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An Overview of Secondary Stereotypies

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An Overview of Secondary Stereotypes

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Alone

From childhood's hour I have not been
As others were, —I have not seen
As others saw, —I could not bring
My passions from a common spring.
From the same source I have not taken
My sorrow; I could not awaken
My heart to joy at the same tone;
And all I loved, I loved alone.
(...)

- Edgar Allan Poe (1829)

Abstract

Introduction:

Stereotypies are distinctly labelled in DSM-V as repetitive, patterned, coordinated, involuntary, and rhythmic, seemingly purposeless movements that could last between seconds and minutes, happen many times per day and can be associated or not with a known medical or genetic condition, neurodevelopmental disorder, or environmental factor. Other diagnostic criteria imply an onset in the early developmental period, interfering with social, academic, or other activities and, in some children, may result in self-injury. Additionally, the presence of stereotypic movements may indicate an undetected neurodevelopmental problem, especially in children ages 1-3 years. Etiologies are likely to be multiple and complex.

Objectives:

The present dissertation intends to review the existing literature in the last ten years (Scope review) related to secondary stereotypies. This review proposes to alert the medical community about the relevance of this topic, through a complete description of the currently available characterization of the subgroups belonging to this pathological entity, its differential diagnostics and treatment approaches.

Methodology:

The researched articles and bibliographic reviews were done with the electronic data base from PubMed and Elsevier along with the query “stereotypies”, “secondary stereotypies”, “restricted and repetitive behaviours”, “neurologic developmental disorders”, “children”, “etiology” and “diagnosis”. There were considered only the articles done in the last 10 years (between 2011-2021). Literature regarding stereotypies classification, both primary and secondary, was reviewed to include most of the previously described types and to a better understanding of stereotypies.

Development:

The diagnostic approach of secondary stereotypies presents a challenge for the medical community. This starts immediately in the differential diagnosis, which must be based on positive findings and include a detailed neurological and/or genetic evaluation. It is not clear why only some individuals within different neurologic developmental disorders exhibit stereotypies.

Until now, the classification of stereotypies hasn't been reviewed and put together, so we cannot have an idea of possible connections between different neurodevelopmental disorders. Based on the previous work done by the clinical neurology community, it was considered that secondary stereotypies need a definitive description because their phenomenology is intriguing, and terminology or definitions have been subject to recent discussion. For that reason and for a more organized revision I propose a narrative review that puts together most secondary stereotypies studied in different diseases.

Conclusions:

The current knowledge about secondary stereotypies, provided by scientific advances and clinical trials developed to date, establishes the combination of direct and indirect observation and intervention methods, as the most effective way to approach these young patients. Also, video recording is assumed to be a fundamental method for visual diagnosis and should always be privileged by physicians and parents, especially in younger patients. Recognition of secondary stereotypies is important in neurologically and developmentally impaired children to avoid pointless

examinations and treatments. A guideline on secondary stereotypies is needed, in order to help physicians when approaching children and their family.

Keywords: “secondary stereotypies”; “restrictive and repetitive behaviours”; “neurodevelopmental syndromes”; “neurological developmental disorders”; “genetic diagnosis”; “children”; “narrative review”.

Resumo

Introdução:

De acordo com o DSM-V, as estereotipias são descritas como movimentos repetitivos, padronizados, coordenados, involuntários, rítmicos e, aparentemente, não deliberados, com uma duração de segundos a minutos, ocorrendo várias vezes por dia, podendo ou não ser associados a uma condição médica ou genética, a um distúrbio do neurodesenvolvimento, ou a um fator ambiental. O seu início precoce no período de desenvolvimento, a sua interferência com a vida social, académica, ou outras atividades, e, em algumas crianças, os seus comportamentos auto-lesivos, constituem outros critérios de diagnósticos destes comportamentos. Para além disso, a presença de movimentos estereotipados pode constituir um indício de doença do neurodesenvolvimento não diagnosticada, principalmente em crianças entre 1-3 anos. Provavelmente, a etiologia relativa a estereotipias será múltipla e bastante complexa, por isso, ainda é desconhecida.

Objetivos

A presente tese constitui uma revisão da literatura referente aos últimos dez anos acerca de estereotipias secundárias. Com esta revisão propõe-se alertar a comunidade médica acerca da relevância deste tema, pretendendo-se fazer uma descrição completa e recente da caracterização dos subgrupos de estereotipias secundárias, os seus diagnósticos diferenciais e abordagens de tratamento.

Metodologia:

A pesquisa de artigos e revisões bibliográficas foi feita com recurso à base de dados da Pubmed e Elsevier, juntamente com os seguintes termos de pesquisa: “stereotypies”, “restricted and repetitive behaviours”, “neurologic developmental disorders”, “children”, “etiology” e “diagnosis”. Apenas foram considerados os artigos dos últimos dez anos, entre 2011-2021. A literatura acerca de estereotipias, quer primárias, quer secundárias, foi revista de forma a incluir maior parte das anteriormente descritas e para um melhor entendimento das mesmas.

Desenvolvimento:

O diagnóstico de estereotipias secundárias apresenta-se como um desafio perante a comunidade médica. Esta instigação começa desde logo nos diagnósticos diferenciais, que são baseados em achados positivos e incluem um exame neurológico detalhado e, até mesmo, uma avaliação genética. De facto, não é evidente porque só alguns dos indivíduos com doenças do neurodesenvolvimento apresentam estereotipias.

Até então, a revisão da classificação de estereotipias secundárias não permite verificar se existem de facto dependências entre diferentes distúrbios neurológicos. Com base nos trabalhos previamente realizados pela comunidade médica de neurologia, as estereotipias secundárias necessitam de uma definição definitiva e concisa, tendo em conta a sua apresentação intrigante e o facto da sua fisiopatologia e significado serem motivos recentes de discussão. Por esta razão e com intuito de realizar uma revisão organizada, propôs-se a presente revisão bibliográfica onde estão retratadas as estereotipias secundárias a diversas doenças.

