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Overview of management of infection-related movement disorders with focus on specific-infections

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ABSTRACT

Infections are important treatable causes of secondary movement disorders (MD) that can have heterogeneous presentations. According to various studies, infection-related movement disorders (IRMD) account for around 10–20% of secondary MD. Certain infections have a predilection for causing various MD, and some MD phenomenologies, such as acute cerebellar ataxia and opsoclonus-myoclonus-ataxia syndromes (OMAS), suggest a strong possibility of an underlying infectious cause. The underlying pathophysiology is multifaceted, including direct neuronal damage due to neurotropism, granulomas, abscesses causing structural damage, and inflammatory and autoimmune responses triggered by infections. Understanding the prevalence, spectrum, and pattern of these IRMD and common infections that are responsible helps in early diagnosis, and instituting appropriate, timely treatment, thereby improving the overall prognosis and avoiding unnecessary investigations. In this review, we aim to provide a brief overview of common infections associated with MD, common clinical presentations of IRMD, their underlying pathophysiology, and overall approach to their treatment, with a focus on specific treatments of prevalent and treatable IRMD.

1. Introduction

Infectious diseases, especially neurological infections as a whole contributes towards significant morbidity and mortality. With improving prevention and management strategies the burden is decreasing but is still a major concern in tropical and poor socio-economic countries. Infections are one of the common causes of secondary movement disorders accounting for around 10–20 % of secondary MD, according to various studies [1–4]. The prevalence, spectrum and pattern of IRMD may vary based on the nature of the infections, host factors, geography, latency from the infections to the development of MD, and the underlying mechanisms of developing MD. Understanding the role of these factors in IRMD helps in early diagnosis and instituting appropriate, timely treatment, thereby improving the overall prognosis. It also aids in ruling out IRMD with reasonable certainty to focus on the possible alternative etiology. Although the concept of IRMD is well established, literature about the prevalence, patterns, prognosis, and management of them are limited. There are various studies with specific focus on a particular syndrome such as post-encephalitic parkinsonism, Sydenham's chorea, post-infectious ataxia etc. or specific infections such as movement disorders in human immunodeficiency virus infection, tuberculosis, neurocysticercosis, post infectious cerebellar ataxia etc. [5–9]. However, literature on IRMD prevalence, pattern, prognosis and management as a whole is lacking [1,4,10,11]. This narrative review aims to provide a brief overview of the common infections associated with MD, their common clinical presentations, underlying pathophysiology, and overall approach to their treatment, emphasizing specific treatments of prevalent and treatable IRMD.

2. Infections commonly associated with movement disorders

MD can be observed in varying frequency in almost all neuroinvasive infections. However, some infections (Fig. 1) are commonly considered in the differential diagnosis of MD due to their higher propensity to involve basal ganglia (e.g. flavivirus, toxoplasmosis); owing to classical phenomenological presentation with particular infections (e.g. varicella, malaria or enteric fever in post-infectious cerebellar ataxia, post-streptococcus Sydenham chorea (SC) in pediatric acute onset chorea, various infections in opsoclonus-myoclonus-ataxia syndrome or OMAS); or the infection is quite prevalent in a region and is known to cause MD (e.g. tuberculosis, neurocysticercosis etc.) (Fig. 1).

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Among the bacterial infections, group A beta-haemolytic streptococcus (GABHS), *Mycobacterium tuberculosis*, *Treponema pallidum* and *Tropheryma whipplei* are commonly associated with MD. In addition, other bacteria such as *Salmonella typhi*, *Orientia tsutsugamushi*, *Mycoplasma pneumoniae*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Corynebacterium diphtheriae*, *Clostridium tetani* and meningitis secondary to *Neisseria meningitides*, *Hemophilus influenza*, *Streptococcus pneumoniae* [6,11–22] have also been reported to result in MD. Viral encephalitis can result in MD either during the acute state or as a part of post-encephalitic sequelae [23]. Flaviviruses (Japanese encephalitis virus (JEV), dengue virus, West Nile virus (WNV)) has a predilection to affect basal ganglia structures resulting in dystonia-parkinsonism [9,23–26]. Herpes simplex virus (HSV), varicella, mumps, measles, enterovirus, Influenza-A, Epstein-Barr virus and other viral infections can cause acute ataxia, OMAS and chorea-dystonic syndromes [10,11,27–29]. Recently coronavirus disease 2019 (COVID-19) and congenital Zika virus-related MD have also been reported [30–32]. Human immunodeficiency virus (HIV) related MD can be directly due to HIV encephalopathy or secondary to opportunistic infections. Other infections that can lead to IRMD are parasitic (cerebral malaria and neurotoxoplasmosis), helminthic (neurocysticercosis), and fungal infections (cryptococcosis and histoplasmosis) [5,18,29,33–39]. Creutzfeldt-Jacob disease, a neurodegenerative condition caused by an abnormal infectious prion protein, can also manifest with MD, including myoclonus, ataxia and parkinsonism. Unfortunately, the disease is rapidly progressive and fatal, with no treatment available [40].

3. Pathophysiology of infection related movement disorders

It is paramount to know about the underlying pathophysiology in the management of IRMD. Apart from the responsible organism, the management also depends to a large extent on the mechanism with which these infections are leading to a particular MD. There are multiple mechanisms by which IRMD can develop as illustrated in Fig. 2. In many cases there may be multiple mechanisms in action for a single organism, for a particular clinical presentation or even in a particular patient. For example, tuberculosis can result in parkinsonism secondary to tuberculoma of basal ganglia, vasculitis infarctions due to basal meningitis or secondary to hydrocephalus [6]. Similarly, chorea can be due to space occupying lesion in central nervous system (CNS) toxoplasma abscess, direct neuronal injury in HIV virus encephalitis or secondary to autoimmune process as in SC or post-HSV NMDA encephalitis [9,37,38,41]. Ataxia in a patient with AIDS can be due to HIV induced cerebellar dysfunction, progressive multifocal leukoencephalopathy (PMLE) by JC virus infection, efavirenz toxicity or a varying combination of all [37,42–44]. Management may depend on the underlying suspected organism, phenotype, possible mechanism in action and host factors.

Post-infectious mediated aberrant inflammatory response plays an important role in the pathophysiology of IRMD as evident by self-limiting nature and steroid responsiveness noted in some of the IRMD. There are multiple mechanisms by which an infectious pathogen can induce autoimmunity. Molecular mimicry is an immunological phenomenon where epitopes present on pathogens may mimic or can be similar to a peptide sequence of host antigens thereby misdirecting the activated host immunity to aberrantly act against the host antigen and resulting in autoimmune process. Sydenham chorea is a classic example of this phenomenon where it is shown that antibodies against group-A streptococcal carbohydrate cross-react with human neuronal cells resulting in chorea [8,45]. Second mechanism is epitope spreading where the initial highly specific immune response against an antigen gradually broaden during the inflammation to include new epitope in the same antigen or the release and presentation of "hidden" auto- antigens encountered during tissue injury. Apart from molecular mimicry, this mechanism is also postulated in post herpes simplex encephalitis trigger anti-NMDA receptor encephalitis [46]. Third mechanism is bystander activation wherein apart from anti-dependent activation of immune response to a highly virulent pathogen, lymphocytes, especially T-cells can get activated via in an antigen-independent manner that can result in cytokine storm [47,48]. This can result in dysfunction of blood brain barrier and neuronal dysfunction as seen in for example post-malarial ataxia, dengue related neurological syndromes and more recently COVID-19 related neurological syndromes [49,50]. The fourth mechanism is persistent infection induced polyclonal B-cell activation that may result in the production of autoantibodies that contribute to the development of autoimmunity as seen in for example hepatitis C virus [51].

