pill-rolling’ tremor was rarely described [68, 72]. Gait and postural reflexes impairment was reported in 90% of cases, usually presenting very early in the disease course [61, 62, 66, 68, 70, 71, 74, 76, 77, 79]. Cognitive impairment was described in six cases [63, 65, 70, 74, 80], and emotional lability in two [63, 74].

The second, rarer phenotype was of ‘combined parkinsonism’, with additional features such as prominent and early cognitive difficulties and dystonia. Concomitant chorea [73], seizures [63, 66, 67], oculogyric crises [63], pyramidal signs [61, 64, 66, 68, 70, 74, 77], hemiparesis/hemiplegia [66, 76], cranial nerve palsies [72, 77], and mutism [63, 66, 70], were reported in other cases. Behavioural disorders and auditory hallucinations occurred either spontaneously [61, 64] or during steroid therapy [63, 67]. Acute onset of reduced consciousness was also reported [66, 68].

Investigations

Brain MRI findings were heterogenous without clinico-radiological correlations. Nearly half of the cases showed no abnormalities [65, 67-70, 73-75], whereas 37% showed deep WM T2-hyperintensities [61, 66, 71, 76-79]. BG calcification [62, 64, 71], stroke [78] or cerebral atrophy [63], were infrequently seen. Pre-synaptic dopaminergic PET/SPECT imaging was normal in 3/3 cases [73, 77, 80].

CSF analysis was available in 15 cases. Findings were normal in 47% of cases [63, 71, 75-77, 80]. The remainder had non-specific alterations like elevated protein [61, 66, 79], positive IgG index [65] or pleocytosis [67-69].

Blood count (available in 13 cases) demonstrated cytopenias in 85% of cases [61, 64, 66-68, 74-77, 79]. ANAs were positive in all cases [63, 64, 66-79], except for the case of secondary CNS vasculitis-parkinsonism [61], and anti-dsDNAs were present in 70% of cases [63, 64, 66-68, 70-72, 74-76, 80]; aCL were positive in 40% [66, 74, 76, 77] and LA in 50% of cases tested [64, 66, 68, 73, 76], respectively.

Treatment

A good response to immunotherapy was reported in 78% of cases; various combinations of corticosteroids, cyclophosphamide, hydroxychloroquine, azathioprine, mycophenolate, plasma exchange, rituximab, and intravenous immunoglobulin (IVIG) were used [61, 63, 64, 66, 68, 69, 71-77, 79, 80]. Complete recovery occurred in 38% [61, 63, 64, 66, 71, 72, 76], although the improvement was never formally quantified using clinical scales. Radiological improvement (brain MRI/SPECT) was reported in 33% of cases [66, 71, 73, 79, 80]. Levodopa response was seen in 43% of cases [64, 65, 67, 69, 70, 74], in one case with subsequent development of motor fluctuations and peak-dose dyskinesia that were managed with combined thalamic deep brain stimulation and long-term steroid therapy [74].

APS-parkinsonism

APS-parkinsonism is very rare. We identified seven cases of parkinsonism in PAPS [81-86], and one in SLE-APS [87].

Epidemiology

Median age at onset was 53 years (range, 44 – 60, 57% female). Parkinsonism most commonly preceded the diagnosis of APS (71%) [82, 83, 85-87], on average by 4 years (range, 5 months – 6 years).

Clinical manifestations

Parkinsonism was generally asymmetric, subacute in onset and slowly progressive. Gait impairment was frequent [81, 83, 85, 87], and most cases had additional atypical features in line with corticobasal syndrome (CBS) [82, 83, 85, 87] and/or PSP-Richardson syndrome [83, 85-87] phenotypes. One case initially presented with focal dystonia (writer's cramp), and later developed parkinsonism [84]. Systemic manifestations of APS such as livedo reticularis, were present in the majority (71%) of cases [82, 83, 85-87].