Conclusões:

O conhecimento atual sobre estereotipias secundárias, proporcionado pelos avanços científicos e ensaios clínicos desenvolvidos até à data, estabelece a combinação de métodos de observação e intervenção direta e indireta, como a forma mais eficaz de abordar estes pacientes jovens. Além disso, a gravação de vídeo é assumida como um método fundamental para o

diagnóstico e deve ser sempre privilegiada por médicos e pais, especialmente em crianças. O reconhecimento de estereotípias secundárias é importante em crianças com distúrbios neurológicos e do desenvolvimento, para evitar exames e tratamentos desnecessários. De notar que está em falta uma norma de orientação para as estereotípias secundárias, a fim de ajudar os médicos no acompanhamento destas crianças e dos seus pais.

Palavras-chave: “secondary stereotypies”; “restrictive and repetitive behaviours”; “neurodevelopmental syndromes”; “neurologic developmental disorders”; “genetic diagnosis”; “children”; “narrative review”.

List of abbreviations

ASD – Autism Spectrum Disorder

ASLD – Adenylosuccinate lyase Deficiency

CdLS – Cornelia de Lange Syndrome

DSM-V - Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

EEG – Electroencephalogram

FXS – Fragile X Syndrome

ICD-11 – International Classification of Diseases, Eleventh Edition

ID – Intellectual Disability

MeCP2 – Methyl-CpG-binding protein 2

NAC – N- Acetylcysteine

NCLs- Neuronal ceroid lipofuscinoses

PANS – Pediatric Acute-onset Neuropsychiatric Syndrome

PNEMs – Non-epileptic Paroxysmal Events

PTHS – Pitt-Hopkins syndrome

RES - Rhombencephalosynapsis

RTT – Rett Syndrome

SMS – Smith Magenis Syndrome

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Introduction

Stereotypies^{1,2}, are described in DSM-V as involuntary, coordinated, patterned, repetitive, rhythmic, seemingly purposeless movements or expressions³, with typical onset in early childhood. Typically, they could last between seconds and minutes, happen many times per day, affect normal activities⁴ and are distractible⁵. When these behaviours become object of attention for their exuberant presentation by its own and need an urgent treatment approach, the term stereotypic movement disorder emerges. Stereotypies can increase when children are experiencing boredom and equally during extreme excitement or enjoyment. Also stereotyped self-injurious behaviours can occur, such as head banging, face slapping, eye poking, and biting of body parts^{1,2}. They can present in those with normal development and without an identified physiological effect of a substance, medical or genetic condition, neurodevelopmental disorder, or environmental factor, known as physiologic (primary stereotypies)^{3,4,6,7}, or can be pathologic when linked to a disorder and endure over time (secondary stereotypies)^{3,4,6,7}. Further classification incorporates vocal and motor stereotypies, subdivided in simple motor stereotypies, such as leg shaking, hair twirling, nail biting, and complex motor stereotypies, for example hand flapping, hand/arm waving, orofacial movements^{5,8}. In a comparative study of primary and secondary stereotypies, Ghosh et al. demonstrated that the group of children with secondary stereotypies had a greater percentage of cases with complex stereotypies⁶.

Regarding to the pathophysiological mechanism, there are diverging theories comprising the hypothesis of self-gratifying behaviours in children with no appropriate arousal (such as visual or hearing impairments, autism, and mental retardation), the idea of an effort to concentrate or reduce external distractions, a variation of obsessive-compulsive disorder or urge control, and a form of imaginative activities⁹⁻¹². Shafer et al. suggested that motor stereotypies are a manifestation of poor sensorimotor integration¹³. Nevertheless, the accurate neuroanatomical localization isn't certain yet as the diagnostic evaluation is ordinary in nearly all children.

Stereotypies are often confused with other events. Therefore, children are often referred to pediatric neurologists to proceed further with the clinical history and a better semiologic observation.

Simple stereotypic movements are frequent during infancy and early childhood, and normally resolve with time. In contrast, complex stereotypies are less common in typically developing children. However, in normal development infants the daily routine is not affected, and usually the movements do not cause child distress.

Motor tics and stereotypies can look alike and sometimes can be misdiagnosed because they are the most frequent pathological repetitive motor behaviours arising in the neurodevelopmental period^{4,8,14}. DSM-V¹ refers to tics as a sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations and despite certain resemblance with stereotypies phenomenology, it's crucial to discriminate their clinical features¹⁰. Firstly, their variability over time, considering that stereotypies cluster in longer periods compared to tics with the tendency to involve the same muscle groups in a consistent pattern, which creates the impression of rhythmicity of movement⁸. Other differentiating criteria is the topographical distribution, while tics may implicate nearly any body muscle, stereotypies, on the other hand, are more signified in the distal upper extremities, concurrently with the trunk and mouth stretching phenomena. Moreover, chronic tic disorders have a rostro-caudal progression with the ocular and facial regions being the ones affected earlier. Furthermore, their pathophysiology persists partially intangible, although it has been confirmed the involvement of cortico-basal ganglia circuitry in one as well as the other^{8,15}. Dissimilar to tic disorders, stereotypies produce no premonitory urges, consequently children cannot predict and attempt to suppress their movements¹⁴.

Other than tics, obsessive-compulsive disorder is differentiated from stereotypic movements by the absence of obsessions and rules applied strictly¹. In stereotypic movement disorder, behaviours are apparently propelled but apparently aimless. Similarly, trichotillomania and excoriation disorder^{1,2} are characterized by body-focused repetitive behaviours and should be ruled out, since stereotyped movements barely consist of hair-pulling or skin-picking behaviours. By contrary, and even if the two self-injurious previously referred are present, there is a tendency for them to be coordinated, patterned and predictable using the same muscle groups.