4. Approach to a patient with suspected infection related movement disorders

While approaching a patient with suspected IRMD, the important step is to characterize the phenotype which aids in identifying the possible organism, planning the appropriate investigations and initiating timely empirical therapy. In some cases, the causative organisms may not be identified at all. The therapy must be initiated and continued only on the circumstantial evidence or based on the classical presentation of a particular syndrome (e.g., SC, OMAS, pediatric acute cerebellar ataxia etc.). In a patient with recent onset of MD, presence of systemic signs of infection such as fever, rashes or skin lesions, lymphadenopathy, hepatosplenomegaly, unexpected weight loss, or multi system involvement should raise a possibility of infection [10]. Neurologically, acute to subacute onset focal neuro deficits, encephalopathy, meningeal signs, new onset seizures, multiaxial neurological involvement suggest a possibility of infectious etiology. Infections should be considered in differential diagnosis in certain MD syndromes such as pediatric onset chorea, acute to subacute onset pediatric cerebellar ataxia, OMAS, MD after acute encephalitis or during or after a systemic infection etc. [1].

The temporal association of infection and development of MD may vary from presentation concurrent to infection with acute direct neuronal injury (JEV, WNV, abscess), can be delayed by weeks to

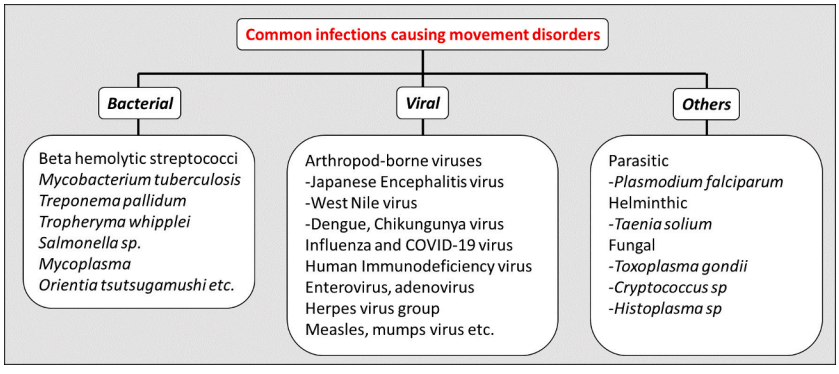

Fig. 1. Common infections causing movement disorders.

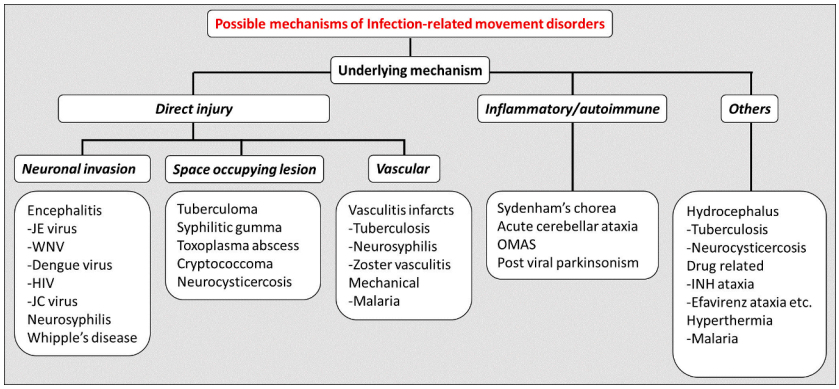

Fig. 2. Postulated mechanisms of Infection related movement disorders.

months in those with autoimmune/inflammatory mechanism (e.g.: SC, opsoclonus myoclonus ataxia, acute ataxia, post-herpes autoimmune encephalitis etc.) or by years in case of latent dormant organism or slow virus infections such as HIV associated MD, SSPE, latent neurosyphilis, Whipple's disease etc. [10]. The presentation can be as isolated phenomenology such as SC, post-infectious cerebellar ataxia, hemiballismus or can be with mixed MD as often seen in post-encephalitic MD and OMAS. Often, there are other associated neurological involvement such as cognitive-behavioral impairment, seizures, pyramidal signs etc. Certain infections such as JEV, WNV may spontaneously remit but often with devastating and debilitating sequelae [25,26]. In this regard, it is important to note that applying severity and disability scales for various phenomenologies are important at the onset. To name a few, Unified Parkinson's disease rating scale for parkinsonism, Burke-Fahn-Marsden dystonia severity rating scale for dystonia, Fahn-Tolosa-Marin scale for tremor, Universidade Federal de Minas Gerais (UFMG) Sydenham's Chorea Rating Scale (USCRS), unified myoclonus rating scale for myoclonus, and International cooperative ataxia rating scale (ICARS) or scale for assessment and rating of ataxia (SARA) for ataxia. This will help in objectively evaluating the progression and take necessary and appropriate step based on whether there is improvement, stabilization or worsening of various phenomenologies over the course of the disease.

5. Overview of management of infection related movement disorders

Prompt and appropriate management strategy is essential in improving favorable long-term outcomes. The treatment can be challenging due to non-availability of infection specific therapies, inability to identify the causative pathogens, lack of evidence-based guidelines for preferred regimen and duration of therapy, and uncertainty regarding risk–benefit ratio in instituting immunomodulating therapies. Despite these challenges, complete to near complete recovery can be expected in patients with IRMD with institution of early appropriate management [18,52,53]. The management of IRMD is often multipronged and includes early initiation of antimicrobial therapy when available, symptomatic therapy of the underlying MD, correction of the underlying contributing factors, prevention of recurrence and immunomodulation in cases with underlying inflammatory pathophysiology (Figs. 3 and 4).

Effective antimicrobial agents are available for most of the organisms except for viruses. These are essential in the management of IRMD when

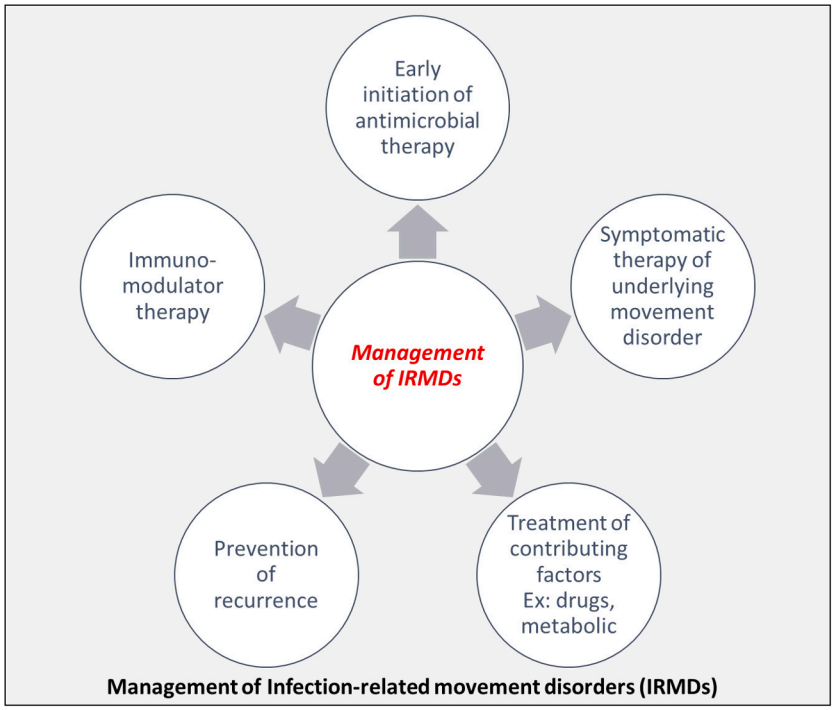

Fig. 3. Multifaceted management approach of infection related movement disorders.

