Self-injurious behaviour in movement disorders: systematic review

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Word count: 4260

References:

- Manuscript: 40
- Supplementary references: 123

Running title: Self-injurious behaviour in movement disorders

Key words: Self-injurious behaviour, movement disorders, self-mutilative behaviour, injuries

Conflict of Interest: The authors disclose no conflicts of interest regarding this manuscript

Contributorship Statement:

Study design: CG/ JFF/ TM/ TP

Study supervision: CG

Study selection: JFF/ TM/ TP

Data extraction: JFF/ TM

Initial draft: CG/ JFF

Revision of the draft for important intellectual content: JFF/ TM/ YW/ TP/ KPB/ CG

Interpretation of results: JFF/ TM/ YW/ TP/ KPB/ CG

Disclosures:

JFF has nothing to disclose

TM is supported by the BIH-Charité Clinician Scientist Program of the Charité-Universitätsmedizin Berlin and the Berlin Institute of Health

YW was supported by Agence National de Recherche grant (ANR), Dystonia Medical research Foundation, travel grant from Merz

TP has nothing to disclose

KPB has grant support from EU 2020 horizon, NIHR RfPB, Wellcome/ MRC, and PD UK and has received honoraria/financial support to speak/attend meetings from Ipsen, Merz, Sun Pharma, Allergan, Teva Lundbeck, and UCB. K.P.B. receives royalties from Oxford University press and a stipend for MDCP editorship.

CG holds research grants from the VolkswagenStiftung (Freigeist Fellowship) and the German Parkinson Society and was also supported by the Deutsche Forschungsgemeinschaft (DFG; GA2031/1-1 and GA2031/1-2).

Abstract:

Self-injurious behaviours are defined as deliberate, repetitive and persistent behaviours that are directed towards the body and lead to physical injury, not associated with sexual arousal and without suicidal intent. In movement disorders, self-injurious behaviours are typically associated with tic disorders, most commonly Tourette syndrome, and neurometabolic conditions, as classic Lesch-Nyhan syndrome. However, beyond these well-known aetiologies, a range of other movement disorder syndromes may also present with self-injurious behaviours, even though this clinical association remains less well-known. Given the scarcity of comprehensive works on this topic, here we performed a systematic review of the literature to delineate the spectrum of movement disorders aetiologies associated with self-injurious behaviours. We report distinct aetiologies, which are clustered in 5 different categorical domains, namely neurodevelopmental, neurometabolic and neurodegenerative disorders, as well as disorders with characteristic structural brain changes and heterogeneous aetiologies (e.g. autoimmune, drug-induced). We also provide insights in the pathophysiology of self-injurious behaviours in these patients and discuss neurobiological key risk factors, which may facilitate their manifestation. Finally, we provide a list of treatments, including practical measures, such as protective devices, as well as behavioural interventions, pharmacological and neurosurgical therapies.

1. Introduction:

The term of self-injurious behaviour (SIB) encompasses deliberate, typically repetitive and persistent behaviours directed towards the body leading to demonstrable physical injury in the absence of suicidal intent or sexual arousal [1]. SIB is typically observed in neurodevelopmental and neuropsychiatric disorders, often with variable degrees of intellectual disability, but it may also occur after exposure to psychotropic substances [2, 3] and during psychotic experiences [4]. Estimates of SIB prevalence vary considering the broad range of aetiologies from 4% in the general population to more than 50% in different genetic syndromes [5, 6]. It may affect any body part and can manifest with marked variability in frequency, duration and intensity [1]. Importantly, SIB may often be associated with serious medical, including life-threatening, complications [7].

Within the field of movement disorders, SIB is most commonly associated with tic disorders, notably Tourette syndrome (TS), and is considered characteristic for patients with classic Lesch-Nyhan syndrome (LNS) [8, 9]. However, beyond these well-known aetiologies, a range of other movement disorder syndromes may also present with SIB, even though this clinical association remains less-well known. Importantly, in some of these patients, SIB may often outweigh the disability induced by the movement disorder, and hence early identification and management of SIB may constitute a top priority. There have been no papers to date to systematically address this topic, both on the range of conditions and their management. Therefore, we performed a systematically survey of the literature in order to provide a comprehensive list of movement disorders aetiologies associated with SIB, identify specific neurobiological risk factors in these disorders and discuss the available treatment strategies. We also complement these data with further cases from our own consultations and document characteristic examples covering a wide range of SIB in different movement disorders. The main goal of this review is to inform movement disorders specialists, general neurologists and neuropsychiatrists on this important issue and to guide diagnostic reasoning and treatment strategies when patients present both with movement disorders and SIB.