Also, habits, mannerisms, paroxysmal dyskinesias, and benign hereditary chorea should likewise be excluded, as well as involuntary movements related with neurological condition or abnormal involuntary movements (abnormal head movements, tremor, cramp, spasm, fasciculation, and other).

Subki et al. proposed an etiological classification of motor stereotypies and within secondary stereotypies group were mentioned autism spectrum disorder (ASD), mental retardation, sensory deprivation, inborn errors of metabolism, genetic (e.g. Rett syndrome, Lesch-Nylan, Cornelia de Lange, Angelman syndrome and Fragile X syndrome)⁵, drug-induced, infection, tumor, trauma, and psychiatric causes¹⁰. Chebli et al. estimated that the prevalence of stereotypies in children with developmental disabilities is close to 61%, and in children with ASD it can be higher at 88%¹⁶. In fact, ASD is the most common developmental disorders related to stereotypies and for that reason the most studied so far. There is an extensive list of body parts and types of movements (e.g. visual – staring at an object or the fingers “out of the corner of the eyes”, hand/finger – shaking, tapping, waving) described in terms of stereotypies associated with autism¹⁷.

This review will focus on summarizing what is known about secondary stereotypies to obtain a greater understanding about their possible underlying connections between a specific disorder and its stereotypies, also to pinpoint incomplete knowledge that should be addressed in upcoming studies.

Methodology

For the accomplishment of this dissertation, it was considered the revision of recent literature (*"Scope review"*) regarding secondary stereotypies. For that reason, between September 2021 and April 2022, research was done along with the query (*MeSH words*) "stereotypies", "secondary stereotypies", "restricted and repetitive behaviours", "neurologic developmental disorders", "children", "etiology", "diagnosis", in PubMed and Elsevier. To begin with, original articles of investigation published in the last ten years were chosen and entirely analysed. Moreover, the literature previous to that data was studied towards a better understanding of stereotypies.

Secondary Stereotypes

Intellectual disability

According to DSM-V, intellectual disability (ID), now known as intellectual developmental disorder, is a condition that incorporates both intellectual and adaptive functioning deficits in three domains, which are conceptual, social, and practical, and with an onset during child-development period¹. To make the diagnosis of intellectual disability is necessary a clinical assessment and individualized as well as standardized testing of intellectual and adaptive function. Prevalence of ID in general population is just about 1%, and it's a recurring comorbidity of stereotypic movement disorder (with or without self-injurious behaviour). Stereotypes like body rocking, complex hand and finger movement, and hand flapping are frequent among individuals with intellectual disabled children¹⁸.

Schroeder's research group explored the risk factors for stereotyped and other behaviours among 180 young children (mostly below the age of 3 years) at risk for intellectual and developmental disabilities¹⁹. These investigators pointed five primary risk factors (age, gender, clinical diagnosis, intellectual level, communication level) and seven secondary interest factors (family income, parental education, visual impairment, hearing impairment, dental problems, nutritional deficiency, and seizures), that were examined in a two parts study (first one was a cross-sectional study at the beginning of assessment, and the second one a longitudinal study for follow-up). Concerning to stereotypes, results showed higher stereotyped behaviours in older children and in boys more than girls. Moreover, children at risk for ASD presented more frequent stereotyped behaviour than children in the Down syndrome or other intellectual disabilities group. Intellectual and communication levels were not positively related to higher frequency of stereotypes in this study. Secondary risk factors failed to reach statistical significance, perhaps because this population as a very young age and these factors would only have a higher influence at an older age, although stereotyped behaviour was already detected at children with only 6 months.

To address the limitations correlated to the previous study and learn more about the developmental trajectory, Medeiros et al. evaluated behaviours like stereotypies in a longitudinal research done in Peru to 160 children with risk for intellectual delay²⁰. This investigation revealed that stereotypies appeared to be stable, and their severity diminished over a period of one year, possibly due to early intervention received along the study. In the other hand, it was clear that children with higher frequency of stereotypies also displayed higher frequency and severity in the future.

Regarding genetic causes of intellectual disability, Down syndrome is the most common one²¹. ID is as well genetically linked to GRIN2B mutations, even if least frequently²². For that reason, ID behaviour phenotype associated to GRIN2B gene has been analysed by Freunscht et al., considering five children aged between 3 and 14 years that showed stereotypic behaviours with inclination for intense stimulus, such as pounding, rocking and loud sounds, along with self-injurious behaviours occasionally.

Usually ID co-occurs with several conditions, specially autism spectrum disorders^{1,2}, so it's important to distinguish them. Pedersen et al. studied a sample of 2816 8-year-old children to evaluate the DSM criteria that best differentiated ID from ASD and concluded that restricted and repetitive behaviours, particularly motor stereotypies, were the greatest discerners between children with ID with some characteristics of ASD from those with co-occurring ID and ASD²³.

Autism spectrum disorders

Stereotypies, as a part of restricted and repetitive behaviours (RRBs), are a core diagnostic feature in Autism spectrum disorder, that usually appear in the developmental period^{24–26}. RRBs described in ASD are classified as lower-level behaviours, where stereotypies are included, and higher-level behaviours^{7,27}. Direct reports of patients with autism describe them as a calming technique, needed to concentrate and to manage with overwhelming sensory surroundings²⁶.

In fact, the prevalence of motor stereotypies in ASD has been stated as 88%, the highest percentage across specific disorders¹⁶. Similarly, and more recently, Melo et al. assessed through systematic review the same frequency measure, registering a prevalence of motor stereotypies linked to ASD of 97,5%²⁸, a value significantly superior than the one obtained by Chebli et al. in the first study¹⁶.

Until now there is scarce information about how stereotypies are expressed in early development. Parmeggiani et al. studied a sample of Italian children with ASD, concluding that the average age at onset of stereotypies were 24 months and recurred in 45,7% of the cases, where the mean age at onset was 13,6 months and the range was between 3 and 48 months²⁹. In this research, stereotypies represented the major early feature of ASD inside the stereotyped behaviours category.