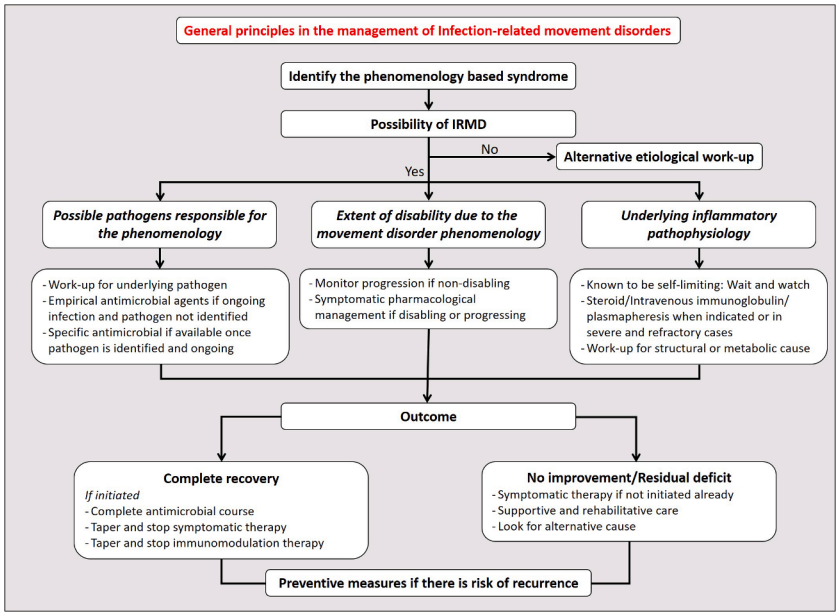

Fig. 4. Flowchart depicting general principles in the management of infection related movement disorders.

the infection is active and ongoing. The drug of choice, route of administration and the duration of therapy may vary based on the presence or absence of neurological involvement (e.g., cerebral malaria, neurosyphilis, CNS-TB etc.) However, specific guidelines regarding the management in the presence of neurological involvement compared to those without, are lacking. Barring few viruses, antiviral therapy for many viruses such as Flavivirus are not available and often the management is only symptomatic. Antimicrobial treatment or some of the common infections known to cause MD are listed in Table 1.

Understandably, whenever possible, symptomatic treatment (Table 2) of the underlying MD semiology is the mainstay of management of IRMD. However, in cases where the symptoms are known to be transient and non-disabling, watchful approach may be sufficient. For instance, in cases with parkinsonism related to infections, dopaminergic medications may be warranted for a short-term for disabling parkinsonism till the symptoms resolve. However, in cases where the MD are expected to be long lasting or persistent as in post-encephalitic MD, long term medications are necessary to improve the quality of life. Other options that are uncommonly used for drug refractory secondary MD includes botulinum toxin for focal or segmental dystonia and myoclonus, and functional stereotactic surgeries such as lesioning and deep brain stimulation for dystonia and tremor [54,55].

Immunomodulators such as steroid, intravenous immunoglobulin (IVIg) and plasmapheresis are frequently used in various IRMD with inflammatory/autoimmune pathophysiology. However, when the symptoms are mild, non-disabling and are expected to resolve completely with the control of underlying infections, symptomatic therapy and appropriate antimicrobials are often sufficient [21,28,56]. The phenotype, patient's comorbidities, presumed underlying pathophysiology and the risk benefit ratio should be considered before deciding the need for immunotherapy. In view of the paucity of robust clinical trial data, the decision must be made after discussing these with the patient and the caregiver. Spontaneous remissions without immunotherapy are known in many of these disorders [21,26,57]. However, few studies have shown early remission, reduced risk of relapse and improved long-term disability with immunotherapy [56–59]. In cases with suboptimal response to these first line immunotherapies or in those where relapses are expected, second line or long term immunomodulators such as azathioprine, mycophenolate mofetil, rituximab or cyclophosphamide have been used provided the underlying infection is resolved [59].

6. Management of specific infection-related movement disorders

6.1. Sydenham chorea

Sydenham chorea, also called as Sydenham disease, is the commonest cause of chorea in children in the endemic region [10,52]. It is an autoimmune disorder with typical age at onset of 8–15 years, and occurs in response to GABHS pharyngitis. Unlike other cardinal manifestations of ARF, chorea can develop in 10–30 % of patients with acute rheumatic fever (ARF) after a prolonged latency of 1 to 6 months [10,11,53]. The chorea is of brief and jerky in nature, rapidly generalizes but 20 % of cases can remain with hemichorea (Video 1) [11]. It is often associated with other motor signs in the form of dysarthria, hypotonia, motor impersistence, tics, imbalance, ballism, dystonia and other MD [58]. Rarely, the hypotonia and chorea may be severe to result in bedridden state labelled as "chorea paralytica". Neuropsychiatric symptoms are also not uncommon [58]. Associated systemic symptoms such as cardiac involvement can be seen in around two-thirds of the cases and arthritis in around one-thirds [58]. The antibodies against GABHS cross-react with either neuronal extracellular surface and/or intracellular antigens especially in the basal ganglia through the process of molecular mimicry. Diagnosis is often clinical owing to the prolonged latency of chorea and often absence of other cardinal manifestations of ARF and evidence of antecedent GABHS pharyngitis. Investigations includes cardiac evaluation, blood investigations for evidence of inflammatory markers and antistreptococcal antibody titer, and imaging mostly to rule out alternative causes. Antistreptococcal titers can be elevated in 15–30 % of the cases [58]. MRI brain is often normal except for mildly enlarged basal ganglia structures in a few and rarely T2 hyperintensity of basal ganglia.

Chorea is expected to resolve over 1–6 months with good recovery, but persistence of chorea for 2 years has been reported by a study in up to 50 % of the cases[60,61]. Recurrences are not uncommon and can occur in 15–40 % of the cases with common triggers being poor adherence to secondary prophylaxis, oral contraceptive agents and pregnancy [60]. Management of SC involve three steps [8]:

i. Antibiotic treatment for streptococcus
ii. Symptomatic control of the chorea
iii. Immunotherapy to control immune and inflammatory response

Table 1
Antimicrobial and immunomodulatory therapy for common infections causing movement disorders.