2. Methods:

Systematic literature search in Pubmed (MEDLINE 1966-2019) and EMBASE (1947-2019) was performed in May 2019 based on MeSH-Terms (Pubmed) and corresponding key-words (EMBASE): (("self-injurious behaviour" OR "self-mutilation") AND ("movement disorders" OR "dyskinesia" OR "myoclonus" OR "psychomotor disorders" OR "dystonic disorders" OR "tic disorder" OR "parkinsonian disorders" OR "hyperkinesia" OR "stereotypic movement disorder" OR "stereotyped behaviour" OR "ataxia" OR "tremor" OR "athetosis" OR "basal ganglia diseases" OR "motor skills disorder" OR "spasticity")) NOT ("risk-taking" OR "dangerous behaviours" OR "sexual dysfunctions, psychological" OR "suicide" OR "suicide, attempted" OR "body modification, non-therapeutic" OR "suicidal ideation"). Preset filters were applied for the categories "English language" and "human". Data extraction and study selection was performed by JFF and TM. Studies were screened by title and abstract for clinical information combining basic patient characteristics like age, sex, number of patients and comorbidities and the presence of SIB, together with any kind of movement disorder. As recently proposed, SIB was defined as typically repetitive, *"persistent, non-accidental and not-socially accepted behaviour resulting in demonstrable, self-inflicted physical injury, without intent of suicide or sexual arousal"* [1, 10].

In the first screening step clinical studies (e.g. cross-sectional and case-control studies, controlled trials), case series and case reports were selected. Reviews were also included for cross-referencing. In vitro and animal research studies, as well as duplicates, comments and meeting protocols were excluded. All selected and available studies were then read in full-text. Only clinical studies and cases were included, where a clear association between the presence of SIB and movement disorders was demonstrated. Cases in which signs of suicidality or sexual arousal were associated with SIB were excluded, as were reports with insufficient clinical information (e.g. inconclusive clinical data, including age, clinical features, number of patients, etc.). Patients with SIB and functional movement disorders, including dystonia-causalgia syndrome, were not included in our study selection. The process of literature search, which was conducted in accordance with the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) can be seen in figure 1 [11].

From all selected articles we extracted the following data: Patient age, sex, method of SIB assessment, SIB onset, SIB forms and topography, presence of movement disorders and their aetiology, as well as neuropsychiatric comorbidities and different treatment strategies. Operational terms to cluster different SIB forms were used based on previous literature (see table 1) [12]. Repetitive amputational attempts, as well as the deliberate ingestion of dangerous liquids without suicidal intention were also captured as SIB. Movement disorders aetiologies associated with SIB were grouped in five categories, as follows: “neurodevelopmental disorders”, “neurometabolic disorders”, “neurodegenerative disorders”, “disorders with characteristic structural brain changes” and “others”, which includes cases in which their aetiologies did not clearly belong to any previous category, or where no specific aetiology was given. Treatments were captured and reported if they led to a significant reduction or cessation of SIB.

Form of self-injurious behaviour:	Operational definition:	Exemplary forms of self-injurious behaviour (SIB):
Hitting	Movement of hand or body part down onto and striking other body parts	Hitting body part with hands, self-punching, self-hitting, self-slapping, self-striking
Banging	Forceful movement of body part, possibly outside the physiological range of motion, with or without contact of object surface	Head banging, elbow banging, banging against objects, head jerking tic, hyperextending knees, stomping tic,
Biting	Enclosing body part between teeth with subsequent scrunching or cutting motion	Self-biting, self-chewing
Poking	Pressing fingers onto or drilling finger(s) into another body part	Eye-gouging, eye-poking, eye-pinching, pressing on eyeballs
Penetrative	Penetration and disintegration of skin, mucous membranes, or natural body orifices with objects	Self-stabbing, self-penetration with objects, inserting objects into wounds, piercing of tongue with sharp objects
Picking/scratching	Using fingernail(s) to scratch and disintegrate skin surface	Self-picking, skin-picking, skin-scratching, self-scratching, self-pinching
Burning	Using heat to cause burn-injuries to any kind of body part	Self-burning with cigarette ends, putting body parts into boiling water, putting body parts into frying pans
Pulling	Grasping motion and subsequent yanking of skin appendages/body parts/devices with fingers	Trichotillomania, pulling eyebrows, attempts to pull out tongue, pulling-out of catheters, teeth extraction, nail yanking
Rubbing/grinding	Abrasive scrubbing of body part against each other	Lip rubbing, rubbing hands, teeth grinding
Amputational	Disintegrating body parts with sharp objects	Attempt to sever arm with knife, attempt to cut off genitals, throat cutting
Swallowing	Ingestion of dangerous substances or body parts to cause internal injury	Ingestion of dangerous liquids, putting objects/body parts into throat, attempt for self-intoxication
Others	Not belonging in any of the other categories	Self-induced gagging, self-strangulation, forced Valsalva maneuver, self-dropping to ground, putting finger into wheelchair spokes
Not otherwise specified	Inconclusive descriptions or missing reports	Self-hurting, self-mutilation, self-mutilative behaviour, self-destructive behaviour, self-injury, movements with self-hurting consequence, self-inflicted lesions, producing wounds, not reported, self-injurious behaviour