As addressed earlier, stereotypies can be motor or vocal, the last ones being monosyllable vocalizations, non-contextual words or phrases, and non-appropriate laughing and groaning^{30,31}. Intending to appraise machine learning potential for measuring vocal stereotypies, Min and Fetzner performed two experiments, the initial one to detect vocal stereotypies in children with ASD using a traditional machine learning algorithm, showing high precision results (between 73% and 93%)³², and the second one with the assistance of an artificial neural network, obtaining once more high accuracy (85%) in detecting vocal stereotypies³³. Also, Dufour et al. attempted to strike the challenging approaches when measuring vocal stereotypies directly observed applying an artificial neural network with more than 1500 minutes of audio data from 8 children with ASD³⁴. This way an

artificial neural network that measures vocal stereotypies was successfully created, as it can detect these vocal phenomena with a high correlation rate (near or above 0.80).

Normally medical practitioners have a difficult task when they have to make evaluations in their office about stereotypies that mostly take place in routine life of patients with ASD. In this direction, motor stereotypies were studied in children with ASD, so that the problems with outdated measuring techniques would be overcome, this time using wireless three-axis accelerometers and algorithms for pattern identification, detecting automatically body rocking and hand flapping³⁵. Goodwin et al. found that 90% of motor stereotypies were detected successfully by pattern recognition algorithms, demonstrating the importance of these instruments that could assist more efficient and precise studies of behavioural and pharmacological interventions. Likewise, Gonçalves et al. tested the Kinect sensor from Microsoft along with gesture algorithms to automatically detect in real-time hand flapping stereotypy, with the intention that in the future this method could be used to approach autistic children³⁶.

More recently, scientists have been working in improving technological methods, like a smartwatch-based system, that facilitate monitoring motor stereotypies in real-time while children with ASD are in different circumstances of day-to-day life³⁷. Sarker and his colleagues reached 92,6% accuracy when adults imitating autistic children's stereotypic behaviours were using the smartwatch. Their best model identified stereotypies such as hand flapping and head banging, while confounding play-type movements were present. Next step of work should involve a field survey on children with ASD to a better validation of this method.

Another way to solve this limitation presented during observational interviews is with direct observation methods, such as video recording. In this case, it will be possible a better description and characterization of each unique clinical presentation that autistic children can present²⁸, thus allowing to make a systemic classification¹². As a matter of, Grossi et al.⁷, inspired by Melo et al.'s work, examined stereotypic patterns of 67 autistic children through videos recorded by healthcare professionals during ordinary life for three months. First found out that the lower the number of stereotypies, lower the ASD severity, like Péter et al. have ascertained³⁸, and second that there is no correlation of either simple or complex stereotypies with ASD severity. Moreover, motor

stereotypies patterns have arisen in the whole body and upper limb above average (74%), succeeded by mouth and hands (19,8%), with 73% of them appearing throughout a calmness state. Since their team learnt that an individual could display complex and simple stereotypies at the same time, that inspires a future classification done according to the subject rather than the type of stereotypies exhibited. The same work using video recording sessions was done by Lanzarini et al., this time aiming to study the prevalence of phonic stereotypies using videos recorded in a monitored setting during hospital appointments³¹. Of the 35 children with ASD, 83% of them have presented phonic stereotypies, being the most common subtypes the noncommunicative vocalizations (60%), the monosyllables (37,1%), and the echolalic stereotypies (22,9%). The previous results corroborated with the work done earlier by Mayes and Calhoun in a bigger survey, reporting 85% of 777 autistic children with phonic stereotypies³⁹.

Regarding gender, Antezana et al. noted male patients usually exhibited more lower-level RRBs, in particular hand and finger movements, and female patients show more self-injurious behaviours (another type of lower-level RRBs), such as hair and skin pulling⁴⁰. This is conflicting with Wang and his colleagues conclusions in a survey done in China with 1064 toddlers with ASD, where results indicated that non-verbal autistic girls had more body stereotypies, such as repetitive circling and jumping than boys⁴¹. Nevertheless, the discrepancy of gender across studies done with autistic children can explain the variations and sometimes the inconsistent results, which makes it difficult to carry out with a stereotypy profile in children with ASD^{7,28}.

Considering the neuropsychological perspective, one of the hypotheses that explains RRBs in ASD is the dysfunction in executive functions, including impulse management, flexibility of thoughts, and behaviour. Valeri and colleagues supported this theory stating that deficit in inhibition is associated with the inefficient ability to regulate RRBs⁴². This team discovered that children with ASD were prone to commit more errors when trying to suppress responses compared to children with normal development.

Another biopsychological correlation done in literature includes lower-level behaviours, like stereotypies, associated to alterations in dopamine projections⁴³. Besides that, some studies revealed hypoconnectivity among the precentral and postcentral gyrus, left posterior insula, and

left posterior putamen linked to stereotypies in childhood and adolescence periods⁴⁴. Another correlation was demonstrated by Estes et al. while investigating young children with ASD, revealing a decreased volume in the right globus pallidus and the putamen of both sides and concluded these findings were related with more severe stereotypies⁴⁵.

Likewise, electroencephalogram (EEG) abnormalities were analysed as a potential neurophysiological biomarker of severity in ASD by Nicotera et al.. This team meant to appraise, among other factors, the potential connections between EEG abnormalities and stereotypies. The results indicated that 64,28% of the patients with normal EEG had no stereotypies, and a small number of stereotypies were reported in the EEG abnormality groups (non-epileptiform and epileptiform abnormalities' groups had collectively 55,5%). Still, the major finding revealed that the epileptiform abnormalities' group attained a higher percentage of individuals with incapacitating motor stereotypies (38,8%) compared to the normal EEG group (11,9%)⁴⁶.

As previously stated, stereotypies in ASD are a diagnostic challenge since they can be easily confounded in younger patients, especially with tics. With that in mind, Termine and his collaborators attempted to evaluate video recordings of stereotypies in young children with severe ASD with the purpose of assessing the prevalence of potential co-morbid tics¹⁴. Findings suggested a high rate of tics as a comorbidity of severe ASD patients with stereotypies.