Organism	Antimicrobial or immunomodulator regimen	Common presentation	Differential diagnosis	Predisposing features
Bacterial infection				
Beta haemolytic streptococcus (Prophylaxis)	*Acute infection and secondary prophylaxis* Penicillin G Benzathine - IM – 1.2 MU (0.6 MU if weight < 27 kg) Every 3–4 weeks for – 5 years or 18 years of age without carditis – 10 years or 21 years of age with mild carditis - Lifetime with moderate or severe carditis Alternative antibiotics Penicillin V-Oral-500 mg twice a day for 10 days f/b 250 mg daily OR Azithromycin-Oral-500 mg/d (12/mg/kg/d) for 5 days f/b 250 mg/d (6 mg/kg/d) *Immunotherapy in severe/paralytic chorea* Prednisolone - Oral – 1–2 mg/kg/d – 1–4 weeks followed by taper over 4–6 weeks OR Methylprednisolone - IV – 25–30 mg/kg/d (maximum 1000 mg/d) for 3–5 days followed by oral steroid taper	Sydenham chorea, hypotonia, motor impersistence, tics, ballism, dystonia	*Inflammatory/ autoimmune:* SLE, APLA syndrome, NMDA encephalitis etc. *Metabolic:* dyselectrolytemia, thyroid abnormality, hypoparathyroidism, polycythaemia vera. *Vascular: Stroke,* Moyamoya syndrome, post-pump chorea *Child onset genetic chorea* *Other infections:* Diphtheria, CNS toxoplasmosis, tuberculosis *Others:* Toxins like manganese, paraneoplastic	Endemic region, poor socioeconomic status
CNS Tuberculosis	Intensive phase of HRZE is followed by acontinuation phase of HR(E) for a total of 12–18 months With steroids in stage-2 and 3 for around 8 weeks	Parkinsonism, tremor, chorea, dystonia, ataxia	*Other structural causes:* bacterial or fungal abscess, tumour, infarcts, haemorrhage *Metabolic, toxins*	Immunocompromised state, poor socioeconomic state, endemic region
Neurosyphilis	Aqueous Penicillin G - IV – 3–4 MU every 4 h for 14 days OR Ceftriaxone - IV – 2 gm twice a day – 14 days	Parkinsonism, chorea, tremor, myoclonus, and rarely ataxia and dystonia	Chronic manifestations associated with tertiary neurosyphilis can mimic various inflammatory and neurodegenerative causes	Immunocompromised state, history of sexually transmitted disease
Whipple's disease	Ceftriaxone - IV – 2 gm twice a day – 2–4 weeks OR Aqueous Penicillin G - IV – 3–4 MU every 4 h Followed by maintenance phase of TMP-SMX – 160/800 mg daily for a total of 1 year	Parkinsonism, ataxia, oromandibular myorhythmia, myoclonus	Owing to slow progression, can mimic various autoimmune/inflammatory and neurodegenerative conditions like dementia, atypical parkinsonism	Old age, occupational exposure to farm, animals, sewage, impaired immune response
Enteric fever	Ceftriaxone - IV – 1–2 gm twice a day for 10–14 days OR in case of resistance strain Meropenam - IV – 1–2 g thrice daily for 10–14 days	Ataxia, myoclonus	Other causes of post-infectious cerebellar ataxia and acute ataxias such as metabolic, toxin, structural, vascular	Poor hygiene and sanitation, endemic region
Scrub typhus	Doxycycline - IV/oral – 100 mg twice daily for 7–10 days OR Azithromycin - IV/oral – 500 mg daily for 5–7 days	Ataxia, myoclonus, tremor	Other causes of post-infectious cerebellar ataxia and OMAS.	Endemic region, travel to tropical countries
Mycoplasma	Azithromycin - IV/oral – 500 mg daily for 5–7 days	Ataxia, myoclonus, choreoathetoid movements, parkinsonism	Other causes of post-infectious and inflammatory cerebellar ataxia, OMAS, chorea and parkinsonism.	Crowded environment
Viral infections				
HIV	Recommended regimen of HAART according to the regional guidelines	Parkinsonism, ataxia, myoclonus, chorea, tremor	Other chronic neuroinfections such as neurosyphilis, neuro Whipple's, insidious onset can mimic other inflammatory and neurodegenerative disorders	Unprotected sex with multiple partners, sharing needles, IV drug abuses
HSV, VZV	Acyclovir - IV – 10 mg/kg thrice daily for 2 weeks	Chorea, stereotypies, ataxia	Autoimmune encephalitis, other acute causes of chorea, and other post-infectious causes of ataxia	Age; immunodeficiency
Others				
Severe Malaria	Artesunate - IV followed by oral – 2.4 mg/kg at 0, 12 and 24 h followed daily once for 7 days OR Quinine - IV in 5 % dextrose – 20 mg/kg loading dose followed by 10 mg/kg thrice a day for 7 days	Ataxia, tremor, myoclonus	Other causes of post-infectious and non-infectious causes of acute ataxias and OMAS.	Endemic region, travel history to endemic regions, old age.
Neurocysticercosis	Should be given along with steroid cover and antiepileptic.To be avoided in severe cerebral edema, raised intracranial pressure leading to herniation or ocular cysticercosis.	Choreo-ballism, dystonia, parkinsonism	Other space occupying lesions involving basal ganglia ex: tuberculoma, toxoplasmosis, bacterial abscess etc.	Poor personal hygiene, poor sanitation, eating undercooked beef or pork.

(*continued on next page*)

Table 1 (*continued*)

Organism	Antimicrobial or immunomodulator regimen	Common presentation	Differential diagnosis	Predisposing features
	Parenchymal – 1–2 viable cysts Albendazole - oral – 15 mg/kg divided twice daily (maximum 1200 mg/d) for 10–14 days Parenchymal - >2 viable cysts Albendazole as above with Praziquantel - Oral – 50 mg/kg/d in three divided doses for 1–14 days Ventricular cysticercosis - Surgical removal preferrable minimally invasive approach if feasible, followed by cysticidal therapy till radiological resolution of cysts			
CNS toxoplasmosis	*Induction phase*Sulfadiazine (1000 mg for weight < 60 kg, 1500 mg if > 60 kg) four times dailywith pyrimethamine (200 mg loading dose followed by 50 mg/d if < 60 kg, 75 mg/d if > 60 kg) and Leucovorin (10–25 mg/d) for 6 weeks *Continuation phase*Sulfadiazine (100–1500 mg twice a day) with Pyrimethamine (25–50 mg/d) and Leucovorin *Alternative*TMP-SMX (5 mg/kg TMP and 25 mg/kg SMX twice daily) induction phase followed by TMP-SMX (160/800 mg) twice daily as continuation phase *OR*Sulfadiazine can be replaced by Clindamycin (oral or IV – 600 mg four times daily followed by twice daily)	Hemiballismus	Other space occupying lesions involving basal ganglia ex: tuberculoma, neurocysticercosis, bacterial abscess etc.	Immunocompromised state
CNS Cryptococcosis	*Induction therapy* Amphotericin 3–4 mg/kg plus Flucytocin25 mg/kg PO four times daily till CSF culture is negative *Consolidation phase* Fluconazole 400 mg daily for at least 8 weeks *Maintenance phase* Fluconazole 200 mg daily for at least 12 months and CD4 count > 200 cell/micL for at least 6-months	Hemiballismus, parkinsonism	Other space occupying lesions involving basal ganglia ex: tuberculoma, toxoplasmosis, bacterial abscess etc.	Immunocompromised state
Immunomodulators				
Post infectious cerebellar ataxia	Often self-limiting without immunotherapy. Steroid or IVIg can be considered if persistent after 1–2 weeks or is severe and disabling at the onset Methylprednisolone - IV – 25–30 mg/kg/d (Maximum 1000 mg) for 3–5 days IVIg – 2 gm/kg given over 3–5 days	Ataxia, vomiting, irritability, headache.	Other causes of acute ataxia such as vascular, drugs and toxin induced, metabolic, autoimmune disorders etc.	More common in children
OMAS	Most often require immunotherapy at the onset. If mild can be managed conservatively with strict monitoring for improvement *First line*Steroid (preferable IV at a dose mentioned above) followed by oral steroid with or without IVIg or Plasmapheresis *Second line* Rituximab or cyclophosphamide if there is no response by 2–4 weeks despite control of the underlying infection	Ataxia, myoclonus, opsoclonus, altered sensorium, vomiting, irritability, headache, seizures.	Paraneoplastic causes such as neuroblastoma and ganglioneuroma related in children and breast carcinoma related in adults, secondary to anti-Ri, anti-Yo, anti-Hu, ant-amphiphysin etc.	Children and old age

CNS: Central nervous system; d: day; HAART: Highly active antiretroviral therapy; HIV: Human immunodeficiency virus; HRZE: Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E); HSV: Herpes simplex virus; IV: Intravenous; IVIg: Intravenous immunoglobulin; mg: milligram; MU: Million units; OMAS: Opsoclonus myoclonus ataxia syndrome; TMP-SMZ: Trimethoprim-Sulfamethoxazole; VZV: Varicella zoster virus.

6.1.1. Antibiotic treatment for streptococcus

This step involves both elimination of active carriage of GABHS and secondary prophylaxis to prevent recurrent infection. Deep intra muscular injection of Penicillin G Benzathine (Table 1) is effective to eradicate the active infection as well as the first dose of long-term secondary prophylaxis. This must be continued and given every 3–4 weeks for secondary prophylaxis with the duration dependant on the carditis (Table 1). Alternative options are oral penicillin V if injectables cannot

Table 2
Commonly used medication for symptomatic control of various movement disorder phenomenologies and their usual doses.

