Prague Medical REPORT

(Sborník lékařský)

Multidisciplinary Biomedical Journal
of the First Faculty of Medicine,
Charles University

Vol. 125 (2024) No. 3

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Pharmacokinetic-based Dosing Individualization of Mycophenolate Mofetil in Solid Organ Transplanted Patients

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Received April 15, 2024; Accepted July 28, 2024.

Key words: Mycophenolate mofetil – Mycophenolic acid – Personalized medicine – Pharmacokinetics – Therapeutic drug monitoring – Immunosuppressants

Abstract: Mycophenolate mofetil (MMF) is an immunosuppressant drug approved for prophylaxis of transplant rejection in patients undergoing solid organ transplantation and is further employed in management of various autoimmune disorders. MMF exhibits notable pharmacokinetic inter- and intraindividual variability necessitating tailored therapeutic approaches to achieve optimal therapeutic outcomes while mitigating risks of adverse effects. The objective of this review was to summarize factors that influence the pharmacokinetics of MMF and its active metabolite mycophenolic acid in order to deduce recommendations for personalized treatment strategies. Presumed predictors were analysed in relation to each of the four pharmacokinetic phases, providing tools and targets for MMF dosing optimization amenable to clinical implementation.

This study was supported by the Ministry of Health, Czech Republic (MH CZ – DRO – VFN00064165), and by the Charles University project Cooperatio (research area PHAR).

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https://doi.org/10.14712/23362936.2024.18

Introduction

Mycophenolate mofetil (MMF), the 2-(4-morpholinyl)ethyl ester prodrug of mycophenolic acid (MPA), is widely used as an immunosuppressive drug for the prophylaxis of organ rejection in recipients of allogeneic kidney, heart, or liver transplants (in combination with other immunosuppressants). Many reports have also been published that describe off-label use of mycophenolate mofetil in a wide range of nontransplant conditions, particularly autoimmune disorders (e.g. rheumatoid arthritis, systemic lupus erythematosus, psoriasis, granulomatosis, uveitis, and inflammatory bowel disease) (Bergan et al., 2021). However, in this review, we focus on its approved indications.

MPA is a purine analog that exerts its immunosuppressive effects by noncompetitive and reversible inhibition of inosine monophosphate dehydrogenase (IMPHD), a key enzyme in the *de novo* pathway of purine biosynthesis, which is essential for DNA replication during cell proliferation. MPA thus specifically blocks the proliferation and clonal expansion of T and B lymphocytes, providing an immunosuppressive effect (Monchaud and Marquet, 2009; Bergan et al., 2021).

MMF belongs to class II substances according to the Biopharmaceutics Classification System and exhibits a strong pH-dependent solubility profile (Yu et al., 2002). Following oral administration, MMF is rapidly absorbed and hydrolyzed to MPA by carboxyesterases in the stomach, small intestine, blood, liver, and tissues (Monchaud and Marquet, 2009). Maximum MPA plasma concentrations occur generally within 1 hour after MMF administration (Zhang and Chow, 2017). The bioavailability of MPA after oral administration of MMF is 94.1% in healthy volunteers, and thus indicates almost complete absorption (Zhang and Chow, 2017). MPA is poorly distributed into cellular factions (<5%), but is highly bound (97–99%) to serum albumin (Monchaud and Marquet, 2009; Zhang and Chow, 2017). Median apparent volume of distribution ranged between 101.5 and 176.1 l in thoracic transplant patients (Ting et al., 2008). MPA is extensively metabolized by the uridine 5'-diphospho-glucuronosyltransferase (UGT) system in the liver, gastrointestinal tract, and kidneys forming inactive MPA 7-O-glucuronide (via UGT 1A9 and UGT 1A8), and pharmacologically active acyl – MPA glucuronide (via UGT 2B7) (Zhang and Chow, 2017; Bergan et al., 2021). MPA is excreted primarily in urine in the form of MPA 7-O-glucuronide (87%), while only negligible amounts of MPA (<1% of dose) are excreted unchanged (Zhang and Chow, 2017). MPA 7-O-glucuronide is also excreted into bile by multidrug resistance-associated protein 2 (MRP2), and undergoes enterohepatic circulation (Zhang and Chow, 2017; Bergan et al., 2021). This phenomenon results in a second MPA peak at 6–12 hours after administration. It has been reported that up to 40% of the AUC (area under the curve) may arise from enterohepatic circulation (Zhang and Chow, 2017). The median apparent clearance value ranged from 12.7 to 36 l/h in

thoracic organ transplant patients (Ting et al., 2008). The mean elimination half-life of MPA is reported to range between 8 and 16 hours (Bergan et al., 2021).

Such complex pharmacokinetics suggests high variability, which is confirmed by studies reporting variability in the MPA exposure of up to 82% (Bullingham et al., 1996). Given that MMF is part of treatment regimens playing a key role in graft survival in patients undergoing a plethora of types of transplantations, it is pivotal to ensure adequate and personalized dosing, inter- and intraindividual variability of MMF accounted for. The aim of our review is to gather current knowledge about factors affecting MPA pharmacokinetics which can be thereupon utilized for individualization of treatment with MMF.