Investigations

Brain MRI typically showed both cortical and subcortical ischemic lesions and periventricular WM changes [81, 83-87], sometimes with cortical atrophy [83, 84, 87]. However, one patient with CBS-like parkinsonism had widespread cortical atrophy without ischemic lesions, and normal presynaptic dopaminergic imaging [82]. CSF analysis was reported in only one case, with normal findings [83]. Blood count revealed thrombocytopenia in 67% of cases [82, 84, 86, 87], and was normal in the remainder [83, 85]. All cases were positive for aCL, and 83% for LAs [81-83, 85, 86].

Treatment

Cases were generally unresponsive to treatment with immunotherapy, levodopa or anti-coagulation [81, 83, 85, 86].

Other SAD-associated parkinsonism

Reports of parkinsonism with other SADs are extremely sparse. Rheumatoid arthritis (RA) appears to be associated with an overall lower risk of PD, especially if treated with biologic disease-modifying antirheumatic drugs [88]. Acute parkinsonism has been described in rheumatoid meningitis [89, 90], and two cases describe the development of parkinsonism concomitantly or before the development of RA [91, 92]- these may simply be coincidental. However, RA and PD share common genetic risk variants [93], so their relationship may require further scrutiny, ideally through longitudinal studies. One case of BD-parkinsonism was reported in a 20-year-old man presenting with acute pallidopyramidal syndrome, signs of diencephalic involvement (sleep disturbances), and no response to immunotherapy and levodopa [94]. One case of parkinsonism with neurosarcoidosis was also reported in a 58-year-old woman, likely secondary to BG infiltration [95].

Dystonia

Dystonia is the rarest described movement disorder in SADs, being only infrequently reported in association with PSS (eight cases) [96-101], SLE (two cases) [102, 103], APS (three cases) [104], and CD (one case) [105]. The phenotype associated with PSS-dystonia is described below, whereas details of the remaining are summarised in Table 3.

Though the data is limited, two phenotypes of PSS-dystonia appear to emerge. The first (50% of cases; median age at onset 57.5 years, range 36-67; 75% female) is characterised by subacute and slowly progressive focal or segmental dystonia predominantly affecting the craniocervical region [98-101]. Brain MRI is often normal [99-101] though, one woman with blepharospasm exhibited multiple T2-hyperintense lesions in BG, thalamus, periventricular WM and brainstem [98]. Overall, the response to immunotherapy and possible causative inflammatory CNS lesions observed in some [98-100], may indicate a true disease association rather than coincident primary dystonia.

The second phenotype, occurring in younger individuals (median age at onset 47 years, range 36-57; 75% female) consisted of paroxysmal dystonic attacks involving one or both limbs on one side of the body [96, 97]. The episodes typically lasted less than 2 minutes, occurred several times per day and were painful, reminiscent of painful tonic spasms seen in demyelinating disorders. Interestingly, inflammatory and/or ischaemic lesions were often detected either in the brain [96] or spinal cord [97]. CSF was normal in $\frac{3}{4}$ of these cases [96, 97],

and showed inflammatory changes (OCB-not specified if CSF-restricted, and mild pleocytosis) in one case [97]. Although there is an overlap of PSS and neuromyelitis optica, aquaporin-4 (AQP4) antibodies were not tested in these cases [106]. Full clinical remission was reported in the single case associated with spinal cord infarct [97]. A transient response to phenytoin and steroids was reported in another [97], while in the remaining cases, responses to immunotherapy or symptomatic treatments like carbamazepine and baclofen were mixed [96, 97].

Ataxia

Cerebellar ataxia (CA) is a characteristic feature of two particular SADs, namely CD and BD [107]. As both topics in their own right have been extensively reviewed elsewhere [108, 109], we focus on defining lesser-known associations of ataxia with other SADs.