Medication	Indications	Dosage
Baclofen	Dystonia	5–60 mg/d, oral
Carbamazepine	Chorea, SSPE - myoclonus	10–20 mg/kg
Clonazepam	Myoclonus, dystonia, tremor, chorea, ballism	0.5—–5 mg/d in 2–3 divided doses
Gabapentin	Tremor	Starting dose of 100–300 mg/d slowly increase up to 1200–2400 mg/d in three divided doses or till tolerated
Haloperidol	Chorea, ballism	"Start slow and go slow" 0.025 mg/kg/d divided in 1–2 divided doses increase slowly up to 0.05–0.1 mg/kg/d or 4–5 mg/d
Levetiracetam	Myoclonus, chorea	20–60 mg/kg/d in two divided doses
Levodopa with carbidopa	Parkinsonism, dystonia	"Start slow and go slow" Initiate slowly at 200 mg/d and slowly titrate to 400–800 mg/d or till tolerable level with 50–75 mg carbidopa per d in three doses.
Olanzapine	Chorea, ballism	5–10 mg/d
Pimozide	Chorea, ballism	1–2 mg/d
Piracetam	Myoclonus	4.8–24 mg/kg/d
Primidone	Tremor	Start 100–150 mg/d in 2–3 divided doses and titrate slowly up to 750 mg/d or till tolerated
Propranolol	Tremor	20–40 mg/d in two divided doses titrate up to 80–160 mg/d, monitoring for pulse rate
Risperidone	Chorea, ballism	1–2 mg/d
Topiramate	Tremor	Start with 50–100 mg/d in 2 divided doses titrate up to 400 mg/d
Tetrabenazine	Dystonia, chorea	Starting dose of 25 mg/d, slowly titrate up to 75–150 mg/d in three divided doses
Valproate	Chorea, ballism, myoclonus	200–500 mg/d or 20 mg/kg/d maximum up to 1500 mg/d

d: day; mg: milligram; SSPE: Subacute sclerosing panencephalitis.

be given and azithromycin in patients allergic to penicillin. Other alternatives are cephalosporins and clindamycin.

6.1.2. Symptomatic control of the chorea

In patients where the chorea is mild and non-disabling, symptomatic therapy may not be required as these medications do not change the overall recovery or the recurrence rate of chorea[8,58]. When symptomatic therapy is considered, antiseizure medications (ASM) and dopamine antagonists are the two groups of medications commonly used.

Among ASM, valproic acid (Table 2) is the preferred agent due to the overall efficacy and the side effect profile[58]. Increased GABA level in the brain is one of the mechanisms. Multiple case reports and case series have proven the efficacy of valproate with the response noted over 1–10 days and remission could be achieved in 1–4 weeks[58,62,63]. Carbamazepine (10–20 mg/kg/day) has also been used for the symptomatic treatment with good efficacy[58,64,65]. The response was noted in 2–14 days with complete remission over 2–12 weeks[58]. Diazepam, levetiracetam and phenobarbital are the other ASMs used sparingly [58,66,67].

Dopamine antagonists are the other group of medications that are frequently used in SC. Haloperidol (4–5 mg/day), pimozide (1–2 mg/day), chlorpromazine, risperidone (1–2 mg/day) and olanzapine (5–10 mg/day) have been used for the symptomatic therapy[58]. Haloperidol is used in start-slow and go-slow regimen (Table 2). Risperidone is started at 1 mg/d in two divided dose and after two weeks if not controlled increased to 2 mg/d. Patients with SC have increased propensity to develop parkinsonism and other extra pyramidal side effects to these medications[68]. Overall, both typical and atypical antipsychotics have good efficacy, but considering both efficacy and side effect profile, ASMs are preferred over dopamine antagonists[58]. Tetrabenazine (25 mg 2–3 times a day), has been tried in few cases with response noted over 2 weeks in 2 cases but no response in another[8,58].

6.1.3. Immunotherapy to control immune and inflammatory response

Immunomodulatory therapies are considered either in severe paralytic chorea or when refractory to the symptomatic therapies. Both oral prednisolone and intravenous methylprednisolone (Table 1) have been effective with response noted in a week and remission in 1–8 weeks [58,69–71]. In a double-blind randomised placebo-controlled study of oral steroid versus placebo, patients on prednisolone had shorter time to remission (54 days versus 120 days) but no significant difference in overall remission and relapse rate [72]. Rarely, IVIG (2 gm/kg/d over 3–5 days) and plasmapheresis have been used as both second line for refractory cases and as a first line with good response. However, cost, accessibility issues and lack of robust data limits its use only to refractory cases [58].

Overall, in the management of SC, antibiotic therapy should be initiated and has been proven effective in reducing the recurrence of SC [8]. Symptomatic therapy can be considered if the chorea is disabling. Valproate or carbamazepine would be the preferred first line considering the risk and benefits compared to neuroleptics [58]. In refractory cases, atypical antipsychotics, preferably risperidone or olanzapine can be considered. Steroid can be considered in those who are refractory to symptomatic therapy or in severe or paralytic chorea with or without symptomatic therapy. There are no specific guidelines for the duration of symptomatic and immunomodulators therapies. Tapering of these can be considered after 1 month of symptom free interval [58].

6.2. Tuberculosis

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* is the foremost cause of death among infectious diseases. CNS-TB represents approximately 1 % of all cases of TB [6,10,73]. Tremor, choreoathetosis, hemiballismus, dystonia, myoclonus, ataxia and parkinsonism are estimated to occur in 0.5 % to 30 % of CNS-TB, depending on the presence or absence of tuberculomas [6,7,73–79]. Tremor is the most common phenomenology observed in around on-thirds to two-thirds of the cases followed by chorea and dystonia [6,76,77]. MD overall and especially chorea tends to occur in younger age group and tremor is more common in patients with long standing and severe disease [6]. In general, chorea and dystonia correlate with deeper and contralateral lesions in the basal ganglia whereas tremor with more cortical or cerebellar lesions [6]. Possible mechanism includes brain edema, intraparenchymal tuberculomas, cerebral vasculitis related infarctions, and hydrocephalus that predominantly affects basal ganglia and its connections to diencephalon, cortex, brainstem and cerebellum. Imaging can be normal in up to 50 % of cases, and in the rest can show evidence of leptomeningeal exudates, tuberculomas, vascular infarcts and hydrocephalus [6,73].

MD in CNS-TB are often self-limiting, resolving in a few weeks once the infection is controlled especially in those with diffuse CNS disease or normal imaging [6,7,74,77]. MD can develop during the tuberculosis treatment either due to the development of new tuberculoma secondary to paradoxical worsening or because of drugs such as ataxia secondary to isoniazid. Functional changes in neuronal activities and its connections and neurotransmitter dysfunction in the basal ganglia structures may explain this self-limiting nature and early resolution of MD in CNS-TB. However, residual parenchymal abnormalities such as infarcts and gliosis can result in improved but persistent MD especially dystonia, parkinsonism and cerebellar dysfunction [76,78].

Antitubercular therapy consists of an intensive phase comprising of isoniazid, rifampicin, pyrazinamide, and ethambutol for 2–3 months followed by a continuation phase of isoniazid and rifampicin with or without ethambutol for 8–18 months or titrated as per the response. The treatment regimen differs between various guidelines. In case of CNS-TB

stage 2 and 3, 8 weeks course of steroid in tapering dose is advised and has been shown to improve mortality [80–82]. Ventriculoperitoneal shunt may be required in patients with hydrocephalus either not responding to medications or is resulting in significant mass effects [83]. Aspirin helps in reducing the recurrence of infarcts in patients with tuberculous vasculitis, however, with no effect on long term morbidity or mortality [84].