Table 1. Operationalized forms and corresponding definitions of SIB for standardised counting of different descriptions (exemplary SIB forms) registered in literature.

3. Results:

3.1. Aetiological overview:

In total, 137 studies (individual studies and corresponding references provided as supplementary table 1, list of supplementary references in supplement 2) reporting 1407 SIB patients within 48 aetiological entities were identified with our systematic literature review (see also fig. 2). SIB assessment methodology was reported in only 28/137 reports (structured or semi-structured interviews, direct observational data). Illustrated examples of SIB from our own clinics are shown in figure 3.

3.1.1. Neurodevelopmental disorders

The majority of identified patients with SIB and movement disorders (n=1198) belonged to the group of neurodevelopmental disorders. Among those, most patients had a diagnosis of TS (n=718) [7, 13–18] [S1–S25], with SIB prevalence ranging between 14% and 66% [15] [S5]. SIB manifestation followed the onset of tics with a lag of several years and an average age at onset around 10 years (range: 4-18y) [14, 16, 18] [S6, S7, S10, S12, S14–S16, S20, S21, S24]. SIB in TS typically involved the head, including eyes, lips, teeth and intraoral soft tissue. Most common SIB in TS involved skin picking and self-biting or self-hitting behaviours [7, 14, 16–18] [S1, S6–S25]. Isolated cases presented with severe SIB, including amputation attempts, severe eye poking or head banging, self-strangulation, as well as drinking dangerous liquids [7] [S1, S14, S18].

Fragile X syndrome (FXS, n=143 SIB cases; 4 studies) was the second most common aetiology in this category, typically presenting with stereotypic behaviour and SIB [S26–S29]. Where information was available, the onset of SIB was reported to occur in childhood [S28]. Self-hitting or self-biting in FXS patients was the predominant SIB [S27, S28]. Motor stereotypies were also the main movement disorder in patients with Cri du chat syndrome (n=67 SIB cases) who also presented with SIB. There was marked variability regarding the type of SIB in these patients, including self-hitting, self-biting, banging against objects, forced vomiting, putting objects/fingers into body orifices or self-luxation of shoulder and patella [S30–S32]. Other aetiologies included Smith-Magenis syndrome (n=37 SIB cases) [S32–S34], Lowe syndrome (n=36 SIB

cases) [35], Cornelia de Lange syndrome (n=30 SIB cases) [12], Rett syndrome (n=3) [S36, S37], GNAO1 encephalopathy (n=2) [S38], Prader-Willi syndrome (n=1) [S39], Angelman syndrome (n=1) [S32], Salt-and-pepper syndrome (n=2) [S40], Gaucher's disease type II (n=1) [S41], mitochondriopathy (n=1) [S42], Primrose syndrome (n=1) [S43] and chromosomal aberrations like Tourettism associated with *Xq25* microduplication (n=1) [S44], *17q23.2* duplication (n=1) [S45], *1q24-q25* microdeletion (n=1) [S46], *18q* deletion syndrome (n=1) [S47], Trisomy 13 (n=1) [S32] and Trisomy 21 (n=1; case from our clinics, also see figure 3).

