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CARPAL TUNNEL SYNDROME IN PATIENTS WITH MUCOPOLYSACCHARIDOSIS: A LITERATURE REVIEW

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ABSTRACT

Mucopolysaccharidoses (MPS) are hereditary and progressive metabolic disorders caused by inborn errors of metabolism (EM) that lead to a deficiency of enzymes that act on cell lysosomes.These enzymes are specifically involved in the metabolism of glycosaminoglycans (GAG), which start to accumulate in cells, tissues and organs. Carpal tunnel syndrome (CTS) is a neuropathy caused by entrapment of the median nerve (MN) at the level of the carpal tunnel (CT). Although CTS is the most common neuropathy caused by entrapment in adults, it is extremely rare in children, however, the most common etiology in the pediatric population, excluding the idiopathic one, is the MPS. Objective: To review and describe the main aspects of the relationship between carpal tunnel syndrome and mucopolysaccharidoses. Methods: Articles published between 2015 and 2020 indexed in PubMed, LILACS and Scielo databases were consulted. Conclusion: The results of this study allow us to conclude that the main cause of CTS in children and adolescents is MPS, a spectrum of systemic diseases with variable and unpredictable presentation. In addition, parents of patients with MPS report a worse perception of hand function and the child's ability to perform activities of daily living. An efficient screening protocol employing neuroconduction studies or even MN ultrasound should be used, as the benefit of early intervention in CTS been demonstrated in different studies in patients with MPS.

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INTRODUCTION

Mucopolysaccharidoses (MPS) are a group of inherited metabolic diseases that result in the progressive lysosomal accumulation of glycosaminoglycans (GAG) in cells and tissues. GAG accumulation manifests with facial dysmorphism, hepatosplenomegaly, joint stiffness and contracture, heart valve dysfunction, obstructive sleep apnea, visual and hearing abnormalities, cognitivedelay and developmental regression. There are seven distinct subtypes of MPS with some overlap in signs, symptoms, and variable severity of phenotype (Patel, 2020). Progressive and invasive musculoskeletal manifestations are traces of MPS. In mucopolysaccaharidosis type I (higher incidence subtype), for example, GAG accumulation in cartilage,tendons, and joint capsule tissues results in musculoskeletal defects, including occipitocervical instability, spinal stenosis, thoracolumbar kyphosis, developmental dysplasia of the hip, osteonecrosis of the femoral head, progressive genu valgum, joint stiffness, carpal tunnel syndrome (CTS) and trigger fingers that generally lead to significant joint pain, discomfort and functional disability, often requiring surgical intervention (Viskochil, 2017).

CTS is a peripheral compressive neuropathy caused by the compression of the median nerve (MN) at the level of the carpal canal or tunnel (CT).CTS is among the most common musculoskeletal manifestations of MPS, almost always reported in MPS types I, II, IV and VI. Excess tissue GAG leads to thickening of the flexor retinaculum (FR), resulting in impaired mobility of the tendons, tenosynovitis, MN entrapment, and the typical "claw" hand deformity (4th and 5th fingers with metacarpal hyperextension-phalangeal and partial flexion of the interphalanges). If left untreated, severe compression of the MN can resulte in irreversible damage, (Wright, 2019). In this context, this study aimed to review and describe the main aspects of the relationship between carpal tunnel syndrome and mucopolysaccharidosis, detailing the results of the most recent studies involving this topic.

METHODOLOGY

This study is a narrative review of the literature prepared between June and December 2021, seeking to better clarify the relationship between mucopolysaccharidosis and carpal tunnel syndrome.