6.3. Neurosyphilis

Syphilis, caused by spirochete *Treponema pallidum*, is regarded as "the great mimicker" owing to its varied symptoms and signs. The clinical manifestations can be classified into four distinct stages: primary syphilis (chancre weeks after post inoculation), secondary syphilis (malaise, fever, rash, condyloma lata, mucous patches, meningitis etc. around 4–10 weeks post inoculation), early (<1 year) and latent (>1 year) syphilis of relative asymptomatic phase and tertiary syphilis (cardiovascular and neurological manifestations months to years post inoculation) [16,17,85]. Neurosyphilis can be primarily grouped into meningovascular and parenchymal forms. Patients with neurosyphilis, especially in tertiary stages can rarely develop MD either as a presenting feature or accompanied with other classical presentation. Tong et al identified 7 patients with MD in their retrospective study of 169 patients with neurosyphilis [85]. Tremor, chorea, myoclonus and parkinsonism are commonly reported with rare reports of cerebellar ataxia, athetosis, dystonia and ballism [16,17]. Parkinsonism can be in the form of akinetic rigid syndrome, corticobasal syndrome or progressive supranuclear palsy phenotypes [16]. MD in meningovascular syphilis is secondary to ischemic lesions in basal ganglia, midbrain and cerebellum with the presentations similar to those seen due to other causes resulting in lesions in these locations. Parenchymal lesions can present with MD due to direct invasion and inflammation of the basal ganglia, mid brain and cerebellar structures or in rare cases secondary to hydrocephalus.

The first step in management is confirming the diagnosis of syphilis as it is rare and can present with atypical phenotypes making diagnosis difficult. Inflammatory CSF findings with lymphocytic pleocytosis and elevated protein, and a positive Venereal Disease Research Laboratory (VDRL) test for syphilis in CSF confirms the diagnosis. CSF VDRL even though is highly specific, lack sensitivity and if negative in a suspected case, can consider CSF treponemal tests (Fluorescent treponemal antibody or *Treponemal pallidum* hemagglutination tests) may be considered for diagnosis. A course of intravenous aqueous Penicillin G (Table 1) is recommended for neurosyphilis [86,87]. An effective alternative is intravenous ceftriaxone [88–90]. More than a 4-fold reduction in the non-treponemal test titer indicated successful treatment. Follow-up CSF examination is recommended every 6 months until the abnormality resolves. If CSF cell count has not diminished after 6 months or remain abnormal after 2 years, then retreatment is indicated. With antibiotic treatment, good to complete recovery is expected, especially of chorea and tremor, whereas less improvement is observed more often in parkinsonism, dystonia and ataxia [16,17,87]. Symptomatic therapy such as levodopa-carbidopa in parkinsonism may be warranted in disabling and persisting symptoms.

6.4. Other bacterial infections related movement disorders

Whipple disease (WD) is a rare infectious disease caused by *Tropheryma whippelei*. It can present with chronic progressive ataxia, occulomasticatory myorhythmia, myoclonus and parkinsonism along with cognitive dysfunction and other neurological signs [53]. Other MD rarely described are dystonia, tremor, and chorea. Overall, MD can be observed in a half of patients with neurological WD. The treatment includes either intravenous ceftriaxone or aqueous Penicillin G for 2–4 weeks followed by the maintenance therapy with trimethoprim and sulfamethoxazole (TMP-SMX) for a total of 1 year (Table 1) [91]. Gradual improvement can be expected although may not be complete in all.

Enteric fever is another bacterial infection which can cause MD. In a study by Sejvar et al, 40 out of 303 patients had neurological findings, of which ataxia was noted in 22 patients, parkinsonism in eight and tremor in four. Complete resolution over 1–2 months with antibiotic therapy (Table 1) was noted in the majority [20].

Scrub typhus can also present with MD predominantly ataxia and opsoclonus-myoclonus-ataxia syndrome which is often self-limiting once the infection is controlled by antibiotics (Table 1). Even though steroid and IVIG have been used in the management owing to the underlying inflammatory pathophysiology, complete resolution of MD phenomenology with antibiotics alone has also been observed [21].

6.5. HIV and opportunistic infection-related movement disorders

Neurological complications are common in patients affected with HIV-AIDS seen in around two-thirds of the cases. This may be secondary to direct neuro invasion by HIV virus, due to various opportunistic neuroinfections (toxoplasma, cryptococcus, tuberculosis, JC virus to name few), immune mediated mechanisms, primary CNS lymphoma and other neoplasm related or due to drugs including the highly active antiretro viral therapy (HAART). Although initial studies reported MD in around 3 % of HIV-positive patients with neurological involvement, recent studies have shown this can be as high as 50 %, especially the prevalence increasing with advancing disease[9,11,37,92]. The whole spectrum of MD can occur in patients with HIV, of which tremor and parkinsonism appears to be most commonly seen in AIDS-dementia complex. Certain phenomenologies such as hemichorea-hemiballismus (HCHB) and acute-subacute asymmetrical ataxia point towards specific underlying opportunistic infections- toxoplasma and PMLE respectively.

6.6. Direct HIV related movement disorders

Common MD resulting from direct HIV infections are postural tremor and symmetrical predominantly akinetic-rigid form of parkinsonism. Both these phenomenologies often occur as part of AIDS-dementia complex due to direct invasion of basal ganglia structures by HIV viral particles and ensuing neurodegeneration and inflammation [93,94]. Autopsy studies have shown histological evidence of panencephalitis in 90 % of the patients and basal ganglia was involved in over three-fourth of these cases [95]. Some patients may have Holmes tremor in which case other signs of midbrain dysfunction are often present. Other causes of tremor in HIV-positive patients can be due to structural lesions secondary to opportunistic infection in brainstem and cerebellar regions or drug induced as sometimes associated with cotrimoxazole [92]. The tremor is seldom severe enough to warrant specific therapy and more importantly signifies an advanced stage of the disease. Various antitremor medications have been tried with mixed results. Like tremor, parkinsonism also frequently occurs as a part of AIDS-dementia complex in patients with HIV. Usually, patients have symmetrical parkinsonism with postural instability without rest tremor and is often levodopa nonresponsive. However, based on few reports where levodopa responsiveness has been noted, a reasonable trial of levodopa is warranted [92,96–98]. Initiating HAART in those who are drug naïve has resulted in gradual improvement of parkinsonian syndrome over weeks to months [92,99,100]. There are few reports of other MD secondary to direct HIV infection such as generalized chorea, progressive cerebellar ataxia and myoclonus. Response to HAART in these patients are variable and overall, they have poor prognosis compared to these phenomenologies secondary to opportunistic infection.

6.7. Opportunistic infections related movement disorders

Opportunistic neuroinfections in HIV patients often involves the subcortical and basal ganglia structures resulting in various MD. Acute

HCHB in a patient with HIV should indicate CNS toxoplasma abscess unless proved otherwise [94,101]. Other MD associated with CNS toxoplasmosis are hemidystonia, parkinsonism and akathisia [101,102]. Toxoplasmosis is responsible for more than 50 % cases of HCHB cases in patients with HIV. Other causes identified are infarct secondary to zoster vasculitis, histoplasma, JC virus infection and tuberculosis [103,104]. Treatment of CNS toxoplasmosis (Table 1) is by sulfadiazine, pyrimethamine and leucovorin and includes induction phase for 6 weeks followed by a continuation phase till CD4 count is maintained > 200 cells/microL for at least 6 months on HAART [105]. Alternative but equally efficacious regimen is TMP-SMX [105]. In those with sulfa allergy, sulfadiazine can be replaced with clindamycin keeping pyrimethamine and leucovorin at same dose. Radiological and clinical improvement is noted in 70–80 % cases by 10–14 days. In non-responders in presumptive toxoplasmosis, an alternative diagnosis should be considered [106]. PMLE due to JCV infection is another important opportunistic infection that can cause MD presenting with subacute asymmetrical ataxia (Video 2). MRI brain may show hyperintensity of cerebellum, middle cerebellar peduncles and pons. Prompt initiation of HAART is the treatment of choice and stabilization can be expected if not complete improvement. It is important to note that CNS lymphoma is a close clinical and radiological differential for space occupying opportunistic infections in patients with HIV [107]. However, in a review of primary CNS lymphoma with movement disorders presentation, none were associated with HIV [108].