We also identified 149 cases with probable neurodevelopmental disorder in whom motor stereotypies and intellectual disability were characteristic, but further clinical details, beyond the presence of autistic features in some of them, were sparsely provided (mean age: 33,9y) [19] [S48–S50]. In these cases, the most commonly reported forms of SIB were self-hitting, self-biting, self-picking and banging behaviours [S48–50].

To summarize, a range of different neurodevelopmental conditions may present both with movement disorders and SIB. Within this category, the top three aetiologies include tic disorders and TS, Fragile X syndrome and Cri du chat syndrome. An association of movement disorders with intellectual disability is characteristic.

3.1.2. Neurometabolic disorders

In total, 168 patients with SIB and movement disorders were included in this category. LNS was the predominant aetiology (n=162) [20–25] [S51–S84], including two female patients [21] [S61]. SIB in LNS was characteristic but did not occur in all LNS patients [S77]. The somatotopy of SIB in LNS was more pronounced for the mouth (n=63) and fingers/hands (n=57) [21–24] [S51–S55, S57–S84], with characteristic self-biting of lips or fingers first manifesting around the age of 3y (n=85) [20, 21] [S51, S53, S58–S65, S68–S73, S75, S76, S81–S83]. Only one study provided long-term follow up data of LNS patients, in whom a fluctuating course of SIB was observed, with a slight decrease around the age of 10y [S72].

3 more cases from literature were identified with the following aetiologies: 6-Pyruvoyl-tetrahydropterin synthase (PTPS)-deficiency [S85], late-treated Phenylketonuria

(PKU) [S86] and hepatolenticular degeneration [S87]. In the case of a male in his 70s with PKU, fluctuations in his serum phenylalanine levels correlated with the frequency and intensity of SIB (i.e. banging different body parts against hard objects) [S86]. We also report two siblings from our clinics with serine deficiency syndrome and compulsive hair pulling as well as self-biting (see also figure 3E, F).

3.1.3. Neurodegenerative disorders

11 patients (7 males) between 29 and 54 years with neuroacanthocytosis (NAC) were identified [S88–S97]. Patients with NAC typically exhibited self-biting behaviours, except one case with self-injurious repetitive head scratching [S88]. The mean onset of SIB was 35.7 years (reported in 6 cases) [S89–S92, S95]. Self-biting was mostly localized in the oral area (tongue/oral mucosa/cheeks/mouth/lip/teeth) (n=10/11 patients).

SIB was additionally documented in 2 patients with pantothenate-kinase associated neurodegeneration (PKAN) and one patient with neurodegeneration with brain iron accumulation (NBIA) (n=3, mean age: 9.3y, 1 male; age of SIB onset: 11y [n=1]) [S98–S100], two cases with hereditary spastic paraplegia (HSP) due to mutations in the *B4GALNT1* gene (n=2, adult age, not further specified) [S101], one patient with dementia and myoclonus diagnosed with Alzheimer's disease due to *presenilin 1* gene mutation (n=1, 35y, male) [S102] and one patient with corticobasal syndrome associated with the presence of antiglycine receptor antibodies (n=1, age: 55y, male) [S103]. SIB was also documented in a patient with juvenile parkinsonism due to an *FBOX07* mutation syndrome under rasagiline therapy (1mg/d) (n=1, male, age: 16y) [S104]. More recently, two females with SCA17 and severe repetitive self-scratching were also reported [S105].

3.1.4. Characteristic structural brain changes

SIB was also described in seven syndromes with characteristic structural brain changes (10 patients, 6 males) including three patients diagnosed with Gomez-Lopez-Hernandez syndrome (n=3, age: Range 3-11y [n=1; age not reported], 1 male) [S106–S108] and two patients with Joubert syndrome (mean age: 5y, 1 male) [S109]. Further isolated cases included the following aetiologies: *RTTN* (rotatin) missense mutation (5.8y, male) [S110], hypomyelination with atrophy of the basal ganglia and cerebellum

(H-ABC) (n=1, 13y, female) [S111], megalencephalic leukencephalopathy (n=1, 10y, male) [S112], rhombencephalosynapsis (n=1, 22y, male) [S113], and Chiari malformation type II (n=1; age: 2.8y, male) [S114]. Brain structure abnormalities in these disorders affected cortical gyri, subcortical fibers, basal ganglia, corpus callosum, cerebellum, pons, brainstem, cisterna magna, and fourth ventricle. SIB onset in these cases was variable from 3 to 19 years (reported in 3 studies) [S107, S110, S113] and included self-biting, compulsive self-touching or rubbing behaviour leading to skin injuries [S107, S112, S113]. Interestingly, in the case with Chiari malformation type II, SIB onset coincided with the occurrence of quadriplegia and an inability to communicate [S112].