Consultations were carried out on articles published between 2016 and 2021 indexed in PubMed, LILACS and Scielo databases. In the search strategy, the following expressions were used as descriptors and keywords: "carpal tunnel syndrome", "mucopolysaccharidosis", "median neurophaty", and "lysosomal storage diseases"; in addition to their respective subtopics and combinations. Articles included in these databases in the last 5 years written in English, Portuguese, Spanish and French were included. The following inclusion criteria were used: trials or reviews of patients with mucopolysaccharidosis and diagnosis of carpal tunnel syndrome, regardless of gender, age or initial treatment; studies that evaluated the diagnosis, screening and treatment of CTS in patients with MPS; articles that covered updates and new trends about CTS secondary to MPS. Trials that did not meet the aforementioned inclusion criteria, as well as those that included conditions other than MPS associated with CTS, such as pregnancy, acute trauma, RA, diabetes mellitus, among others, were excluded.

RESULTS

The search in the databases resulted in the selection of 6 articles that met the established inclusion criteria. After analysis and categorization, the studies were organized in a filing format in order to summarize the results, thus establishing the latest evidence and updates on the correlation between MPS and CTS (Argenta, 2017). Patel et al., 2020, leading a research on articles published between 1960 and 2018, stated that nerve conduction studies remain the most useful form of investigation for screening and diagnosis of CTS in MPS. Median Nerve and Carpal Tunnel Ultrasound has been proven to be an attractive alternative or adjunct to nerve conduction studies as a screening and diagnostic modality for CTS in MPS patients, as it is very tolerable in children, with a reported sensitivity of up to 95%. The most used initiation and frequency of screening for CTS in MPS were once every 1 or 2 years from the diagnosis of MPS (Argenta, 2017). Viskochil et al., 2017, retrospectively collected data from the MPS I Registry, a voluntary, observational database developed to track the clinical progression and management of MPS I patients worldwide. They obtained 994 patients classified as severe (Hurler syndrome) or attenuated (Hurler-Scheie or Scheie syndromes) MPS I. Among these, 291 had a diagnosis of CTS based on abnormal ENMG or MN decompression surgery. The means of the first diagnosis of CTS were: 5 years and 2 months (minimum 10 months/maximum 16 years and 2 months); and 9 years and 11 months (minimum 1 year and 8 months. /Maximum 44 years and 1 month) for patients with severe and attenuated MPS I, respectively. Most patients had the first diagnosis of MPS I (94 %) or even after its treatment (hematopoietic stem cell transplantation and/or enzyme replacement therapy) (74%). For 11% of patients with attenuated disease, the diagnosis of MPS I by an average of 7 years and 6 months (Dabaj, 2019). In turn, Bäumer et al., 2016, performed a clinical trial with twenty-four patients (13 men and 11 women), whose mean age was 7 years and 11 months (range 6 months to 29 years) selected with diagnosis of CTS and MPS. They measured the frequency of CTS and ENMG and MN US abnormalities in MPS patients, and compared pre- and 1-year postoperative outcomes with a control group. In 26% of patients with MPS, clinical signs of CTS were present. 77% of patients met electrophysiological criteria and 92% met ultrasound parameters for CTS. Postoperatively, ENMG showed an improvement in patterns, while US results remained unchanged. In the control group, age and height correlated with the cross-sectional area of the nerve, but not with the wrist-forearm relationship (Baumer, 2016). In the same vein, Argenta and Davit in 2017, published a case report of late-onset CTS in a 12-year-old boy diagnosed with Hunter syndrome, followed by a review on the literature. The patient was a 12-year-old boy diagnosed at age 3 with Hunter Syndrome after demonstrating delay in developmental milestones. He had minimal CTS clinical symptoms but advanced median nerve damage on electroneuromyography. He underwent bilateral carpal tunnel release with median nerve neurolysis and flexor tenosynovectomy. The intraoperative examination showed the presence of median nerve compression and moderate tenosynovial hypertrophy of the flexor tendons, bilaterally. In conclusion, parents reported mild subjective improvement in dexterity and fine motor skills postoperatively (McBride, 2021). In 2019, Dabaj et al. performed a retrospective study including all patients with MPS referred to the electrodiagnostic laboratory of an academic center during a 10-year period. One hundred and three neuroconduction examinations were performed on 48 patients with MPS. The median age at diagnosis of MPS was 2.1 years versus 4.9 years at diagnosis of CTS. Analysis of the series revealed that the electrophysiological abnormalities of CTS could have started much earlier (before 2 years of age or even at the time of diagnosis of MPS). The diagnosis was based on the results of sensory nerve conduction velocity and distal motor latency, in addition, the motor nerve conduction velocity through the wrist was taken into account. Bilateral CTS was frequent (88% of cases) in MPS types in the population of this study and, in addition, was observed from the first year of life, and may not be associated with obvious clinical symptoms. Neuroconduction studies have mostly helped with regard to monitoring and early detection of CTS recurrences, leading to early intervention and a better recovery of the condition (Chammas, 2014).
Finally, McBride et al., 2021, produced an evidence-based literature review and clinical practice resources on the therapy of neuropathies in patients with MPS, emphasizing, above all, studies that addressed enzyme replacement therapy (ERT), the hematopoietic stem cell transplantation (HSCT) and new gene therapies (GT). For this, they implemented consultations to articles published between 2004 and 2020. They came to the conclusion that the therapeutic options for disorders involved in MPS have advanced dramatically in the last 10 years. However, neuropathic diseases secondary to MPS still lack adequate treatment and management. Thus, new delivery methods are needed for ERTs to act on the central and peripheral nervous system, even crossing the blood-brain barrier. HSCT is one of the new treatments established for some types of MPS and is being explored. GT promises to be an ideal treatment for MPS neuropathies, with an excellent safety profile in studies to date (McBride, 2021).