6.8. COVID-19 related movement disorders

During the recent COVID-19 pandemic, a broad range of de novo MD were observed and reported in some patients with COVID-19 developing during or after the infection. Ataxia and/or myoclonus was the most common phenomenology constituting more than three-fourth of the reported cases followed by parkinsonism, tremor, chorea, dystonia, functional tics etc. [32]. However, the overall risk of developing MD after COVID-19 is marginal. The various possible mechanisms postulated are post-infectious immune-mediated, direct invasion of the CNS, hypoxia, metabolic, drug related or strategic infarcts. In around four-fifths of patients, the MD subsided within days to 2 months either spontaneously or after various immunotherapies and symptomatic management [32,50]. In a follow-up study of COVID-19 related MD, 22 % of patients had persistence of MD after a follow-up of around 8 weeks [32]. Severe COVID-19 and encephalopathy were the risk factors for persistence and akinetic rigid syndrome recovered later compared to other phenotypes. In total, less than one-fifths of patients continued to be on symptomatic therapy while others were not on any symptomatic therapy. Even though around half of the patients received some form of immunotherapy, mostly in hyperkinetic syndromes, the authors reported that the data is insufficient to comment on its role in the time of recovery or the outcome [32].

6.9. Cerebral malaria

Cerebral malaria, caused by *Plasmodium falciparum,* can have MD manifestations. Cerebellar ataxia is the most common phenomenology observed and can occur during the acute episode, as a sequela of cerebral malaria, as delayed cerebellar ataxia (DCA) or as a part of post-malarial neurological syndrome (PMNS). In a study by Kochar et al, out of 3188 patients with falciparum malaria, cerebellar syndrome was observed in 49 patients [109]. Nine patients had it in acute stage and resolved with anti-malarial therapy, 22 patients had as a severe malaria sequela, and 18 patients had DCA. Cerebellar ataxia as a neurological sequela occurred in 22/440 patients with cerebral malaria and these patients improved over 6–16 weeks after regaining consciousness [110].

PMNS is a syndrome that develops post recovery from malaria and clearance of parasitemia [49]. It can be divided into three clinical stages: (i) a mild form of isolated cerebellar ataxia (referred as DCA) or tremor, (ii) a mild encephalopathic form with confusion and seizures,; and (iii) a severe encephalopathic form with aphasia, myoclonus, tremor and ataxia. DCA can develop in uncomplicated malaria as well. In addition, dystonia, parkinsonism and OMAS has also been reported [10,87,111]. The postulated mechanisms are a combination of mechanical (plugging of parasitized red blood cells in vasculature), inflammatory, humoral, and metabolic (hypoglycemia, hypoperfusion and hyperthermia) factors [110]. Purkinje cells are sensitive to hyperthermia and may be transiently dysfunctional explaining cerebellar syndromes.

Most of these MD are self-limiting with almost complete recovery [110]. Intravenous antimalarial artesunate (Table 1) is the drug of choice in cerebral malaria and quinine is an alternative if artesunate is not available. Other artemisinin derivatives such as artemether can be administered in uncomplicated malaria. Antimalarial is not required in PMNS and DCA if parasitemia clearance is established. They are self-limiting with complete resolution expected in days to weeks. Short course of both oral and intravenous steroid has been tried in severe and persistent cases owing to the underlying inflammatory pathophysiology with quick response in these patients. However, there is no significant difference in overall recovery [49,112].

6.10. Neurocysticercosis

Neurocysticercosis (NCC), caused by larval stage of *Taenia solium,* is the most common helminthic infection of the nervous system. The clinical symptoms depend on the location and number of parasites, and whether they are alive, degenerating or calcified. Seizure is the most frequent manifestation. Even though cysticerci can often involve basal ganglia, MD are rare owing to the small size, chronicity, slow growth and limited inflammatory response [10,73]. In a study by Cosentino et al, despite the MRI evidence of basal ganglia infestation in one quarter of the individuals, none had MD [113]. According to a study by Alarcon et al, among 590 patients with NCC, 23 developed MD. Parkinsonism (15 patients) was most common followed by tremor, dystonia, chorea and ataxia [5]. In most of the patients with parkinsonism and tremor, the underlying pathophysiology proposed was cerebello-thalamic and nigrostriatal dysfunction secondary to hydrocephalus. It was substantiated by improvement in these symptoms by ventriculo-peritoneal shunt [73,114]. Peri mesencephalic cysts or encephalitis may be the reason in those few in whom parkinsonism persists despite shunting. In contrast, chorea and dystonia correlate better with contralateral basal ganglia lesion (Video 3) [73].

Cysticidal medications is the mainstay of treatment. In the study by Alarcon et al, all patients with tremor, dystonia and chorea and 8 out of 15 patients with parkinsonism recovered. The remaining 7 patients with parkinsonism required treatment with steroids, surgery and long-term levodopa therapy[5]. Albendazole (Table 1), the drug of choice for the treatment of viable cysts, is given for a duration of 10–14 days. In patients with more than 2 cysts, addition of praziquantel (Table 1) has been found to be better compared to monotherapy with albendazole. If feasible, surgical removal, preferably by minimally invasive procedure, should be considered for ventricular cysts before starting cysticidal medications. Moreover, ventricular and subarachnoid cysts require prolonged duration of therapy until radiological resolution is achieved. Adjuvant steroid should be started at least a day before in all patients receiving the cysticidal drugs. Both prednisolone (1 mg/kg/day) and dexamethasone (0.1 mg/kg/day) has been used and needs to be continued till the completion of albendazole followed by quick taper. Anthelmintics are not recommended in calcified NCC. In ocular NCC, surgical removal is the preferred therapy. In case of cerebral edema due to NCC encephalitis with raised intracranial tension and impending herniation or hydrocephalus, steroid and surgical measure to correct these should be considered before starting albendazole [115].

6.11. Post-infectious cerebellar ataxia

Post-infectious cerebellar ataxia or also known as acute cerebellar ataxia (ACA) is commonly seen in children after viral infections (video 4) but can also affect adolescent and adults and occur after bacterial and malarial infections. It accounts for around half of pediatric acute ataxias [28]. Common infections implicated are varicella, coxsackievirus, echovirus, enterovirus, adenovirus, human herpes virus-6 (HHV6), mumps, measles, parvovirus-B19, *Borrelia burgdorferi*, salmonella, rickettsia, mycoplasma, and recently COVID-19 [20–22,28,30,32,116,117]. In a study, out of 39 children with ACA, a prodromal febrile illness was noted in 74.4 % cases of which 31 % had varicella, 20 % had mumps, 15 % had non-specific viral infection, 5 % had mycoplasma, and 3 % had EBV. Average latency from prodromal illness to ataxia was around 9 days and full recovery was noted over 2 weeks [28]. Gait disturbance is the primary symptom and is often associated with other cerebellar signs, vomiting, irritability, and headache in varying combination. Altered sensorium, seizures, opsoclonus, myoclonus, meningismus, focal or asymmetrical neurological findings, motor and sensory dysfunction should raise a suspicion of an alternative cause. CSF analysis and MRI brain is often normal and if abnormal mostly reveal nonspecific lymphocytic pleocytosis and mildly elevated protein in CSF and nonspecific bilateral cerebellar diffuse hyperintensity on MRI [28,116].

Spontaneous and complete resolution of ataxia is expected over 2–4 weeks in the majority [28,52]. Persistence or worsening of ataxia or development of new neurological sign should warrant workup for an alternative cause. Reports suggest good outcome in refractory cases with immunomodulators [28]. Based on the limited evidence, antiviral medication does not appear to alter the disease course consistent with the hypothesis that the disease is mostly post-infectious inflammatory process.