Gluten-ataxia (GA)

GA is the most frequent neurological disturbance in CD, with estimated prevalence varying between 19%-41% [110]. In specialised tertiary referral centres, GA accounts for a substantial proportion of sporadic ataxias [111]. It is usually cerebellar, though can be sensory [112], and can associate with myoclonus (progressive myoclonic ataxia) [113]. Screening for gluten sensitivity using anti-gliadin IgG and IgA, anti-endomysial (EMA), anti-transglutaminase (TG) 2, and anti-TG6 antibodies (the latter being present in up to 62% in GA compared with 45% in CD) [114], are important in any patient presenting with idiopathic progressive CA [108]. The response to gluten-free diet depends on the duration of ataxia prior to diagnosis [108].

BD-ataxia

Cerebellar ataxia is the most common manifestation of neuro-BD, occurring in 66.7% of BD patients, and generally post-dating the diagnosis [115]. Two phenotypes have been described: acute usually self-limiting ataxia (70%), and chronic progressive ataxia (30%), the latter usually accompanied by cognitive impairment [109, 116, 117]. The acute type mainly affects males (75%), with median age at onset of 39 years (range, 35 – 55) [118-121], whereas the chronic type is more common in females (67%), with similar age at onset [116, 117, 122]. Acute ataxic presentations generally show focal haemorrhagic or ischaemic cerebellar, brainstem or diencephalic lesions on MRI (with or without evidence of vascular occlusion). In contrast, chronic BD ataxia generally shows cerebellar or brainstem atrophy, with or without leukoencephalopathy [109, 116, 117, 122]. Overall, CSF findings are generally non-specific. Acute BD-ataxia responds well to immunotherapy (steroid, cyclophosphamide, or methotrexate) [118-121], but chronic ataxia does not.

SLE-ataxia

Epidemiology

All 20 identified cases of SLE-ataxia were female. Mean age at onset was 28.5 years (range 15 – 71). Ataxia never pre-dated the diagnosis of SLE (65% followed the diagnosis, the remainder occurred at the same time).

Clinical manifestations

Two major ataxic phenotypes were observed:

The first (13/20 cases) consisted of acute, rapidly progressive ataxia, dysarthria, nystagmus, and cranial nerve palsies. Reduced consciousness was reported in 25% of cases. Psychiatric features [123, 124] and systemic manifestations such as fever, diarrhoea and vomiting, were rare [124-128].

The second phenotype (7/20 cases) was characterised by subacute, slowly progressive ataxia with dysarthria or nystagmus [129-135]. Cognition and psychiatric profiles, when described, were normal.

Investigations

In the acute SLE-ataxia group, MRI and CSF analysis generally segregated into one of two profiles:

- 1) Ischaemic lesions in the cerebellum/brainstem (31%), mostly associated with normal or non-specific CSF findings [126, 136-138];
- 2) Reversible, edematous lesions in the cerebellum/brainstem (31%) or bilateral temporal and frontal lobes (8%), associated with non-specific or inflammatory CSF changes (pleocytosis) [123-125, 127, 136].

MRI in the remainder showed generalised atrophy [139], non-specific T2-hyperintense subcortical lesions [136], or no abnormalities [126].

The most frequent blood count abnormalities were leukopenia and anemia. ANAs were positive in all tested cases, and anti-dsDNAs positive in 55%. Antiphospholipid antibodies, when tested, were rarely positive (aCL, tested in 9 out of 13 cases, positive in 33%; LA, tested in 7 out of 13 cases, positive in 29%).

In the chronic-progressive subtype, six out of seven showed cerebellar atrophy on MRI [129, 130, 132-135] and one had normal neuroimaging [131]. CSF analysis showed inflammatory changes (elevated IgG index or unmatched OCBs) in 80% of cases [131, 133-135] and no abnormalities in the remainder [130]. Autoimmunity panel showed positive ANA and anti-dsDNA in 83% of cases [129-134], while antiphospholipid antibodies (LA, anti- β 2GPI, or aCL) were positive in 20% of cases [129, 131, 133].