DISCUSSION

Lysosomal storage diseases (LSD) are a group of different pathologies with an overall prevalence that varies between 1/1,500 and 1/7,000 live births (summing all diseases in the group). From an epidemiological point of view, they affect all gender ethnicities equally, except in specific cases in which the condition is linked to the X chromosome. LSD are diagnosed mainly in childhood,but several attenuated forms are diagnosed in adults (Suarez-Guerrero, 2016). Clinical manifestations will depend on the enzymatic defect and differential expression in organs and systems. Most LSD are characterized by a broad phenotypic spectrum of nonspecific manifestations, leading to considerable diagnostic and even therapeutic problems. In this context, it is worth mentioning mucopolysaccharidoses, mucolipidoses, glycoprotein storage disease, among others (Grzeszczak, 2021). Mucopolysaccharidoses (MPS) are lysosomal overload diseases characterized by the accumulation of mucopolysaccharides (also called glycosaminoglycans (GAG) in tissues and organs. Most are diagnosed in childhood, but some milder clinical forms may only be noticed in adulthood. The clinical picture is multisystemic and often has an insidious progression (Shapiro, 2021). In general, MPS affect the functional ability of patients and their quality of life, especially when the disease preserves cognitive capacity. In this context, it is known that the level of activity of the hands is one of the most important elements for the psychomotor development and for the performance of tasks of daily living of children. In fact, hand function can limit motor and sensory activities, producing clinical symptoms with the potential to directly and negatively affect the quality or life of these patients, especially when pathological conditions are delayed in diagnosis (Andre, 2021). In children and adolescents diagnosed with MPS, the deposition of GAGs in muscle and skeletal tissue is one of the main pathophysiological characteristics, affecting capsules and ligaments, tendonsand synovial membranes, among others. GAGs may be responsible for limiting joint mobility, especially in tendons and tendon sheaths. Therefore, there is marked inflammatory joint stiffness, especially in the hand, where multiple tendons, nerves and