3.1.5. Others

SIB was further reported in anti-NMDA receptor encephalitis (n=1, age: 34y, male) [S115], secondary to meningitis in infancy (n=1, age: 14.2y, female) [S116], secondary to cerebral damage due to a traffic accident (n=1, age 12y, male) [S117], following perinatal brain damage (cerebral palsy: n=1, age: 1.9y; hypoxia at birth: n=1; age: 2.5y) [S32] and in the context of hydrocephalus (n=1, age: 16y, male) [S118]. Drug related SIB was also reported in 2 cases (increase of ropirinole dosage in Parkinson's disease: n=1; age: in the 50s, male; subsequent to intramuscular flupentixol injection: n=1, age: 21y; male) [26] [S119]. One case with oromandibular dystonia (n=1, age: 1.4y, female) [S120] and one case with stereotypic movement disorder in the form of repetitive head banging in the absence of intellectual disability and no further clinical specifiers were also identified [27].

3.2. Pathophysiological insights and risk factors

Although the exact pathophysiology of SIB remains elusive and a range of intrapersonal and interpersonal factors should be considered in the scientific analysis of why an individual engages in SIB, the pattern of results we report supports the presence of three key risk neurobiological factors for the manifestation of SIB in patients with movement disorders (see also figure 4). First, for the majority of syndromes presenting with SIB (25/48 aetiological categories) including TS, FXS, Smith-Magenis syndrome, Primrose syndrome or *RITN* mutation, restricted behavioural patterns were characteristic. This included not only the movement disorder itself (e.g. tics or stereotypies), but also other clinical features ranging from mental

rumination, to obsessive-compulsive behaviours or even full-blown obsessive-compulsive disorder (OCD). For example, the diagnosis of the neurodevelopmental Cornelia de Lange syndrome in itself was not associated with SIB, however the occurrence of restricted behaviours like stereotypies or compulsions in these patients increased the risk of SIB [12]. In TS, not only the severity and complexity of tics, but also the presence of OCD was associated with SIB [13], and indeed, in the majority of individually documented patients with TS and SIB we identified, OCD coexisted with tics. Although not all studies in TS could replicate this association [28], obsessive thoughts may include pathological mental rumination related to non-purposeful SIB. Obsessional worries about self-injury and the subsequent feeling of relief after the execution of SIB may, therefore, support the maintenance of a vicious reinforcement circle [14]. In general, restricted patterns of behavioural output, for example the continuous presence of stereotypic movements, coupled with behavioural inflexibility (e.g. the need to repeat certain actions) are relevant risk factors for the presence of SIB in movement disorders.

Restricted behavioural patterns are closely linked with SIB and overall highly prevalent in people with neurodevelopmental disorders and particularly with intellectual disability [29, 30]. Specifically, SIB is overall common in populations with intellectual disability [31]. Indeed, in about half of the aetiologies we identified, as for example FXS, Cri du chat syndrome and Rett syndrome, the presence of intellectual disability was characteristic. There is a large literature on this topic and several theories regarding pathophysiological implications have been proposed [32]. A clear link between the level of intellectual disability (defined as severe/profound vs mild/moderate intellectual disability) and the manifestation of SIB has been previously reported [33]. Factors including both the processing of sensory input, including pain thresholds and nociceptive signalling, as well as the capacity to communicate and express these experiences might promote SIB, at least in a subgroup of these patients [34]. The additional presence of autistic features, which further limit expressional capacity, was further associated with SIB [33].

Another hypothesis refers to the control of noxious stimuli, involving the endogenous opioid system. For example, acute pain following self-inflicted injuries could result in activation of inhibitory pathways for noxious stimuli and alleviate chronic pain [35]. Finally, the role of impulsivity should also be mentioned in this context, as indeed

several studies have documented its significance as a predictor in the manifestation of SIB in different clinical populations [13, 36].