Regarding treatment methods, there are only some options, from non-pharmacologic to pharmacologic, available to approach stereotypies in ASD children. Non-pharmacologic therapies include behavioural interventions that are divided in two groups, the ones that block the individual before engaging in the behaviour and redirection it^{47,48} (positive outcomes are documented, especially in vocal stereotypies in autistic children³⁰), and the others that help preventing stereotypies to occur (e.g., taking a nap, choosing preferred activities, or physical exercising)²⁷. Regarding these procedures, Schmitz et al. considered the impact of physical exercise on ASD children with stereotypies. It was understood that low to moderate intensity exercises are a key factor to reduce these behaviours at 60 min after exercising, unlike high intensity workouts that seem to aggravate stereotypies in autistic children⁴⁹. Later that year, Tse et al. attempted to show that each stereotypy needs different exercise approaches in order to be reduced and to generate a

beneficial change in behaviours. This team successfully have shown that when children with ASD are asked to do a ball tapping exercise, only the ones with hand flapping stereotypies were decreased, while body rocking stereotypies didn't show any improvements⁵⁰.

On the other hand, pharmacologic possibilities have been emerging to target directly the pathophysiology cause of stereotypies, for instance defects in glutamate pathways, as Hardan et al. did in a pilot trial of oral N-Acetylcysteine (NAC) with autistic children, obtaining significant improvement in stereotyped behaviours in all subscales that were applied and statistical differentiation among two of them⁵¹. Another therapy tested that presented as effective evidence in treating stereotypies was risperidone combined with celecoxib, a cyclooxygenase-2 inhibitor⁵², since anti-inflammatory markers, specially interleukins 1 β , 6, 8 and 12, have been linked to stereotypies. Recently second generation antipsychotics were pointed by Pillay and colleagues for being valuable in terms of reducing stereotypies in children with ASD⁵³, a result supported by another survey done by D'Alò et al.⁵⁴. In fact, aripiprazole, a second-generation antipsychotic, used in the past to treat irritability states in ASD children, was the main focus of Hirsch and Pringsheim's work and revealed promising results in terms of diminishing the number of stereotypies in children with ASD after a short period treatment with aripiprazole⁵⁵.

Sensorial deficits

Visual and hearing deficits

As stated earlier, secondary stereotypies can appear as a result of sensory impairments, specifically visual and auditory. A small amount of work was found while researching this theme in the last ten years. However, in 2009, Gal et al. investigated stereotypies in development and sensory disabled children, and attained the prevalence of stereotypies in different conditions, where visual and hearing impairment were second and fourth of the most common, with 86% and 67,9% respectively⁵⁶. These investigators also referred that those visual impaired children presented more eye movements and eye gouging, whereas hearing impaired ones didn't have specific stereotypies (were mostly repetition of noises, or words) that could distinguish them from children with other conditions, like intellectual disability. To this date there is no clear understanding of which pathologic mechanism is responsible for stereotypies behind visual and hearing impairments, although some researchers suppose these phenomena result from an effort of sensorial stimulation.

About blind children, the type and the severity of stereotypies that are displayed depend on the sensorial deficit level. Molloy and Rowe verified this theory while examining visually impaired children, and the results revealed that the behaviours that involve eye manipulation, like eye poking, are correlated with visual deficits. Other stereotypies were associated visual deficit, like body and head movements, especially in completely blind children, whereas partially blind children tended to display more eye manipulatory movements and rocking⁵⁷. Further research into the risk factors and the prevalence for stereotypies in visually impaired children was performed by Sarimski and Lang through parents' report. In this investigation it was found not only that stereotypies are more frequent and severe in blind children than in children with only partial visual impairments, but also that variables like social and communicative abilities are extremely correlated with stereotyped behaviours' frequency, by minimizing them⁵⁸.

Specific syndromes

Rett syndrome

Rett syndrome (RTT) is a disorder of neurodevelopment that usually occurs in association with intellectual disability, as well as motor and communicative deficits, including four typical features, one of which is midline hand stereotypy^{59–61}, indicators of regression period, and almost exclusive of female gender. This stereotypic movements often begin between 12 and 24 months, although the diagnosis comes much later, particularly when children are not exhibiting Rett's typical hand stereotypies, like hand wringing⁶⁰. Other stereotypies linked to RTT reported in different video studies of children in the first months of life were opening and closing hands repetitively, disproportionately hand patting, wrist and arms twisting, repetitive uni- or bilateral hand pronation with wrist flexion, putting the side of palms together, lifting both hands and separating them⁶². Hand stereotypies categorization lacks precision in the terms used in different studies, so it's important that the medical community starts using standard terms⁶¹.

Between 95-97% of cases of RTT^{59,63} are associated to a methyl-CpG-binding protein 2 (MECP2)^{64–66} gene mutation, and is clearly connected to the increased severity of Rett syndrome, which is in turn correlated to hand use and stereotypies onset age⁶³. However, other gene mutations had been described, like FOX1^{67(p. 1),68–71}, CDKL5^{72–75}, and MEF2C^{76–78} representing RTT variants, all of them presenting hand stereotypies. Another gene that deserved the attention of Rodan et al. was huntingtin gene mutation, a possible clue for a new Rett-like syndrome, as they documented two of the three family members with midline hand stereotypies, like hand wringing⁷⁹, and in none of them was positively detected one of the previously RTT associated gene. Also, a new variant involving a NACC1 gene mutation has been described by Schoch et al. This team observed 7 individuals affected with this new variant and also presenting hand stereotypies⁸⁰. Hence, the development in the next-generation-sequencing-based techniques applied clinically has caused a remarkable expansion in the documented heterogeneity of genes in RTT^{81,82}.