Influences on absorption

MPA shows nonlinear absorption kinetics, with large inter- and intra-individual variability (de Winter et al., 2011). MMF is rapidly absorbed in the upper gastrointestinal tract due to its high solubility at low pH (Monchaud and Marquet, 2009). On the other hand, dissolution experiments with enteric-coated formulations of mycophenolate sodium have shown that because of the enteric coating, MPA is released to the greatest extent at pH 6.0–6.8. Therefore, the drug is released in the small intestine rather than the stomach resulting in an unpredictable and highly variable t_{max} of 1.5 to 6 hours (Bergan et al., 2021). Absorption is almost complete under physiological conditions; however, gastrointestinal disturbances may result in significantly reduced bioavailability as shown in allogeneic hematopoietic stem cell transplantation recipients (Jacobson et al., 2007). Selective bowel decontamination resulting in changes in the gut microbiota also reduced enterohepatic circulation and consequently MPA bioavailability (Schmidt et al., 2001). MPA exposure can be reduced by 90, 26, and 17% due to chelation by iron supplements (ferrous sulphate), sevelamer, and antacids, respectively, when used concomitantly (Bullingham et al., 1996; Morii et al., 2000; Pieper et al., 2004). Furthermore, cholestyramine can inhibit enterohepatic circulation of MPA and decrease its AUC by 39% (Bullingham et al., 1998). Since dissolution of MMF may be inadequate at elevated pH levels in upper gastrointestinal tract, co-medication with proton pump inhibitors may affect the bioavailability of MPA. However, studies on this issue provide inconsistent results (Bergan et al., 2021). A randomized cross-over study does not show clinically relevant drug-drug interaction between pantoprazole and MMP in renal transplant patients (Rissling et al., 2015). Although pantoprazole slightly affects some MMF pharmacokinetic parameters, it did not have impact on IMPHD activity. Food consumption can decrease MPA C_{max} by 25–40%; however, the overall exposure is similar to that in patients under fasted conditions (Bullingham et al., 1996).

Influences on distribution

Hypoalbuminemia will increase the free fraction of MPA, resulting in reduced exposure due to faster clearance as described in liver transplant patients (Jain et al., 2007). No further factors have been observed to influence the MPA distribution.

Influences on elimination

Age did not significantly affect the pharmacokinetics of MPA (Tang et al., 2017). Renal function and plasma albumin concentration correlate with MPA clearance (Andrews et al., 2015). Since MPA 7-O-glucuronide is eliminated via kidneys, it accumulates in patients with impaired renal function. As a result of the recirculation of MPA 7-O-glucuronide to MPA, the MPA clearance appears to decrease. On the other hand, if patients are co-treated with cyclosporine, the recirculation of MPA 7-O-glucuronide is inhibited and thus MPA exposure decreases (Hesselink et al., 2005). Moreover, the accumulated MPA 7-O-glucuronide can displace MPA from its binding sites. The increase of unbound MPA due to elevated MPA 7-O-glucuronide levels or low albumin concentrations results in higher MPA clearance (Andrews et al., 2015). Cystic fibrosis patients had significantly lower MPA and MPA 7-O-glucuronide exposure when compared to patients without this disease. Trough and peak MPA levels were also reduced, while apparent clearance was significantly higher in patients with cystic fibrosis (Stuckey et al., 2014).

Glucocorticoids may induce UGT activity and thus increase MPA clearance. Discontinuation of glucocorticoids thus leads to a decrease in MPA clearance by 19% during 12-months period after glucocorticoids discontinuation (Cattaneo et al., 2002). However, clinical relevance of this interaction has not been exactly quantified. The only recommendation is to monitor MPA therapy during glucocorticoid discontinuation. In contrast, some non-steroidal anti-inflammatory drugs (niflumic acid, flufenamic acid, mefenamic acid and diflunisal) showed *in vitro* inhibitory effect on glucuronidation of MPA (Vietri et al., 2000). Co-medication with isavuconazole demonstrated 26% decrease in MPA clearance, which was mirrored in AUC increases (Groll et al., 2017). Since co-treatment with azole antifungals is common in solid organ transplanted patients, this drug-drug interaction may be of clinical relevance. Broad-spectrum antibiotics may affect the intestinal glucuronidase activity, thus interrupting enterohepatic circulation. The median MPA trough concentration was reduced by half during co-medication with ciprofloxacin or amoxicillin/clavulanic acid, while co-treatment with norfloxacin and metronidazole led to a decrease in MPA exposure by a third (Benjanuwattra et al., 2020). Rifampin reduces MPA exposure by 17.5% and trough levels by 48.8%, while increasing MPA 7-O-glucuronide exposure by 34.4%. This observation can be attributed to the induction of UGTs by rifampin (Naesens et al., 2006).

In like manner, genetic variability in UGT genes may also alter MPA pharmacokinetics (Hronova et al., 2014). Variants –275T/A and –2152C/T in the promoter region of the *UGT 1A9* gene are associated with an increase in glucuronidation activity, and therefore with a reduced MPA exposure (Hronova et al., 2014). Additionally, 1399 C>T polymorphism in the *UGT 1A9* gene has been described to alter MPA pharmacokinetics; more precisely, MPA trough blood concentrations were significantly higher in TT carriers than in CT and CC carriers (Ciftci et al., 2018). The *UGT 2B7* genotype has also been shown to contribute to the interindividual variability of MPA pharmacokinetics. In pediatric renal transplant recipients, MPA clearance was significantly lower in *UGT 2B7* 802 CC carriers compared to *UGT 2B7* 802 CT and 802 TT genotypes (Zhao et al., 2010). Besides UGTs, impact of polymorphisms in MRP2 transporter gene on MPA disposition was also tested, but rendered inconsistent results (Hronova et al., 2014). The observed higher MPA exposure in Asian patients compared with Caucasian or African American patients can possibly be attributed to the prevalence of gene polymorphisms within ethnic subgroups (Andrews et al., 2015).

Pharmacokinetic/Pharmacodynamic targets

Since the pharmacokinetics of MMF is complex and somewhat erratic, with large intra- and inter-individual variability, routine therapeutic drug monitoring (TDM) and dose individualization would unequivocally be beneficial. According to a consensus report by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology, there is sufficient evidence to recommend dose adjustments to achieve target MPA concentrations (Bergan et al., 2021). Nevertheless, there are several obstacles to routine implementation of this tool. First of all, since MPA plasma AUC has been shown to be the most predictive of clinical outcomes and single-point (trough level) measurement is a relatively poor predictor of MPA exposure, sampling strategy combining 3 concentration measurements within the dosing interval is the recommended method for TDM of MMF (Bergan et al., 2021). Furthermore, a population pharmacokinetic model with good predictive performance used in Bayesian simulation is essential for successful dosage optimization (Sima et al., 2019). Conversely, the population pharmacokinetics of MPA is more difficult to describe and requires models more complex than other immunosuppressants (Bergan et al., 2021). A target MPA $AUC_{0–12h}$ of 30–60 mg×h/l is recommended in kidney transplant recipients treated with MMF in combination with calcineurin inhibitor, with or without glucocorticoids (Bergan et al., 2021). The same target is recommended for liver transplant recipients treated with MMF with tacrolimus without corticoids. The MPA trough level is recommended to be between 1 and 3.5 mg/l, but with a lower level of evidence (Bergan et al., 2021). In *de novo* heart transplantation patients treated with MMF, calcineurin inhibitor and corticoids, MPA $AUC_{0–12h}$