Treatment

Complete or almost complete clinical and radiological recovery after immunotherapy was reported in 85% of acute ataxia cases [124, 125, 127, 136, 138, 139]. Some patients relapsed during steroid tapering but responded to dose increments [127, 136]. A good response to immunotherapy was reported in a smaller proportion (57%) of subacute ataxias [131-134], with the remainder displaying only a partial response [129, 130, 135].

PSS-ataxia

Peripheral sensory ataxia, secondary to sensory neuropathy or neuronopathy, is a classic feature of PSS [140]. In contrast, CA secondary to CNS involvement is rare (17 cases reported) [141-153]. Below, we discuss the latter.

Epidemiology

Median age at onset was 44 years (range, 9 – 65). Most were female (82%). Ataxia presented alongside PSS symptomatology in 56% of cases [141-143, 146, 149-152], and more rarely after (5 months to 5 years) [144, 147, 152] or before (weeks to 1-year) PSS diagnosis [145, 148].

Clinical manifestations

Onset of ataxia was either subacute (55%) or acute (45%). Symmetrical involvement was the norm (89%) and gait ataxia universal (100%). Additional signs such as dysarthria, nystagmus, dysmetria and intention tremor were present in 87.5% of cases; extracerebellar features (e.g., weakness, peripheral sensory abnormalities, hyporeflexia) were rarely reported [148]. Cognitive and/or psychiatric abnormalities were reported in 30-40% [142, 146, 148].

Investigations

The main MRI finding was cerebellar atrophy (59%) [143, 145-148, 150, 152]. Other findings included cerebellar/brainstem oedematous lesions [144, 151] or non-specific WM changes [141, 142, 149]. In three cases, 18 F-FDG PET revealed cerebellar hypometabolism [146, 152].

Inflammatory CSF changes (OCB, pleocytosis) were reported in 46% of cases [142, 149, 152], followed by normal findings (31%) [144, 147, 151, 152] and non-specific abnormalities (23%) [141, 143, 148].

ANA and anti-Ro/SSA and/or -La/SSB antibodies were positive in 93% and 100% of cases, respectively; anti-dsDNA and aPL antibodies were mostly negative.

Treatment

Response to immunotherapy (steroid \pm cyclophosphamide/IVIG) was good (clinical and/or radiological improvement) or moderate (clinical and/or radiological stability) in 81% of cases [141-145, 148-152], whereas in the remainder, symptoms progressed [146, 147, 152].

Other SAD-associated ataxias

One case of ataxia, dementia and parkinsonism associated with PAPS was reported, but the authors noted the possible coincidence of two separate disorders [154]. Another case described acute, recurrent, steroid-responsive cerebellar ataxia in a young girl with positive aCL antibodies but not meeting PAPS diagnostic criteria [155]. Ataxia was also described in immunocompromised patients with RA treated with various drugs, e.g. methotrexate, as a result of leukoencephalopathy or encephalitic process [156, 157], but no cases showed a direct association between ataxia and RA.

Myoclonus

Progressive myoclonus ataxia has rarely been reported in association with CD. Twenty such cases are reviewed here [113, 158-163].

Epidemiology

Median age at onset was 52.5 years (range, 34 – 76) and 70% were male.

Clinical manifestations

Myoclonus preceded other disease manifestations in 59% of cases. It mainly affected the limbs, being most prominent on action, and was always accompanied by ataxia. Less commonly, spontaneous and/or stimulus-sensitive (to touch, pinprick and tendon taps) myoclonus was observed. Up to 30% of patients reported seizures.

A more complex syndrome presenting earlier in life (usually childhood), and characterised by prominent epilepsy, accompanied by ataxia and myoclonus, thus falling in the category of progressive myoclonic epilepsy, has also been associated with CD [164, 165]. One isolated case of opsoclonus-myoclonus and ataxia associated with CD has been described as the initial manifestation of CD in a 2-year-old boy [166].