Concerning risk factors associated with hand stereotypies in Rett syndrome, there's still much to understand. In Quest's et al. work, RTT hand stereotypies were not related with low or high states of stress in any of the 5 females studied, some of them were children. It seemed that hand stereotypy may not be yet considered a response to stress indicator in RTT patients, till more studies are done with a bigger clinical trial and with more "stressful" situations⁸³.

Stallworth and his colleagues attempted to portray hand stereotypies in a survey with 1123 females suffering from RTT, having obtained higher frequencies of hand stereotypies in individuals with classic RTT and severe MECP2, and realizing that the most common were clapping/tapping and hand mouthing decreased over time. Other than that, it was confirmed the heterogeneity within types of hand stereotypies across variants of RTT, and the severity of stereotypies was correlated with the worst hand function⁸⁴. More recently, Hirano et al. conducted a research based in an inquiry form done to Japanese families that have children with RTT and discovered that of 72 RTT patients, all had some type of hand stereotypy, being hand mouthing the most common, succeeded by clapping/tapping⁸⁵, as in Stallworth's study⁸⁴. Also, only 72,1% of RTT patients in this study received intervention to decrease hand stereotypies, such as splints for the hand and fingers, massages, holding hands and sensory play, resulting in a substantial reduction of those behaviours and improvement in the hand function. Nonetheless, all the children that had intervention registered more contractures and more current problems, showing that these children only will benefit from intervention when the right procedures to their personal needs were found.

To differentiate RTT from ASD, Goldman and Temudo studied 20 children with RTT and another 20 with ASD, comparing their hand stereotypies through video examination since this feature is shared by both disorders. These investigators discovered defining traits between RTT and ASD groups, as RTT's hand stereotypies appeared complex, continuous, mostly in body midline, and engaging mouthing, whereas ASD ones were simple, two-sided, intermittent, and with frequent involvement of objects⁸⁶.

There are not many treatment options for stereotypies in RTT, despite newly findings are placing communication interventions as an opportunity to target stereotypies, and not just language competences. As Stasolla et al. that utilizing two therapeutic interventions, PECS and VOCA, usually used as strategies for augmentative and alternative communication, learnt that those tactics reduced

the three girls' stereotypies. This might be because promoting positive engagement and encouraging alterations in the surrounding environment had demonstrated to have a positive outcome on managing stereotypies, so further investigation should be done to a larger patient sample⁸⁷. Whereas in Lim's et al. scoping review are reported other options targeting stereotypies reduction, such as the use of splints (in Hirano's study⁸⁵), gentle physical interruption of hand mouthing, interactive games involving objects, and operant conditioning⁸⁸.

Angelman syndrome

Described for the first time by Angelman in 1965 as the "puppet child" syndrome, Angelman syndrome is a rare neurodevelopmental disorder that features delayed development, severe ID, missing speech, epilepsy, exuberant behaviour with happy demeanour, and motor impairment, due to a UBE3A gene mutation possibly caused by several anomalies in chromosome 15^{89,90}. Although stereotypies are a core feature of this disorder manifested in all patients, there are no specific stereotypies related to Angelman's syndrome⁹¹. Thus, there are more common ones, like hand flapping, and less common ones, such as spinning⁹². In fact, young patients with Angelman syndrome had continuously low stereotypy scores confirmed in Sadhwani's et al. survey⁹⁰.

Fragile X syndrome

Fragile X syndrome (FXS) is originated by a mutation in the FMR1 gene (fragile X mental retardation 1) and is a common cause of ID that affects males the most. Stereotypies have a highly prevalence in Fragile X syndrome, achieving 90,6% in Hall's et al. investigation with FXS boys, exhibiting the behaviour on a daily frequency⁹³. Likewise, Newman's et al. research showed that within 47

children with FXS examined, all of them had engaged in stereotypies. A high correlation between anxiety and stereotypies was also reported in this study⁹⁴. As for the most predominant stereotypies in FXS children, it's known to be hand stereotypies, so Zhang et al. studied the onset and characteristics of this type of stereotypy in 13 children with FXS. Results showed that the majority of children had initiated hand stereotypies by 24 months, and the more frequent subtypes were hand flapping, succeeded by hand pronation/supination⁹⁵.

In terms of differential diagnosis, FXS can be easily mistaken for ASD, and can even co-exist, which makes it harder to distinguished them by their stereotypies presentation, as their exhibition even overlap, as seen in a study done by Wolff et al.⁹⁶.

Smith Magenis syndrome

Smith Magenis syndrome (SMS) is another neurodevelopmental disorder originated by a mutation in RAI1 gene causing craniofacial anomalies, neurologic and behaviour disorders. When referring to SMS' behaviours, stereotypies are the main topic that should be analysed, with a unique profile the most frequent ones are self-hugging, hand wringing and licking⁹². Corroborating with literature, Gamba et al. evaluated 7 SMS children and all of them exhibited self-hugging stereotypy⁹⁷.

Pitt- Hopkins syndrome

Pitt-Hopkins syndrome (PTHS) is a rare single gene disorder featuring developmental delay, epilepsy, specific facial characteristics, respiratory anomalies, and repetitive behaviours, caused by a mutation or deletion in the TCF4 gene. Characterized by frequent non-specific motor stereotypies, PTHS children usually present hand and finger flapping/twisting, and body rocking⁹⁸⁻¹⁰⁰.

Williams syndrome

Williams syndrome (WS) is a neurodevelopmental disorder caused by a microdeletion in chromosome 7 and is characterized by a hypersociability state, compromised cognition, ID, and abnormal behaviour. With the purpose of assessing WS behavioural profile, Braga et al. studied 8 pre-school children with WS, showing that stereotypies were the main behavioural problem, among them were verbal stereotypies, as yelling and screaming, and motor stereotypies, as arm swinging, rolling head, bouncing and running around and whirling. This survey results also shown that verbal and adaptative impairments typical of WS might be the cause of problematic behaviours, like stereotypies¹⁰¹. More recently, Huston and collaborators observed 60 young subjects with WS, detecting at least on stereotypy in 50 of them, and the most common ones were rocking back and forth, succeeded by repetitive body and hands movements. Less frequent stereotypies were self-rubbing, paces, twirling things, sustained finger movements and waving/shaking arms. Also is was noted that children under stimulant medication had more frequent and severe stereotypies¹⁰². In Royston's et al. research, body stereotypies were found to be most common in WS patients when comparing with other stereotypies and other like Prader-Willi and Down syndromes¹⁰³.