The formation and habitual maintenance of SIB, despite its detrimental effects on the body, also points towards aberrant reinforcement of pathological behavioural output. Sources of aberrant reinforcement might be traced back to a specific individual's environment (interpersonal variables, e.g. social attention, escape from task demands or specific stressors) or to intrapersonal conditions (e.g. need for sensory stimulation) [S121, S122]. Although the interplay between environment and neurobiology is complex, the main neurotransmitter underlying repetitive behaviours is dopamine. It is, therefore, not surprising that many of the movement disorders aetiologies we identified have documented abnormalities of dopaminergic neurotransmission, which we believe constitute another risk factor for SIB [S123]. For example, pathological hyperactivity of tonic and phasic dopaminergic expression in TS is suggested to be a key element in the formation of tic behaviours [37]. Importantly, in TS, there is evidence of an association between SIB and increased dopamine transporter capacity in brain areas, including the striatum [15]. In LNS, there is evidence of selective dysfunction of dopaminergic pathways. Although in these cases a reduction, rather than an increase of dopamine in the basal ganglia is characteristic [38], aberrant activation of dopaminergic receptors may lead to SIB. Neonate rats depleted of striatal dopamine following administration of 6-hydroxydopamine do not exhibit profound impairment of motor function compared to rats lesioned during adulthood but become hyperactive upon introducing a D1-receptor agonist and characteristically develop SIB when treated with levodopa [39]. Not surprisingly, therefore, SIB was exceedingly rare in adult patients with neurodegenerative parkinsonism, and we were only able to identify only one case of a male in his 50s with Parkinson's disease, who developed skin-picking behaviour following dose increase of ropinirole, which dissipated upon discontinuation of medication [26]. In line with this are also the aetiologies with characteristic basal ganglia pathology, such as NBIA [S99, S100], NAC [S91, S97], hepatolenticular degeneration [S87], as well as Primrose syndrome associated by calcifications in basal ganglia [S43]. Moreover, invasive neuromodulation, such as deep brain stimulation (DBS) for the treatment of SIB targeted the basal ganglia, including the internal pallidum (GPi) and nucleus accumbens [S19, S75]. Of note, abnormalities of other neurotransmitters, such as the opioid system and other

monoamines, such as serotonin and norepinephrine have also been suggested to contribute to the formation and recurrence of SIB. For example, analysis of cerebrospinal fluid metabolites in LNS patients with SIB yielded additional changes in serotonin and norepinephrine turnover [22]. The effects of pharmacological targeting suggest also the involvement of the opioid system. Both a step-up of a beforehand reduced oxycodone therapy and antiopioid effects of naloxone or naltrexone were reported to reduce SIB [16, 17, 27].

3.3. Treatment

Treatment of SIB in movement disorders is complex, and requires different, often multiple and complementary approaches based on the type of SIB and the underlying aetiology (see also table 2). Crucially, data on the efficacy of the different therapeutic approaches are limited and controlled trials remain an aspiration. Indeed, most of the information we gathered stems from case reports and case series and only 15 reports documented the usage of standardized tools to monitor treatment response. Further, we identified only one randomized controlled trial in LNS patients for ecopipam, a selective D1 receptor antagonist [23].

Restraints or other protective devices are used to physically prohibit the patient from SIB. Examples of such devices and restraints are gloves or hand wrappings to prevent hand-biting or protect from severe lesions by self-hitting [18] [S74, S80], as well as splints to restrain excessive movements (see figure 3B) [S64]. Oral devices include tongue protectors, mouth-/biteguards or lip bumpers [S41, S55, S60, S98]. Although some restraints may not limit the self-injurious behaviour itself, they may reduce its impact and avert more serious injuries, as in the case of helmets, which are used in patients with repetitive head banging [18]. Limiting the impact of SIB through restraints may also support wound healing, and in some cases may even lead to complete cessation of SIB [S54, S114]. Interestingly, patients are not typically averse to use of restraints or protective devices and may report feeling safer [14]. For example, more than 90% of LNS patients preferred using restraints [20].

Behavioural therapy for SIB in movement disorders has mostly been reported in combination with other treatment modalities [14] [S16]. There are two key elements in behavioural therapy of SIB. One is the recognition of triggers and environmental

reinforcers of SIB [S122]. For example, pain or stressful situations are postulated as setting situations for self-injury [40]. SIB in some cases is also understood as a form of communication e.g. to get attention [20]. Once this occurs SIB can become maintained socially motivated e.g. by attention contingent to the act of self-injury [40]. The second element relates to the differential reinforcement of alternative responses, such as non-harmful behaviours. For example, parents of LNS patients reported that talking to the patient in situations without SIB ("when he is good") were very helpful intervention techniques, while punitive measures were the least effective methods [20]. In TS, behavioural therapy led to improved SIB, especially in patients with comorbid compulsive behaviours e.g. in squeezing a stress ball instead of self-scratching [14]. Of note, some forms of SIB might persist even after behavioural therapy, even though with reduced frequency and/or intensity [14] [S7, S16].