areas of reduced diameter favor compressive disorders, such as CTS and claw hand, for example. Finally, the musculoskeletal manifestations of MPS not only limit the function of the upper extremities, but also represent a stigma for the patient (Kobayashi, 2018). Median nerve compression at CT level is the most common peripheral neuropathy in adults, however, its occurrence in childhood is rare, corresponding to less than 1% of CTS cases. This syndrome was first described in the pediatric population in 1958 by Martin and Masse (1958) in a series of 3 cases: no cause was clearly identified, assuming an idiopathic etiology. To date, the most reported etiology of CTS in childhood is idiopathic, however, when ruled out, the most prevalent causes are lysosomal overload diseases: mucopolysaccharidosis 58% of cases and mucolipidosis in 14% of cases (Andre, 2021). Deposition of GAGs causes compression of anatomical areas where the blood supply to the median nerve may be compromised. CTS, characterized by thenar muscle atrophy, loss of hand strength,burning, changes in sensitivity and pain, is usually due to the compressive action resulting from the progressive accumulation of GAGs in the MN and the consequent avascular necrosis of the same (Padua, 2016). Current studies show that, among other impairments, hand function, the ability to perform activities of daily living, satisfaction and school mastery in patients with MPS are lower when compared to the group without MPS, significantly higher than the general population (Baumer, 2016). Within this context, MPS can be divided into 7 subtypes: MPS I or Hurler syndrome (Hurler, Hurler-Scheie and Scheie), MPS II or Hunter syndrome (variants A and B), MPS III or Sanfilippo syndrome (variants AD), MPS IV or Morquio syndrome (variants A and B), MPS VI or Marotaux-Lamy, MPS VII or Sly syndrome, and MPS IX or Natowicz syndrome. (Suarez-Guerrero, 2016). Viskochil et al. (2017) studied 994 patients with severe (Hurler syndrome) or attenuated (Hurler-Scheie or Scheie syndromes) MPS I. Among these, 291 had a diagnosis of CTS based on abnormal ENMG or decompression surgery. Most were diagnosed with CTS after the diagnosis of MPS I (94%) or after its treatment (HSCT and/or ERT) (74%). In only 11% of patients, the diagnosis of CTS preceded the diagnosis of MPS I, by an average of 7 years and 6 months. They argue that CTS is a rare medical complication in pediatric patients and, as a single clue, should alert healthcare professionals to the potential diagnosis of MPS. There may be a significant gap between the diagnosis of CTS and the diagnosis of MPS type I, particularly for patients with an attenuated phenotype. Finally, in MPS I, in general, the lack of symptoms reported by the patient, the challenges of diagnosing CTS in the pediatric population, as well as the benefits of early intervention, argue in favor of performing a standardized screening (Viskochil, 2017). Many patients with MPS have minimal symptoms of peripheral neuropathy and, when present, they are difficult to perceive by parents and caregivers, either due to the communicative difficulty of young age or due to the cognitive deficit inherent to the condition of these children. In addition, many studies emphasize the electrophysiological abnormalities of CTS as precursors of the clinical manifestations themselves, thus alerting to the need for screening protocols in this population (McBride, 2021).