Investigations

The most common brain MRI abnormality was cerebellar atrophy (65% of cases). Duodenal biopsies were suggestive of CD in all cases but one [160]. Serologic findings were difficult to interpret as antibody testing was not performed in all cases and many cases pre-date the introduction of newer assays, e.g. for anti-TG 2/6 antibodies. Neuropathological findings in three cases showed prominent loss of Purkinje cells and marked Bergmann gliosis [113, 163]. When performed, electrophysiological findings supported a cortical origin of myoclonus.

Treatment

Neurological function generally did not improve following gluten-free diet, immunotherapy or treatments for cortical myoclonus (benzodiazepines, levetiracetam etc.).

Other than the main association with CD, myoclonus has also been reported as a neurological manifestation of SLE, including as a presenting feature [72].

Paroxysmal movement disorders

In addition to the likely secondary paroxysmal dystonic attacks (possibly tonic spasms) described above in PSS, other paroxysmal movements have been rarely described in SADs.

Paroxysmal non-kinesigenic dyskinesia (PNKD) was reported as a presenting feature of PAPS in a 29-year-old woman. Involuntary movements reduced after starting anticoagulants and stopping oral contraceptives [167]. Another case of paroxysmal dysarthria-ataxia in PAPS is also described [168].

Two cases of CD presenting with PNKD were described; in both, the gluten-free diet completely resolved the episodes [169, 170]. Intriguingly, a similar entity of ‘paroxysmal gluten-sensitive dyskinesia’ has been recently recognized in other mammalian species (border terriers) [171].

A single case reported a 47-year-old man, with a 5-years history of BD presenting with paroxysmal dysarthria-ataxia; investigations showed periventricular WM and brainstem T2-hyperintense lesions and human leukocyte antigen (HLA)-B5 positivity. Full remission was achieved with carbamazepine [172].

Nocturnal paroxysmal attacks characterized by abdominal muscle contraction, followed by cervico-brachial dystonic jerks, lasting 10–20 seconds and occurring 3–5 times per night were described in a 39-year-old woman during a relapse of BD. Brain MRI and video-EEG recordings during the attacks were normal. The attacks remitted with steroid treatment [173]. Acute onset of unilateral paroxysmal dystonic attacks involving the perioral region and arm, lasting 15–30 seconds and occurring 10–20 times a day, was reported in a 21-year-old woman with a 3-year history of BD. Brain MRI showed a thalamic lesion ipsilateral to the affected arm. An excellent response to steroids with complete resolution of attacks was reported [174].

Tremor

One report suggested that CD patients show a higher prevalence of tremor compared to controls (28% vs 14%) [175]. Palatal tremor was described in BD [176] and in CD alongside ataxia [177]. In a cohort of SLE patients with neuropsychiatric involvement, 20% showed bilateral postural and action tremor [178], but this has not been replicated in other cohorts. Finally, a complex postural limb tremor with superimposed myoclonic jerks was described in one patient with APS [83].

Tics

Tics appear not to be associated with SADs, having been reported only in single cases of SLE [14], APS [83] and CD [179].

CONCLUSIONS, OPEN QUESTIONS AND FUTURE PERSPECTIVES

Our review of the literature suggests a broad spectrum of movement abnormalities in SADs and provides a framework for clinicians to approach such cases. Oftentimes, movement disorders post-date diagnosis of SADs or occur contemporaneously with other systemic manifestations. In these instances, the possibility of an association is usually evident from the history or clinical examination (see Table 1). In cases where movement disorders occur as the initial manifestation of the SAD, arriving at a diagnosis can be more challenging. In these situations, suggestive patient demographics e.g. young females, unusual movement disorder syndromes (e.g. isolated foot myoclonus in CD), abnormal brain imaging or abnormal laboratory investigations are useful clinical clues. Further workup of such cases varies according to the likely underlying disorder (Panel 1), and we find it useful to refer to established diagnostic criteria for individual SADs, which are summarised in Supplementary Material [180–186].