Pharmacological approaches for SIB are diverse. In the absence of randomized pharmacological controlled trials in patients with movement disorders and SIB, in most reports we found the usage of a specific agent was guided by clinical judgement. These included antipsychotics (e.g., quetiapine, haloperidol, risperidone) [S49, S52, S87, S96], anticonvulsants (e.g., gabapentin, pregabalin) [S11, S69], SSRI (e.g., escitalopram) [S87] and drugs acting on the opioid system. Interestingly, both opioid agonists (e.g., oxycodone) and antagonists (e.g., naloxone, naltrexone) have shown efficacy in treating patients with SIB [16, 19, 27]. In some cases, as for example in dystonia-related SIB (e.g., severe self-biting), local treatment with botulinum toxin (e.g., in the masseter muscles to limit the impact of self-biting) has been reported to reduce the injurious impact of repetitive behaviours [S58, S62, S112, S120]. Baclofen successfully reduced both severity of dystonia and the frequency of SIB in 3 patients diagnosed with LNS [24].

Should previous treatments be insufficient, for example in patients with severe SIB (e.g. directly life-threatening SIB or leading to serious medical complications), interventional approaches, such as DBS, might be required. In TS, DBS was reported as effective either as single treatment or combined with anterior capsulotomy (n=1) to reduce or completely ameliorate SIB (n=4; DBS targets: Ncl. accumbens, GPi and thalamic centromedian-parafascicular complex) [7, 18] [S12, S19]. One case series reported 5 patients with TS and SIB who underwent thalamic (n=3) and pallidal (n=2)

DBS for the unwanted behaviours with significant improvement of tics, however the exact effects on SIB were not explicitly reported [S25]. Similarly, symptoms of LNS patients, including SIB, improved after DBS (6 patients; DBS targets: GPi [n=5], pallidal stimulation [n=1]) [S51, S57, S59, S75, S76, S83], NAC (1 patient; DBS target: GPi) [S93]. Psychosurgery approaches such as cingulotomy and limbic leucotomy have also been conducted and led to reductions of SIB in 3 case reports (one report in combination with DBS) [18] [S6, S20]. Electroconvulsive therapy (ECT) in 2 adults with TS improved both tics and behavioural abnormalities, including SIB, after several sessions (7-23 ECT sessions) [S14, S18]. Of note, further practical interventions, such as tooth extraction surgery has been documented in patients with severe self-biting, as for example in LNS [S67, S78].

Finally, in some of the disorders we identified, treatments addressing the underlying aetiology may also improve SIB. For example, in neurometabolic disorders, such as PKU, the dietary regulation of phenylalanine intake was shown to improve SIB [S86]. Similarly, in patients with LNS, oral intake of S-adenosylmethionine (SAM), a dietary supplement which potentially restocks endogenous nucleotides,- but not allopurinol - led to a remarkable reduction of SIB [21, 25]. Interestingly, some effectiveness in LNS patients was also reported for probenecid, an uricosuric agent [S70].

Protective restraints

Mouth guards

Lip bumpers

Bite splints

Gloves

Arm splint

Helmets

Behavioural/psychosocial therapy:

Extinction

Differential reinforcement of other behaviours (DRO)

Noncontingent reinforcement

Pharmacotherapy

Opioid agonists/antagonists (e.g. oxycodone, naloxone)

Antipsychotics (e.g. haloperidol, quetiapine, risperidone)

Botulinum toxin

Baclofen

Anticonvulsants (e.g. gabapentin, pregabalin)

SSRI (e.g. escitalopram)

*SAM**

*Probenecid**

Interventional/surgical therapy

Tooth extraction

DBS

ECT

Psychosurgery

Table 2. Exemplified treatment options for self-injurious behaviour (SIB) in movement disorders.