> 36 mg×h/l or trough level > 2 mg/l is recommended. On the other hand, in lung transplant recipients, no evidence-based target can be proposed (Bergan et al., 2021). In order to improve MMF therapy individualization, range of potential pharmacodynamic biomarkers (e.g., IMPDH activity and expression) has been investigated with promising results. However, none of these biomarkers has been widely implemented in daily practice, partly due to the assays being arduous and labour intensive. All things considered, continued search for novel tools to improve MPA dosage personalization is warranted (Bergan et al., 2021).

Recommendation for dosing individualization, Conclusion

An approved initial MMF dose is 1 g twice a day in adult kidney transplant recipients or 1.5 g twice a day in liver or thoracic transplant patients. However, using this fixed initial dose, only 76.2% of kidney recipients co-treated with tacrolimus achieve the target MPA exposure of 30–60 mg×h/l by day 3, while merely 51.2% of patients reach this target range during co-treatment with cyclosporine (Andrews et al., 2015). The recommendations for individualizing initial dose of MMF can be summarized as follows:

- No dosing algorithms have been found for MMF (Andrews et al., 2015).
- Based on the well-described drug interaction between MPA and cyclosporine, the initial MMF dose increase by 30–50% should be considered in cyclosporine co-treated patients compared to patients co-treated with tacrolimus (Andrews et al., 2015).
- Iron supplements, sevelamer, antacids, and cholestyramine should be administered several hours apart from MMF.
- Special caution should be taken in patients co-medicated with wide-broad antibiotics, azole antifungals and strong inducers or inhibitors of UGTs, but without a specific recommendation on dose adjustment.
- Although there is a rationale for MPA TDM, its implementation into the clinical routine is demanding owing to the laborious sampling strategy along with the complex pharmacokinetics surrounding MMF.

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Cocaine-induced Movement Disorder: A Literature Review

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Received December 13, 2023; Accepted July 28, 2024.

Key words: Cocaine – Tropane alkaloid – Psychostimulant – Drug abuse – Drug-induced – Movement disorder

Abstract: This study aims to describe movement disorders secondary to cocaine use. To our knowledge, while these presentations have been previously reported in the literature, a comprehensive review has not been published yet. We searched six databases from 1986 to 2022 without language restriction. Case reports, case series, and literature reviews have been analysed to find associations between cocaine use and movement disorders. The present study encompasses epidemiology, clinical manifestations, pathophysiology, and diagnostic challenges of abnormal movements associated with cocaine use. This review highlights the importance of proper initial evaluation and investigation taking into account the broad spectrum of differential diagnoses and exclusion of primary movement disorders. The role of the dopaminergic system in movement disorders is reviewed. Cocaine use is associated with movement disorders such as dystonia, parkinsonism, akathisia, and tics. The complex interaction of multiple factors, including other neurological conditions, such as Tourette syndrome, and additional substances of abuse is discussed. The presentation of these manifestations is often heterogeneous and does not follow a specific pattern. In this way, future research is needed to improve our understanding of the pathophysiological mechanisms and develop novel drug targets for these disorders. Increased awareness among the general public and policymakers could translate into reduced stigma and improved care.

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https://doi.org/10.14712/23362936.2024.19

Introduction

Substance use disorder (SUD), or drug addiction, is a complex condition involving genetic, psychiatric, biological and social factors in which affected individuals are unable to control the use of a given substance. This occurs with legal or illegal substances and leads to immediate or late devastating consequences, which often ensue in financial loss, social isolation, stigmatization, unemployment and considerable personal suffering and social burden. This condition is prevalent worldwide in societies of different cultures and stages of economic development. In the United States alone, SUD affects approximately 40 million people, and the annual medical cost attributed to SUD-related hospitalization is estimated at 13.2 billion dollars. Between 2006 and 2014, there was a 40% increase in substance use-related emergency department visits. In a large study examining emergency department visits and inpatient encounters, approximately 10% of all hospitalizations were due to a substance use disorder, and the mean medical cost of a primary SUD diagnosis was over $9,000 (Peterson et al., 2021). Moreover, SUD results in increased vulnerability to infectious diseases, including COVID-19, which translates to an increased healthcare burden. A significant proportion of SUD patients experience homelessness, and more than 50% of the incarcerated population in the United States suffers from SUD (Manhapra et al., 2021). Unfortunately, SUD patients are less likely to have access to healthcare professionals because of the stigmatization related to this condition. Nonetheless, social support is limited, and the marginalization associated with SUDs often leaves individuals unable to break out of the vicious cycle (Volkow, 2020).

A voluntary motor function requires planning, coordination, and execution. If either of these processes or a combination of them is impaired, a movement disorder emerges. Movement disorders are complex and varied. A considerable number of movements noted during the physical examination of an individual will fall under a spectrum, which includes dystonia, akathisia, athetosis, choreiform movements, tremors, bradykinesia, myoclonus, rigidity, and ataxia. Movement disorders are highly variable in presentation and often require careful observation for proper diagnosis. While some, such as neuroleptic malignant syndrome, constitute neurological emergencies, others required extended periods of follow-up for appropriate treatment in the outpatient setting, such as Parkinsonian tremors. Functional neurological disorders are often prevalent in referrals for the specialist and an important differential diagnosis in the movement disorders clinic. Patients with these disorders should also be followed-up and treated accordingly. Movement disorders can be inherited or acquired, and multiple syndromes ranging from Huntington's to MPTP-induced have been described (Rissardo et al., 2023a). Most movement disorders affect the dopaminergic system and the deeper gray matter regions of the brain. Abnormal movements can significantly impact an individual's quality of life and represent a major healthcare expenditure in the United States.