Though overall rare (and possibly underrecognized), awareness of the specific movement disorder phenotypes in SADs is critical for many reasons. First, their appearance often pre-dates SAD diagnosis; knowledge of these associations may prompt an earlier diagnosis of SAD with the respective treatment implications. Second, SAD-movement disorders are potentially treatable, and generally, the earlier a specific treatment is started, the better the long-term outcomes. Third, investigations including MRI and CSF analysis are frequently normal, which may provide a false sense of reassurance. Finally, phenotypically distinct movement disorders within individual SADs may exhibit different responses to immunosuppressive treatments, suggesting distinct pathomechanisms, even within a given disease.

Indeed, although the occurrence of movement disorders in SADs has been long recognised, they are far from being understood. In some cases, there is a direct link with inflammatory lesions causing specific movement disorders (for instance, BD-ataxia with inflammatory cerebellar lesions). In other entities, direct pathogenicity of the rheumatological antibody is – often controversially – discussed. While there has been a suggestion of tissue TG antibodies to be directly pathogenic [114], a subsequent study challenged this assumption [187]. In contrast, serum aPL antibodies may be causative of chorea in SLE [188], as they might exert a direct neural damage by binding the brain endothelium and inducing endothelial dysfunction, leading to microthrombosis, blood vessel inflammation, and disruption of the blood-brain barrier (BBB) [189].

Co-occurring autoimmunity is likely to be the explanation in some cases, e.g. paroxysmal dystonia in PSS. These phenomena are likely to represent the classic painful tonic spasms in neuromyelitis optica with AQP4-antibodies, as the association between both diseases is very strong [106].

However, there may be also other mechanisms at play. Increasing evidence suggests a pathogenic role of inflammation and/or autoimmunity in IPD [190-192], which is supported by genetic pleiotropy with genes associated with autoimmune diseases [93]. For instance, IPD appears to be associated with PSS, and animal models suggest at least some shared disease pathomechanisms involving inflammatory pathways. High-mobility group box 1 (HMGB1)/nuclear factor kappa B (NF- κ B)/ toll-like receptors (TLR) pathway is responsible for inflammation in PSS and is also critical in IPD pathogenesis [193]. Serum HMGB1 and TLR4 levels are significantly increased in IPD patients [194]. In PD animal models, antibodies against HMGB1 reduce inflammation by maintaining BBB integrity and reducing inflammatory cytokines secretion [195]. Similarly, in PSS animal models, the suppression of HMGB1 ameliorates xerostomia via suppressing HMGB1/TLR4/NF- κ B signaling pathway [196]. Another example of a link between SADs and movement disorders is Aicardi-Goutières syndrome (AGS), a genetic interferonopathy typically manifesting in early childhood with developmental delay, dystonia, encephalopathy and basal ganglia calcification. A number of genes can cause AGS, amongst some of which are recognised to confer also susceptibility to SLE or chilblain lupus (e.g., *TREX1*, *SAMHD1*) [197].

It may also be that some SAD-movement disorders are multifactorial. For example, among the many functional models of dystonia that have been proposed, the ‘two-hit’ rodent model of blepharospasm involved superimposing an environmental trigger (dry eye) on minimal striatal dopamine depletion [198]. Dry eyes secondary to PSS may similarly represent the environmental ‘hit’ that predisposes to the development of blepharospasm in these patients, who may have a subclinical dopaminergic deficit [199].

In summary, while the exact pathomechanisms may be unclear, these examples demonstrate that the pathophysiology of movement disorders in SADs may be more complex than just lymphocytic infiltration or antibody binding. We hope that this review will promote further longitudinal studies to examine the possible disease associations described herein. If confirmed, dissecting causative pathomechanisms may improve our understanding of the disease and open up new avenues for treatment.

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