In recent studies, the mean age diagnosis of MPS was 2.1 years versus 4.9 years at diagnosis of CTS in patients with both conditions. The analyses revealed that the electrophysiological abnormalities of CTS can start much earlier (before 2 years of age or even at the time of the diagnosis of MPS). Bilateral CTS is frequent (88% of cases) in the types of MPS studied and, in addition, was observed from the first year of life, and may not be associated with obvious clinical symptoms. Neuro-conduction studies mostly help with regard to monitoring and early detection of CTS recurrences, leading to early intervention and allowing better recovery of the condition (Dabaj, 2019). Baumer et al. (2016) analyzed twenty-four patients (13 men and 11 women), with a mean age of 7 years and 11 months, selected with a diagnosis of CTS and MPS (trial). Eight patients were reassessed one year after the operation using US and ENMG. The frequency of CTS and abnormalities on ENMG and MN US in MPS patients was verified, in addition, preoperative and one-year postoperative results were compared with a control group. In 26% of patients with MPS, clinical signs of CTS were present. 77% of patients met electrophysiological criteria and 92% met ultrasound parameters for CTS. Postoperatively, ENMG showed an improvement in the patterns, while the US results remained unchanged. In the control group, age and height correlated with the cross-sectional area of the nerve, concluding, therefore, that younger patients and, consequently, of smaller stature had a better aspect of MN, that is, with a lighter CTS spectrum, alerting, therefore, about the importance of early diagnosis of this condition (Baumer, 2016). Argenta and Davit (2017), in their case reported, addressed the late presentation of CTS in a 12-year-old identified as having Hunter syndrome (MPS II). The patient in question had been diagnosed at 3 years old, after demonstrating delay in psychomotor developmental milestones, including sphincter incontinence, inability to follow commands, loss of speech, aggressive behavior, increased sensitivity to touch, gait on tiptoe, among others. In addition, he had minimal symptoms of CTS, such as grasping hot objects painlessly, excessive friction in his fingers, dropping objects frequently from his hands, and irritation when trimming his nails. On investigation, he already showed advanced MN damage on electroneuromyography. He then underwent bilateral CT release with median nerve neurolysis and flexor tenosynovectomy. Parents, however, reported slight subjective improvement in dexterity and fine motor skills postoperatively, strengthening the essence of diagnosis and treatments as early as possible (Argenta, 2017). Nerve conduction studies remain the most useful form of investigation for screening and diagnosis of CTS in MPS, in addition, MN and CT US is an attractive alternative or adjunct to ENMG as a screening and diagnostic modality for CTS in patients with MPS, as it is more tolerable in children and has a reported sensitivity of up to 95%. The initiation and periodicity of CTS screening most used in recent studies were once every 1 or 2 years from the diagnosis of MPS (Patel, 2020). Therapeutic options for disorders involved in MPS have advanced dramatically in the last 10 years, however, neuropathic diseases secondary to MPS still lack proper treatment and management. In addition, new delivery methods are needed for ERTs to act on the central and peripheral nervous system, even crossing the blood-brain barrier. Finally, gene therapy holds the promise of an optimal treatment of MPS neuropathies, with an excellent safety profile to date (McBride, 2021). New treatment modalities such as enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT) can significantly improve cardiorespiratory function, cognitive ability, and life expectancy in certain patients with MPS. However, additional evidence is needed on the effects of these systemic therapies on musculoskeletal complications and, in particular, CTS. Effective screening should be employed for those manifestations where the benefit of the intervention has been demonstrated (McBride, 2021). Finally, therapeutic options for disorders involved in MPS have advanced dramatically in recent years, however, neuropathic diseases secondary to MPS still lack adequate treatment and management. Gene therapy promises to be an ideal treatment for MPS neuropathies, with an excellent safety profile in studies to date (Patel, 2020).

CONCLUSION

The results of this study allow us to conclude that the main known cause of CTS in children and adolescents is MPS. In this context, parents of patients with MPS report worse perception of hand function and the child's ability to perform activities of daily living. That said, the difficulty in elucidating the symptoms, either due to the young age of the patient or the cognitive deficit inherent to the disease, can result in a significant gap between the diagnosis of MPS and CTS, thus causing a significant reduction in the quality of life of these patients as well as a decrease in the objective therapeutic efficacy. An efficient screening protocol employing neuroconduction studies or even MN US should be used, as the benefit of early intervention in CTS has been demonstrated. New forms of treatment, such as ERT and HSCT, lack more evidence on their effectiveness in musculoskeletal complications and, in particular, in CTS. This was a narrative review of the literature whose knowledge acquired and reproducible in our pediatric orthopedics outpatient clinic, especially with patients with MPS.

Although this is a small study, it fills gaps in knowledge in this area, helping researchers to better understand the problems involved in MPS and its orthopedic manifestations, especially CTS, in addition to guiding aspects involved in screening, diagnosis and early treatment of these conditions in the child population.

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