While novel approaches are promising and have shown to improve the lives of patients suffering from movement disorders, such as deep brain stimulation in Parkinson's disease, the newly emerging involuntary abnormal movements secondary to illicit substance use represent a significant challenge in terms of development of new therapeutic strategies (Rissardo et al., 2023b).

The association of movement disorders with substance abuse is well known. Tremors during withdrawal in the setting of alcohol use disorder is a classic example. This symptom can be alleviated with benzodiazepines but also occurs in benzodiazepine withdrawal. Many other psychoactive substances can induce motor symptoms. These presentations are highly variable according with different substances, and even for the same substance. Thus, objective characterization of these disorders is extremely challenging. For example, both central nervous system depressants, such as opioids, and stimulants, such as cocaine, can cause myoclonus. MPTP, a known neurotoxic and street-drug contaminant, is associated with parkinsonism and its wide range of motor alterations (Kopin, 1987). Recent studies suggest that methamphetamine use can cause athetotic and choreiform movements that mimic Huntington's disease (Rissardo et al., 2023a). In addition, novel synthetic drugs are making their way into patient populations, sometimes disguised as harmless products such as herbal supplements, bath salts, and others, which can lead users to underestimate their potency. These drugs are still poorly understood and have unpredictable immediate and long-term effects (Wang and Hoyte, 2019).

Cocaine, one of the most common drugs of abuse in the 21st century, is an alkaloid extracted from *Erythroxylum coca*, a plant used in South America for thousands of years. Referred to as the divine plant of the Incas, the coca held a mythical status in their society. Its effect against fatigue and as an appetite suppressant was first recorded in the XV century by the early explorer Amerigo Vespucci. Coca leaves were traditionally chewed for their stimulant properties and played an important role in religious and healing practices (Matuskey, 2012). While this traditional use continues to exist in parts of South America, the coca plant is now notoriously recognized as emblematic of cartel violence. The international process of cocaine prohibition began in 1912 with the Hague Opium Convention. In 1914, federal regulation was introduced in the United States, followed by increasing restrictions that attempted to limit cocaine use to medical and scientific purposes. The Drug Enforcement Administration (DEA) of the United States classifies cocaine as a Schedule II drug (Das, 1993). In the 1970s, the cocaine trade and smuggling led to the rise and fall of one of the most notorious criminals, Pablo Escobar, and made cocaine a top player in the drug scene of America. Cocaine is mainly produced in Peru, Colombia, and Bolivia and is then trafficked to multiple other destinations. In 2019 alone, over 1,400 tons of cocaine were seized internationally (Drake and Scott, 2018).

With approximately 2 million regular users in the United States, cocaine is responsible for 40% of all substance abuse-related emergency department visits (Bravo et al., 2022). Because of stigma, omission, and underreporting, the actual

number of cocaine users may be much higher than estimated. The all-cause mortality from cocaine abuse is high, and the past decade has seen a marked increase in deaths secondary to overdose. On average, regular or problematic cocaine users have an excess mortality risk six times the expected rate for age-matched on-users (Peacock et al., 2021). Cocaine use disorder (CUD) is a serious and urgent public health problem, and the lack of Food and Drug Administration (FDA)-approved treatments is concerning (Kampman, 2019).

Cocaine was first isolated in 1859. In 1884, Carl Koller used this substance in ophthalmic procedures, making cocaine the first local anesthetic in modern medicine. During the same period, Sigmund Freud conducted his studies on cocaine, defending its therapeutic use. Cocaine was later used in many other prescriptions ranging from headaches to toothaches. Examples of adverse effects began to appear. A publication from 1911 mentions motor alterations when cocaine was applied in combination with adrenaline in a tonsillectomy and adenoidectomy. The patient's "*body showed a tendency to become flexed backward, and the eyeballs rolled upwards while the pupils dilated widely. This was at once followed by a violent convulsive seizure, epileptiform in character, with powerful twitching and contraction of the muscles of the limbs and face, and marked retraction of the head*" (Wishart, 1911). This case alone illustrates a wide variety of motor alterations, and while adrenaline administration is a confounding factor, opisthotonos, torticollis, and seizures were all observed when cocaine was used alone (Scharf, 1989; Fines et al., 1997).

The route of cocaine administration may be intravenous, ocular, inhaled, or by contact with any mucous membrane (oral, intranasal, rectal). In the context of drug abuse, cocaine is usually self-administered by snorting cocaine hydrochloride powder or by smoking its freebase form, crack. Individuals with stable living conditions often use cocaine powder, while crack cocaine is associated with heavy use, homelessness, and unstable living situations.

Cocaine abuse directly or indirectly affects multiple organs, from dentition and facial structures to the homeostasis of the nervous, gastrointestinal, respiratory, renal, and cardiovascular systems (Havakuk et al., 2017; Peacock et al., 2021; Bravo et al., 2022). Mental health is significantly impaired, as cocaine affects social functioning and cognition across multiple dimensions, such as working memory, attention span, flexibility of thought, and even empathy (Frazer et al., 2018). Common cardiovascular manifestations include hypertension, tachycardia, and ischemia, with possible myocardial infarction, arrhythmias, and heart failure secondary to vasoconstriction and increased oxygen demand due to stimulation of contractility. Bronchoconstriction, pulmonary edema, and pneumothorax can occur secondarily to cocaine's irritant nature, especially if smoked. Acute pulmonary syndrome manifesting as hemoptysis, pain, and lung infiltrates is a rare but dreaded complication. Cocaine may cause acute kidney injury, renal infarction, malignant hypertension, and rhabdomyolysis secondary to hemodynamic changes. Ischemic and hemorrhagic strokes occur because of blood pressure dysregulation, and seizures

occur because of chronic low-intensity stimulation of the limbic system, known as kindling, even after a single use. Hepatotoxicity, mostly as hepatocellular necrosis, fatty acid infiltration, and alterations to amino acid pathways due to abnormal oxidative stress regulation, have been reported. Increased susceptibility to emergency conditions such as neuroleptic malignant syndrome and serotonin syndrome, which are life-threatening conditions, are occasionally encountered in clinical practice (Frazer et al., 2018; Bravo et al., 2022).