Cornelia de Lange syndrome

Cornelia de Lange syndrome (CdLS) is another genetic syndrome caused by a mutation in cohesion, and with an intellectual disability association, craniofacial anomalies, cognitive impairments, and limb defects¹⁰⁴. In a behavioural perspective, CdLS patients appear to have autistic features¹⁰⁵, especially stereotypies like circling, whirling, twirling¹⁰⁶ and abnormal hand postures¹⁰⁴.

Metabolic and degenerative diseases

Wilson syndrome

Wilson disease (WD) is a metabolic disorder related to organ accumulation of copper, particularly in liver, cornea, and brain. As for behaviour profile in WD, reports of stereotypies are very rare, and mostly about adult patients with finger movements stereotypies¹⁰⁷, so it's not appropriate for this review that is based in children secondary stereotypies. Only one article was found about a 12-year-old Indian girl with WD describing motor stereotypies in both upper limbs, more precisely extension/flexion of metacarpo- and interphalangeal joints along with the same movements in the wrist (essentially tapping fingers and flapping wrists). Following up this patient after chelation therapy, Data et al. observed a reduction in her stereotyped behaviours six months later¹⁰⁸, showing that this behaviours might be precipitated by this disorder.

Adenylosuccinate lyase deficiency

Adenylosuccinate lyase deficiency (ASLD) is a rare hereditary neurometabolic disorder produced by a genetic modification which leads to decrease the efficiency of adenylosuccinate lyase enzyme, and consequently occurs with developmental delay, and frequently with epilepsy and ASD. With the intent of approaching atypical features in ASLD patients, Pérez-Dueñas et al. described a 9-year-old boy that presented with autistic features since his first months of life, like head and trunk rocking, verbal stereotypies, and upper limb stereotypies. Also in this study, another patient presented stereotypies frequently, a 14-year-old boy with rocking, hand flapping, repetitive object handling, and atypical gazing at fingers and objects stereotypies¹⁰⁹.

Succinic semialdehyde dehydrogenase deficiency

Succinic semialdehyde dehydrogenase deficiency (SSDD) is a rare genetic neurometabolic disorder, also called as 4-hydroxybutyric aciduria, usually associated with non-specific symptoms, hence it remains an underdiagnosed disease. Phakey et al. presented a case of a 26-year-old woman that exhibited stereotypies from age 14, more specifically hand and face stereotypies, the last ones consist of wiping and chewing¹¹⁰.

BPAN

B-propeller protein-associated neurodegeneration, or BPAN, is a subtype of neurodegenerative diseases involving brain iron accumulation, and found to be related to WDR45 gene¹¹¹. This disorder is associated with development delay and epilepsy, this conditions usually are stable since early childhood till adolescence. Uchino and colleagues presented for the first time a video report of a 9-year-old girl with BPAN before neurodegeneration. The video showed a girl with midline hand stereotypies, for instance wringing and clapping, similar to RTT's stereotypies¹¹².

Neuronal ceroid lipofuscinoses

Neuronal ceroid lipofuscinoses (NCLs) are a genetic neurodegenerative disorder, in fact the most common one in children. Clinical features of NCLs consist of progressive cognitive and motor impairments, visual loss, seizures, ataxia, and even death at young age. Recently, Kozina and colleagues

reported a 5-year-old girl with NCL type 7, where hand and face stereotypies appeared at the age of 3. As her hand stereotypies look like RTT ones, investigators identified this case report as a RTT-like onset, and a exome sequencing in search for MECP2 mutations was done, however results only showed a MFSD8 mutation that was linked to a NCL late-infantile variant¹¹³.

Epilepsy syndromes

Sunflower syndrome

Sunflower syndrome is a rare epileptic photosensitive syndrome typified by stereotyped reflex seizures triggered while bending their faces up towards the sun¹¹⁴. Indeed, patients with Sunflower syndrome usually are attracted to sunlight, which causes them to produce hand-waving and eye-blinking stereotypies, and sometimes fluttering and rolling of the eyes^{115,116}.

Dravet syndrome

Dravet syndrome (DS) is a severe epileptic syndrome typical of childhood related to SCN1A gene mutation, causing multiple types of seizures, sustained febrile seizures and frequent episodes of status epilepticus¹¹⁷. In recent findings, Sala-Coromina et al. discovered five young patients with a de novo SCN1A gene mutation and DS, some of them also with ASD, exhibiting eyelid stereotypies (clustered and repetitive eyelid closure actions), a never before phenomena documented in Dravet's patients. This atypical movements were seen to be triggered when young children tried to concentrate

and in older ones while they were upset. Hence, this investigators theorized that eyelid stereotypies might be specific to DS patients with SCN1A mutation, rather than to autism itself, since there are no reports of this type of stereotypies correlated to other disorders in literature¹¹⁸.

Early-onset epileptic encephalopathies

Early-onset epileptic encephalopathies (EEE) are a heterogeneous category of disorders, of which disorders related with epilepsy gene GRIN1 and STXBP1 mutations are part of¹¹⁹. Only some cases of stereotyped behaviours have been reported, for example, Romaniello et al. described a 9-year-old girl with a de novo STXBP1 gene mutation with a specific type of hand stereotypies, hand washing¹²⁰, associating this gene alteration to RTT phenotype. Also, Kim and colleagues noted that 3 child patients with STXBP1 encephalopathy presented head stereotypies (one of them with a horizontal particular pattern similar to a 8 figure), and other stereotypies in the upper limb and trunk¹²¹. As for GRIN1 related stereotypies, Ohba et al. reported 3 patients, all of them with hand stereotypies, and varying from hand washing, to hand mouthing or wringing in one patient¹²².