DBS, deep brain stimulation, ECT, electroconvulsive therapy, SAM, S-adenosylmethionine, SSRI, selective serotonin reuptake inhibitor, * in cases with Lesch-Nyhan syndrome

4. Conclusion

Here we document the clinical association of SIB with different movement disorders aetiologies, which we present across distinct categorical domains, including neurodevelopmental, neurometabolic and neurodegenerative conditions, as well as disorders with characteristic structural changes, and those with heterogeneous aetiologies. Tic disorders and TS, Fragile X, Lesch-Nyhan and Cri du Chat syndromes were overall the most commonly reported aetiologies, with the predominant movement disorders being stereotypies and tics, followed by dystonia and/or chorea.

We acknowledge that our literature review may have not captured all possible movement disorders aetiologies and that reporting bias might have influenced the prevalence of SIB identified. At this time, the majority of the literature on SIB in movement disorders, particularly beyond tic disorders or LNS consists mostly of case series and case reports with large methodological heterogeneity, owing largely to the surprisingly rare usage of standardized assessment tools. We therefore were not able to establish specific patterns of SIB for the different aetiologies. We also could not identify population-based studies documenting the prevalence of SIB or prospective long-term cohort studies of risk factors associated with the development and clinical features of SIB over time. Similarly, beyond a single randomized control trial on the usage of ecopipam in LNS, there were no further head-to-head trials testing different therapeutic approaches that would allow differentiating existing treatments by classes of evidence.

However, our extensive review showed that in almost all disorders, the likelihood of SIB occurrence was high in presence of behavioural inflexibility with restricted and repetitive behavioural patterns, intellectual disability and aberrant reward processing, potentially related to abnormal dopaminergic neurotransmission. We therefore

encourage clinicians to use standardized instruments and actively assess for the presence of SIB in patients with movement disorders, as treatment implications are important, even though the quality of existing evidence for the different management practices in all these disorders is unfortunately low. Pragmatic approaches, as restraints and protective devices, as well as behavioural therapies should be first line considerations. Pharmacological interventions may be helpful in some patients, including treating the underlying aetiology, particularly in certain neurometabolic disorders. Invasive treatments, such as DBS, may further be of use in cases with severe and treatment refractory SIB.

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Figure legends:

Figure 1. Flow diagram of data acquisition.

Figure 2. Comprehensive diagram of all captured movement disorder aetiologies associated with SIB.

CBS, corticobasal syndrome, GLHS, Gomez-Lopez-Hernandez syndrome, H-ABC, hypomyelination with atrophy of the basal ganglia and cerebellum, HSP, hereditary spastic paraplegia, MLC, megalencephalic leukoencephalopathy, NBIA, neurodegeneration with brain iron accumulation, NMDA, N-methyl-D-aspartate, PKAN, pantothenate kinase-associated neurodegeneration, PKU, phenylketonuria, *PS-1*, presenilin 1, PTPS, 6-pyruvoyl-tetrahydropterin synthase, *RTTN*, rotatin, SCA17, spinocerebellar ataxia type 17, SIB, self-injurious behavior, TS, Tourette syndrome

¹associated with intellectual disability and/ or autism spectrum disorder, ²associated with *ST3GAL5* genetic mutation, ³associated with *G8363A transfer RNA^{Lys}* genetic mutation, ⁴patients from our clinic, ⁵associated with *B4GALNT1* genetic mutation

Figure 3. Clinical images of self-inflicted injuries and SIB related scars.

A. Scabs of the right ear canal after repetitive self-hitting, which could be prevented by bilateral arm splints (B), in a patient with stereotypic movement disorder and trisomy 21. **C, D.** Scars and excoriation wounds caused by skin picking and self-scratching with stereotypical movement disorder (not otherwise specified) (C. left forearm; D. right lower leg). **E, F.** Occipital loss of hair due to compulsive hair pulling (E) and multiple bulging scars at the right back of the hand (F) due to self-biting in a patient with serine deficiency. **G, H.** Repetitive impacts on the nose and right forehead due to compulsive self-hitting with both fists caused a scarred bulge at nasal bridge and a swollen hematoma in the right frontal area in a patient with Tourette syndrome (G). Mechanical stress resulted in callused marks on both hands in the area of the second metacarpophalangeal joint (H. left hand shown).

Figure 4. Key risk factors for the manifestation of SIB in movement disorders.

Behavioral inflexibility, intellectual disability and pathological reinforcement learning constitute key risk factors leading to increased susceptibility for self-injurious behavior (SIB) in patients with movement disorders. *Other neurotransmitter systems, e.g., the opioid or serotonergic system might also be affected.