The extent of cocaine's effects and their ramifications on different systems is not fully understood. Cocaine's primary mechanism of action is the inhibition of dopamine, norepinephrine, and serotonin reuptake by their respective transporters in presynaptic neurons. The accumulation of these neurotransmitters in the synaptic cleft and consequent activation of postsynaptic receptors, results in several responses. Increased serotonin signalling could contribute to euphoria, overall mood elevation, and susceptibility to seizures. Increased norepinephrine activity results in the typical manifestations of sympathetic overdrive. Increased dopaminergic activity along the mesocorticolimbic impacts the regulation of several important cognitive and affective functions, such as motivation, learning, and emotions. The circuits formed in this pathway constitute the so-called "reward system". In this system, dopaminergic neurons originating in the ventral tegmental area relay to other brain locations. These neurons and their projections in the nucleus accumbens, throughout the limbic system, and prefrontal cortex are implicated, for example, in the euphoric sensation experienced by cocaine users (Bravo et al., 2022). Disruptions in the reward system explain most of the characteristic patterns followed in CUD, with cocaine-seeking behaviour, habit formation, withdrawal, cravings, and ultimately addiction.

While the action of each monoamine in different brain areas can infer its effect, these substances do not work in separate compartments but interact in several points. Cocaine's effects are even more complex considering N-methyl-D-aspartate, sigma, and kappa opioid receptors are also modulated, which may alter their expression and distribution (Bravo et al., 2022). All these systems and their delicate balance are affected and could influence the increased psychomotor activity typical of cocaine use (Figure 1).

Cocaine use disorder is a multifactorial condition, genetic and environmental exposure have an impact on cocaine use patterns. Relatives of those affected by CUD are 4.4 times more likely to develop the condition. Epigenetic modifications in circuits of the cortico-striato-thalamo-cortical system have a role in relapse and drug cravings. Interestingly, only 20% of cocaine users develop CUD, which could be due to genetic susceptibility. For example, the NSF gene, associated with synaptic vesicle turnover, has polymorphic copy number variations that can influence cocaine dependence with an inverse relationship (Fernandez-Castillo et al., 2022).

Like addiction, movement disorders are complex phenomena. Psychostimulants like cocaine alter the function of the basal ganglia directly or indirectly, similar to the mechanism of commonly known and understood movement disorders.

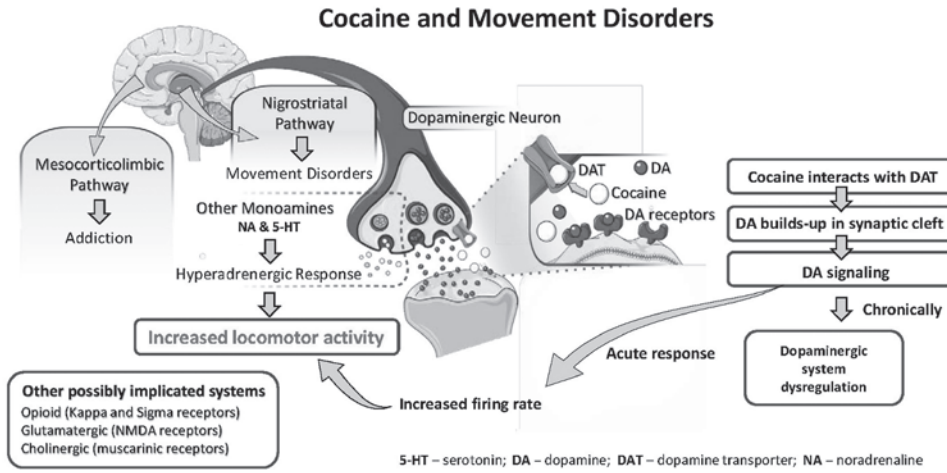

Figure 1 – Hypothetical pathophysiology of movement disorders caused by cocaine use. The figure was partly generated using Servier Medical Art, provided by Servier, licensed under an unported Creative Commons Attribution 3.0 license.

Broadly, tremors, dystonia, ataxia, dyskinesia, bruxism, parkinsonism, stereotypical movements, choreoathetosis, restlessness, and tics are some of the movements. The present review aims to investigate the cases of movement disorder secondary to cocaine use reported in the literature.

Methodology

Search strategy

We searched six databases to locate all the existing reports on movement disorders secondary to cocaine published from 1986 to 2022 in electronic form. Excerpta Medica (Embase), Google Scholar, Latin American and Caribbean Health Sciences Literature (Lilacs), Medline, Scientific Electronic Library Online (Scielo), and ScienceDirect were searched. Search terms were "parkinsonism, tics, dyskinesia, dystonia, stuttering, myoclonus, restless legs syndrome, akathisia, tremor, chorea, restlessness, ataxia, ballism, hyperkinetic, hypokinetic, bradykinesia, movement disorders." These terms were combined with "cocaine and coca" (Table 1).

Inclusion and exclusion criteria

Case reports, case series, original articles, letters to the editor, bulletins, and poster presentations published from 1986 to 2023, without language exclusion criteria, were included to ensure a thorough review. In the cases where the non-English literature was beyond the authors' proficiency (English, French, and Spanish) or when the