6.12. Post-infectious opsoclonus myoclonus ataxia syndrome

OMAS is a rare disorder predominantly affecting children, with a combination of characteristic eye movement abnormalities, multifocal myoclonus, ataxia and sleep disturbance. It is an immune-mediated condition triggered by heterogenous causes, most commonly tumor (neuroblastoma, ganglioneuroma, breast adenocarcinoma etc.) and infections which constitute 20–50 % cases [56,57,59,118]. The causes depend on the age group with paraneoplastic causes frequent in children and elderlies and post-infectious more frequent in adolescents and adults. Associated infections are HIV, hepatitis C, EBV, CMV, HHV6, adenovirus, enterovirus, rotavirus, influenza virus, dengue virus (Video 5), chikungunya virus, WNV, COVID-19, mycoplasma, streptococcus, leptospira, rickettsia, salmonella, neuroborreliosis etc. [18,30,59]. Like ACA, OMAS also predominantly affect children, has ataxia a cardinal sign, has autoimmune pathophysiology and MRI brain and CSF analysis can be normal or nonspecific. However, presence of opsoclonus, myoclonus, irritability, and sleep disturbances help in distinguishing it from ACA. Moreover, OMAS is more severe, require evaluation for underlying neoplasm, can have residual deficits and increased risk of recurrence [118].

Owing to the severity and the risk of persistent long-term disability and recurrence, immunotherapy is started at the earliest. Pulse intravenous steroid with or without IVIg/plasmapheresis is often initiated followed by oral steroid in most of the cases [57,118]. In case of an underlying neoplasm, the treatment should aim at the management of the neoplasm. In case of non-satisfactory response at 2–4 weeks, immunomodulator escalation to cyclophosphamide or rituximab has been suggested [59]. Relapse is observed in around 50 % of the cases according to various studies [56,59,118]. Remission is considered if the patient does not have a relapse despite intercurrent illnesses without immunotherapy. Even though immunomodulators have resulted in an early and better recovery, most evidence are from retrospective studies or case reports. Moreover, spontaneous remission has also been observed without immunotherapy, especially in milder and post-infectious cases[21,26,32,57]. Decision regarding immunotherapy should be taken after considering the severity, underlying cause and the associated risk and benefit.

6.13. Parkinsonism secondary to infections

Parkinsonism secondary to infections have been reported in viral infections (HIV, EBV, CMV, HSV1, dengue, JEV, WNV, coxsackie virus, influenza virus etc.), bacterial infections (CNS-TB, neurosyphilis, Whipple's disease, mycoplasma etc.), neurocysticercosis (Video 3), CNS-toxoplasmosis and cryptococcosis [1,5–7,26,78,119–121]. Arthropod borne viruses such as JEV, WNV have predilection to cause direct neuronal injury to brainstem and basal ganglia structures resulting in parkinsonism. Parkinsonism that develops after a latency are often mediated by aberrant inflammatory response, cytokine release and autoimmune mechanisms, e.g. Influenza virus, COVID-19, HSV, VZV etc. [121]. In case of HIV-AIDS, it can be either directly due to HIV related neuronal damage of basal ganglia and nigral tissue or it can be secondary to the structural damage caused by opportunistic infection (toxoplasmosis, tuberculosis, cryptococcus or JC virus) [37,119]. In case of tuberculosis and neurocysticercosis, hydrocephalus, infection and inflammation of basal ganglia structures or infarcts in these areas due to vasculitis can be the underlying mechanism.

As for any other IRMD, control of the active infection by appropriate antimicrobial agents is the important step and, in some cases, this alone would suffice [30,32]. Symptomatic therapy with levodopa has variable response. Levodopa response may be good in cases where the neuronal damage is in pre-synaptic dopaminergic neuronal regions such as substantia nigra. Caudate and putaminal involvement may have poor levodopa response [119]. HIV related parkinsonism show poor response to levodopa and is better managed with anti-retroviral therapy at the earliest and treating the opportunistic infection. Parkinsonism in WNV and JE can be self-limiting but can result in sequelae with variable levodopa responsiveness [24,26]. COVID-19 related parkinsonism has shown overall good response to levodopa similar to that see in post-encephalitis parkinsonism [119]. Immunomodulator has been tried in suspected post-infectious inflammatory causes with variable response [26]. Steroid and shunt surgery may be warranted in patients with CNS-TB and neurocysticercosis.

7. Conclusion

Infection related movement disorders is a heterogenous group of disorders caused by wide range of infections with multiple underlying pathophysiology and is one of the important causes of secondary or acquired movement disorders. A single infection can have multiple phenomenologies and a particular phenomenology can be secondary to diverse group of infections. Early diagnosis and appropriate treatment are often necessary for better short-term and long-term prognosis. Many are self-limiting and would just require prompt control of the underlying infection and close monitoring. Immunomodulators play a significant role in those with suspected underlying post-infectious inflammatory pathology. However, owing to the significant side effects associated with these agents, a cautious approach must be followed in order to achieve best risk benefit balance.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This research received no specific grant from any funding agency.

Appendix A. Supplementary data Supplementary video legends along with clinical details: Video-1: Sydenham chorea. A fourteen-year-old boy presented with acute onset choreiform movements of right half of body for the past 15 days. There was no significant past history. The video demonstrates chorea predominantly involving right upper limb, lower limb and trunk. Serum antistreptolysin-O titer was elevated and echocardiography showed features of rheumatic heart disease. The patient was started on deep-intramuscular 1.2 million units benzathine penicillin along with carbamazepine 50 mg twice a day for a week followed by 100 mg twice a day. The patient had significant improvement at 1 month follow-up and chorea resolved at 2 months follow-up after which carbamazepine was tapered and stopped. He was advised to continue benzathine penicillin every 28 days as secondary prophylaxis. Video-2: Progressive multifocal leukoencephalopathy. An eighteen-year-old boy with acquired immune deficiency syndrome on anti-retroviral therapy presented with subacute progressive asymmetrical cerebellar ataxia. The video demonstrates appendicular and gait ataxia. In addition, the patient had gaze evoked horizontal nystagmus and dysarthria. MRI brain (shown at the end of the video) showed T2/FLAIR hyperintensity involving right cerebellar hemisphere, middle cerebellar peduncle and pons including "hot cross bun sign". Video-3: Parkinsonism secondary to neurocysticercosis. A 30-year-old man with past history of seizures since past 5 years, presented with subacute progressive slowness, tremulousness and walking difficulty of 6 months duration. The video demonstrates reduced facial expression, monotonous speech, generalized bradykinesia, left upper limb rest tremor with postural and intentional component, parkinsonian gait with festination and postural instability. MRI brain revealed degenerating enhancing cystercercus in right pontine region with perifocal edema (shown in the video) along with multiple cysts in various stages in cerebrum. The patient was started on albendazole 400 mg twice a day for 4 weeks under steroid cover and anti-seizure medications were continued as before. Levodopa-carbidopa (400/100 mg /day in 4 divided doses) was also initiated. Radiological improvement was noted in the follow-up scan done at 6-months. However, clinical improvement was not complete and he continued to require dopaminergic medication for parkinsonism. Video-4: Post-varicella acute cerebellar ataxia. A seven-year-old boy with antecedent recovering chicken pox 10 days prior presented with acute onset slurring of speech, imbalance, vomiting and irritability of 2 days duration. The video demonstrates severe truncal and appendicular ataxia and scabbed exanthems on right forearm. In addition, the patient had dysarthria, generalized hypotonia, and appendicular ataxia (not shown in video). MRI Brain was normal. The patient was given 500 mg intravenous methylprednisolone for 5 days followed by quick taper over 2 weeks by oral steroids. Complete resolution was noted over 10 days with no recurrence. Video-5: Opsoclonus-myoclonus-ataxia syndrome post dengue fever. A 32-year-old female presented with 1 week history of acute onset visual abnormality, involuntary jerks, and imbalance. The patient was recovering from acute dengue fever she had 10 days before. The video (segment-1) demonstrates multifocal asynchronous myoclonus and pan-cerebellar ataxia. In addition, the patient had opsoclonus, nystagmus and dysarthria (not shown in video). The patient was treated with 1000mg of intravenous methylprednisolone for 5 days. The patient improved significantly over 1 week (segment-2) and was asymptomatic at one month follow-up.

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