CNS malformations

Stereotypies related to CNS malformations are an issue that is yet lacking information in literature. Rhombencephalosynapsis (RES) is a genetic cerebellar malformation and the one that it was found in literature in the last ten years. Tully and collaborators addressed this CNS malformation, and while studying 59 patients with this condition, 50 of them (85%) persistently presented with side-to-side and figure-8 head shaking stereotypies, which made this team concluded that this type of

stereotypy is widespread in RES patients. There were other stereotypies mentioned less frequently, like hand stereotypies, as clapping, rubbing and wrist rolling, and body rocking¹²³.

Immunologic and infectious

Anti-NMDAR encephalitis

Anti-N-methyl D-aspartate receptor (anti-NMDAR) encephalitis is a form of autoimmune encephalopathy that occurs in children and the one cause among autoimmune encephalitis that most frequently has stereotypies associated, like repetitive oral movements, grimacing repeatedly, cycling leg stereotypy, nodding head stereotypy, and upper limb and trunk stereotypies, as was described in Mohammad's et al. work¹²⁴.

Anti-LGI1 encephalitis

Another variant of autoimmune encephalitis is related to leucine-rich glioma inactivated 1 (LGI1) antibody; it also comes with stereotyped behaviour associated, although to a lesser extent. Özbek et al. reported a 6-year-old boy with anti-LGI1 encephalitis displaying orolingual stereotypies (oromandibular and tongue protrusion stereotyped movements), and less frequently facial stereotypies¹²⁵.

Others

Narcolepsy with cataplexy

Narcolepsy, a condition that causes daytime sleepiness, often related to cataplexy, a sudden loss of muscle tone status, usually sparked by abrupt emotional changes. Other features present in this disorder within the motor disturbances are stereotypies, as Plazzi and collaborators stated in their work while analysing video records of 39 children during catalepsy episodes. Results showed that whenever children suffered from this narcolepsy with catalepsy episodes, 61% of them exhibited stereotypies when triggered by emotional stimuli, and only 13% ha stereotypies when the emotional trigger was not present. It was also established that children with neurologic abnormalities at examination had higher prevalence of stereotypies, when compared with the ones without neurologic impairments. Some of the stereotypies detected were repetitive finger mouthing, bilateral upper limb movements, and tapping-lips ¹²⁶.

PANS

Pediatric acute-onset neuropsychiatric syndrome (PANS) is a childhood condition, frequently with an overnight onset of neuropsychiatric symptoms including REM sleep behaviour disorder, which involves stereotypies. Gaughan et al. observed this sleep disorder in 15 children with the diagnosis of PANS, and some of them presented with hand and finger stereotypies, in addition to stereotyped head movements¹²⁷. The cause of PANS is still unknown in the majority of cases, although is believed to be activated by infectious processes, metabolic disorders, and additional inflammatory responses.

Non-epileptic paroxysmal events

Non-epileptic paroxysmal events (PNMEs) are classified as psychogenic non-epileptic events or seizures (PNES) and organic paroxysmal events. PNMEs are defined by recurring motor events with an acute onset and ending, that typically mimic epileptic events. Canavese et al. studied 63 young individuals, all of them affected by PNMEs, reporting stereotypies in 6 patients, which was enough to make stereotyped movements the third most frequent feature of PNMEs. However, only 4 of the 6 cases were secondary stereotypies linked to encephalopathies, and mainly involved head and upper limbs stereotyped movements¹²⁸.

Conclusion

To my knowledge, no systematic review concerning secondary stereotypies in children was done, especially with the intention of identifying their particularities to further comprehend their clinical impact, and if the emerging information would be clinically applicable to assist patients' management. Studies found in the last ten years were summarized considering only the ones about children with stereotypies attributed to various etiologies.

As mentioned earlier, secondary stereotypies are a common and incapacitant phenomena, marked by a challenging diagnosis. However, when adopting an early, multidisciplinary, and accurate intervention it could be easier to treat or contain stereotyped behaviours with the purpose of providing better quality of life to younger patients.

The evolution of scientific and technologic knowledge provided important advances when it comes to pathophysiologic mechanisms and biomarkers, definition and diagnosis, and even other correlations associated with stereotypies. Fortunately, genomic discovery and genetic interventions innovations, have highlighted and clarified several new causes of stereotypies.

Generally, the recent results registered in literature contributed to assemble reports and predictors of secondary stereotypies, as they represent the primary cause of more complex and disabling stereotyped behaviours. Therefore, sustained studies of disorders presenting with stereotypies will eventually, through longitudinal data, allow for better recognition of etiologies and comorbid conditions that are shared, that usually are misdiagnosed as tics or obsessive-compulsive disorders.

The most frequent stereotypies observed along this review were hand stereotypies, that are present in most of the syndromes analysed, which makes it harder to link them to a certain disorder. In fact, almost all the syndromes have no specific, or pathognomonic, stereotypies identified, and even in the same syndrome not all the patients have these stereotyped behaviours.

The purpose of this review was served, inaugurating an extensive literature review of studies investigating secondary stereotypies in children the past ten years, so that these findings disseminate to the broader neurodevelopmental disorders' community. The lack of guidelines on how to

approach stereotypes leads to an atmosphere of insecurity among health care professionals. These circumstances can lead to frustration for the attending physician, creating difficulties mostly in the physician-parents relationship, as this review focus only on children and their parents are their responsible for all the medical decisions.

Notwithstanding, further research on whether stereotypes should be pondered as a core feature of specific syndromes other than ASD, on how stereotypes are experienced by children with specific syndromes, in what way stereotypes are manifested during developmental period, the neuropathology behind these phenomena, and more treatment options is required.

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