Table 1 – FreeText and MeSH search terms in the US National Library of Medicine

Category	Search term	Results
Movement disorder	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s”[All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“movement disorders”[MeSH Terms] OR (“movement”[All Fields] AND “disorders”[All Fields]) OR “movement disorders”[All Fields])	577
Parkinsonism	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“parkinson disease”[MeSH Terms] OR (“Parkinson”[All Fields] AND “disease”[All Fields]) OR “parkinson disease”[All Fields] OR “parkinsons”[All Fields] OR “Parkinson”[All Fields] OR “parkinson s”[All Fields] OR “parkinsonian disorders”[MeSH Terms] OR (“parkinsonian”[All Fields] AND “disorders”[All Fields]) OR “parkinsonian disorders”[All Fields] OR “parkinsonism”[All Fields] OR “parkinsonisms”[All Fields] OR “parkinsons s”[All Fields])	554
Dyskinesia	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“dyskinesiae”[All Fields] OR “dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields] OR “dyskinesia”[All Fields])	373
Ballism	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“dyskinesias”[MeSH Terms] OR “dyskinesias”[All Fields] OR “ballism”[All Fields])	355
Restlessness	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“psychomotor agitation”[MeSH Terms] OR (“psychomotor”[All Fields] AND “agitation”[All Fields]) OR “psychomotor agitation” [All Fields] OR “restlessness”[All Fields] OR “restless”[All Fields])	102
Tremor	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“tremor”[MeSH Terms] OR “tremor”[All Fields] OR “tremors” [All Fields] OR “tremoring”[All Fields] OR “tremorous”[All Fields])	99
Akathisia	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“akathisias”[All Fields] OR “psychomotor agitation”[MeSH Terms] OR (“psychomotor”[All Fields] AND “agitation”[All Fields]) OR “psychomotor agitation”[All Fields] OR “akathisia”[All Fields])	82
Dystonia	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“dystonia”[MeSH Terms] OR “dystonia”[All Fields] OR “dystonias”[All Fields] OR “dystonic disorders”[MeSH Terms] OR (“dystonic”[All Fields] AND “disorders”[All Fields]) OR “dystonic disorders”[All Fields])	72

Category	Search term	Results
Ataxia	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“ataxia”[MeSH Terms] OR “ataxia”[All Fields] OR “ataxias” [All Fields])	50
Chorea	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“chorea”[MeSH Terms] OR “chorea”[All Fields] OR “choreas” [All Fields])	38
Bradykinesia	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields] OR “bradykinesia”[All Fields])	23
Myoclonus	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“myoclonus”[MeSH Terms] OR “myoclonus”[All Fields])	17
Hyperkinetic	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“hyperkinetic”[All Fields] OR “hyperkinetics”[All Fields])	16
Hypokinetic	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“hypokinesia”[MeSH Terms] OR “hypokinesia”[All Fields] OR “hypokinetic”[All Fields])	16
Tics	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“tics”[MeSH Terms] OR “tics”[All Fields])	16
Restless legs syndrome	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s” [All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“restless legs syndrome”[MeSH Terms] OR (“restless”[All Fields] AND “legs”[All Fields] AND “syndrome”[All Fields]) OR “restless legs syndrome”[All Fields])	7
Stuttering	(“cocaine”[MeSH Terms] OR “cocaine”[All Fields] OR “cocaine s”[All Fields] OR “cocaines”[All Fields] OR “cocainics”[All Fields]) AND (“stammerers”[All Fields] OR “stammers”[All Fields] OR “stutterer”[All Fields] OR “stutterer s”[All Fields] OR “stutterers” [All Fields] OR “stuttering”[MeSH Terms] OR “stuttering” [All Fields] OR “stammer”[All Fields] OR “stammering”[All Fields] OR “stutter”[All Fields] OR “stuttered”[All Fields] OR “stutters” [All Fields] OR “stutterings”[All Fields])	5
Total		**2402**

English abstract did not provide enough data, such as articles in Dutch and Japanese, Google Translate services were used (De Vries et al., 2018).
The authors independently screened the titles and abstracts of all articles from the initial search. Disagreements between authors were solved through discussion. Cases where the cause of movement disorder was already known, and the motor symptoms were not worsened or were not related to cocaine were excluded. Additionally, cases not accessible by electronic methods, including after a formal request e-mailed to the authors, were excluded.

Data extraction

For cocaine, a total of 2,402 articles were found; 2,001 were inappropriate, and 352 were unrelated to the subject, duplicate, inaccessible electronically, or provided insufficient data (Figure 2). Data abstraction was carried out. When provided, we extracted author, department, year of publication, country of occurrence, number of patients affected, patient's comorbidities, time from first cocaine dose until movement disorder occurrence (movement disorder onset), time from cocaine withdrawal to symptoms improvement (movement disorder recovery), patient's status at follow-up, neuroimaging features, electrodiagnostic studies, and significant findings of clinical history and management. Two independent authors extracted

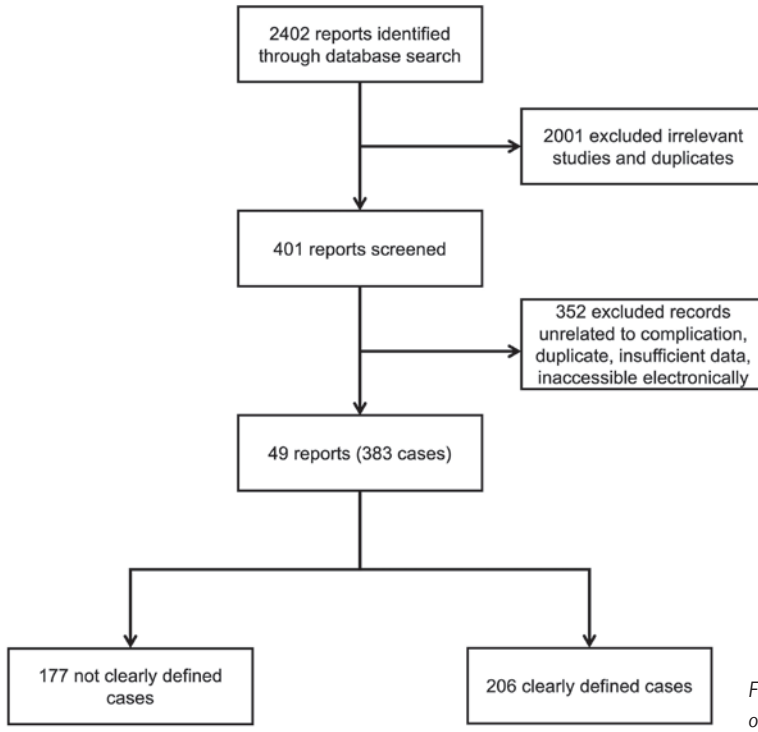

Figure 2 – Flowchart of the screening process.

the data, double-checked to ensure matching, and organized accordingly if the movement disorder was associated with cocaine use.

Statistical analysis
Categorical variables were represented as proportions; continuous variables were represented as means, standard deviation (SD), median, and range.

Definitions
The clinical characteristics and definitions of movement disorders such as parkinsonism, tics, dyskinesia, dystonia, stuttering, myoclonus, restless legs syndrome, akathisia, tremor, chorea, ataxia, and ballism were obtained from Rissardo et al. (2023a).

Results

A total of 49 studies containing 383 cases of movement disorder associated with cocaine were found in the literature (Table 2) (Kumor et al., 1986; Mesulam, 1986; Factor et al., 1988; Merab, 1988; Choy-Kwong and Lipton, 1989; Scharf, 1989; Pascual-Leone and Dhuna, 1990; Rebischung et al., 1990; Farrell and Diehl, 1991; Habal et al., 1991; Hegarty et al., 1991; Cardoso and Jankovic, 1993; Attig et al., 1994; Casas Parera et al., 1994; Daras et al., 1994; Horwitz and Van Harten, 1994; Beltran and Coker, 1995; Bauer, 1996; Daniels et al., 1996; Elkardoudi-Pijnenburg and Van Vliet, 1996; Catalano et al., 1997; Dhopesh et al., 1997; Domingo and Martínez, 1997; Fines et al., 1997; Gingrich et al., 1998; Van Harten et al., 1998; Bartzokis et al., 1999; Weiner et al., 2001; O'Suilleabhain and Giller, 2003; Supervía et al., 2006; Duggal, 2007; Henderson et al., 2007; Kamath and Bajaj, 2007; Maat et al., 2008; Vinkers et al., 2010; Anbarasan et al., 2011; Pinto et al., 2013; Doobay et al., 2017; Narula et al., 2017; Gibb and Nacopoulos, 2018; Illés et al., 2019; Van Esch et al., 2019; Ángel et al., 2021; Mascia and Defazio, 2021; Yeoh et al., 2022; Audi et al., 2023; Kim et al., 2023; Rajmohan et al., 2023; Srichawla et al., 2023). The abnormal movements encountered were 88 dyskinesia, 73 dystonia, 22 parkinsonism, 12 tics, nine catatonias, and two opsoclonus-myoclonus symptoms. A mixture of movement disorders was observed in 177 cases. Most of the individuals reported were from the male sex, accounting for 85.63%.

Discussion

Overview
Cocaine is associated with hyperkinetic movements such as dystonia, myoclonus, chorea, and tics. These effects are well known in the literature and are termed

Table 2 – Literature review of movement disorders associated with cocaine use

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Parkinsonism					
Bauer (1996)	34 (mean) /13 M and 6 F	None	Cocaine dependent, cocaine and alcohol codependent	Hand-tremor	Hand-tremor was not visually obvious but required recording devices
Domingo and Martínez (1997)	35/M	None	Intranasal and intravenous cocaine, cannabis use previously	Tremor, loss of facial expression, and axial mobility	–
O'Suilleabhain and Giller (2003)	38/M	Hepatitis C and moderate depression	Intranasal, smoking (freebase), MDMA, amphetamine, alcohol	Bradykinesia, rigidity. decreased blink rate, left arm tremor at rest, postural arm tremor bilaterally – features suggesting hemiparkinsonism	The clinical features described in this report could be secondary to MDMA use
Illés et al. (2019)	44/M	Gastroesophageal reflux disease and first-degree heart block	Intranasal insufflation	Asymmetric (right) postural hand tremor (isometric tremor syndrome)	Patient' son was evaluated for restless leg syndrome at 13 years of age. Magnetic resonance imaging of the brain for the patient showed the absence of a swallow tail sign indicating Parkinson's disease
Dystonia					
Kumor et al. (1986)	29.5 (mean) /7 M	None	Intravenous cocaine	Acute dystonia – torticollis, oculogyric crisis, truncal involvement	The subjects/ volunteers received cocaine within 72 hours of haloperidol. Although there were no control groups, 6/7 patients developed dystonic reactions
Merab (1988)	35/M	None	Cocaine, unknown route	Facial dystonia	–

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Choy-Kwong and Lipton (1989)	15/F	Adjustment disorder with depressed mood	Freebasing cocaine	Acute dystonia, torticollis, extensor posturing, high pitched vocalization	–
Rebischung et al. (1990)	29.5 (mean) /3 F	None	Freebasing cocaine	Dystonic posturing of head and extremities	Symptoms appeared during the cocaine withdrawal phase
Farrell and Diehl (1991)	29/M	None	Smoke form, crack cocaine	Painful spasms of the masseter muscle	–
Hegarty et al. (1991)	35 (mean) /25 M and 20 F	None	Intranasal, intravenous, freebasing cocaine	Acute dystonia	Prior neuroleptic use did not impact dystonic reaction significantly
Casas Parera et al. (1994)	Undetermined age, multiple subjects	None	Unknown route of cocaine consumption	Seizures and paroxysmal dystonic reactions	–
Horwitz and Van Harten (1994)	25/M	None	Unknown route of cocaine consumption	Acute dystonia	–
Beltran and Coker (1995)	3 hours after birth /M	None	Prenatal exposure – mother used inhalation crack cocaine during the third trimester	Episodic abnormal tonic posturing with head and neck deviation; episodic dorsiflexion	–
	2 months /M	None	Intrauterine cocaine exposure – mother inhaled cocaine	Torticollis (left-sided)	–
	2 months /M	None	Inhalation cocaine in mother – intrauterine exposure	Torticollis (right-sided)	–
Catalano et al. (1997)	34/F	None	Crack cocaine	Acute onset facial (facial muscles and jaw) dystonia	Symptoms resolved immediately with intravenous diphenhydramine
Fines et al. (1997)	32/M	None	Intranasal inhalation of cocaine	Extension of the head, hips, trunk arched forward	Symptoms resolved with diphenhydramine administration
	19/M	None	Intranasal inhalation of cocaine	Acute dystonia (torticollis)	–
Van Harten et al. (1998)	25/M	Mild intellectual disability	Cocaine, unknown route	Severe dystonia	–

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Duggal (2007)	37/M	Psychotic disorder not otherwise specified	Intranasal insufflation	Trismus, trouble swallowing, shortness of breath (pharyngolaryngeal dystonia)	Ziprasidone was considered the primary agent causing dystonia with cocaine use as a risk factor
Henderson et al. (2007)	58/M	Bipolar disorder type II, depression with psychotic features, attention-deficit/hyperactivity disorder, hepatitis C, hypertension	Unspecified route of cocaine use	Jaw muscle dystonia, hands dystonia	Dystonia could be secondary to aripiprazole without the effect of cocaine
Vinkers et al. (2010)	45/M	None	Crack cocaine	Late onset, persistent torticollis	Structural changes in dopamine receptors are conjectured to cause long-term effects
Pinto et al. (2013)	7/M	None	Potential ingestion/inhalation	Exaggerated posturing of extremities, rhythmic movements, fixed rightward case	Cocaine was used by the patient's parents, and they were charged with child neglect in both these cases
	4/M	None	Ingestion of cocaine	Extended right arm, head turned to right (dystonia)	–
Ángel et al. (2021)	33/M	Congenital deafness	Cocaine, unknown route	Severe dystonia – status dystonicus	–
Mascia and Defazio (2021)	46/M	Bipolar disorder, arterial hypertension	Intranasal cocaine insufflation	Involuntary lateral flexion of trunk – referred to as PISA syndrome, Parkinsonism	–
Dyskinesia					
Habal et al. (1991)	24/F	None	Crack cocaine	Slow abnormal involuntary movements of the head (athetosis) of upper extremities and trunk	–

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Habal et al. (1991)	34/F	None	Crack cocaine	Slow, purposeless involuntary movement of the trunk and bilateral upper extremities (athetosis), eye blinking, lip smacking	–
Daras et al. (1994)	34/F	None	Crack cocaine	Lip smacking, eye blinking, choreoathetoid movements of extremities	–
	24/F	None	Crack cocaine	Slow head movements, writhing movements of arms, trunk, and legs	–
	21/F	None	Crack cocaine	Gait ataxia, chorea of head and arms	–
	29/F	None	Crack cocaine	Akathisia, wringing movements of the hand	–
	58/F	None	Intranasal cocaine	Buccolingual dyskinesia, arm, and leg choreoathetoid movements	–
	38/M	None	Crack cocaine	Bradykinesia, mild chorea of fingers	–
	46/M	None	Crack cocaine	Rotations of the shoulder, movements of hand and feet	–
Bartzokis et al. (1999)	39.8 (mean) /71 M	None	Crack cocaine, smoked	Choreoathetoid movements, predominantly non-facial	AIMS was used in the grading of abnormal movement. Younger subjects had higher scores on the AIMS
Weiner et al. (2001)	34/F	Substance use disorder	Intranasal cocaine, intravenous cocaine, alcohol, opiates, and barbiturates	Serpentine movements of the trunk, dystonia, spasms of the abdominal wall, and rocking movements of the body initially associated with pleasurable	–

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
				sensations which later were unpleasant	
Supervía et al. (2006)	22/M	None	Cocaine, unknown route	Choreiform movements of the neck and upper extremities	–
Kamath and Bajaj (2007)	60/M	Hepatitis C, intravenous heroin use, subacute bacterial endocarditis, deep venous thrombosis	Intravenous cocaine	Choreiform movements of all extremities, orofacial dyskinesia	–
Doobay et al. (2017)	32/M	Hypertension, major depressive disorder	NA	Choreoathetoid movements of the head, arm, trunk, and shoulders	The patient was started on selective serotonin reuptake inhibitors for depression four weeks before presentation
Narula et al. (2017)	69/F	Type II diabetes mellitus	Crack cocaine inhalation	Choreoathetoid movements of bilateral upper extremities with left greater than right	–
Gibb and Nacopoulos (2018)	35/M	None	Cocaine ingestion	Buccal lingual dyskinesias and choreiform movements present in all extremities, intermittent tics	First-time cocaine use by the subject
Audi et al. (2023)	27/M	None	Intravenous cocaine and fentanyl, cannabis (likely smoke form)	Choreiform movements of left upper extremity	Chorea was noted after the patient developed anoxic brain injury secondary to drug use. Chorea failed to resolve initially with aripiprazole. The symptoms were attributed to fentanyl withdrawal, and his chorea was resolved with fentanyl

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Rajmohan et al. (2023)	48/M	None	Cocaine/amphetamine/dextro-amphetamine	Writhing movements of the toe, left greater than right	Symptoms persisted months after discontinuation of substances
Tics					
Mesulam (1986)	27/M	Tourette's syndrome with obsessive-compulsive symptoms	Intranasal cocaine	Motor and vocal tics that were under remission	Patient's long-standing tics were controlled with haloperidol and his tics worsened with cocaine lasting a few hours
Factor et al. (1988)	21/M	Tourette's syndrome	Intranasal cocaine	Increased motor and vocal tics	Increased amplitude of tics with cocaine was associated with euphoria
Pascual-Leone and Dhuna (1990)	38/F	Tourette's syndrome	Intranasal cocaine	Recurrence of previous tics – jerking of neck and arms and barking noises, new onset facial tics	First-time cocaine exposure
	21/M	Tourette's syndrome	Crack cocaine, intranasal cocaine (chronic exposure)	Grunting noises, severe jerking tics of face, extremities, and neck	The patient was a chronic user of intranasal cocaine, but tics re-emerged after crack cocaine use
	28/F	None	Intranasal cocaine	Eye blinking, shoulder shrugging, head-turning, grunting, throat clearing	NA
	38/F	None	Intravenous cocaine	Right-sided facial and lower extremity jerks	Motor and vocal tics presented after a large dose of intranasal cocaine
Cardoso and Jankovic (1993)	21/M	Tourette's syndrome, attention deficit hyperactivity disorder	Intranasal cocaine	Wiggling of nose, upward rolling of eyes, right shoulder circumduction	–
	28/M	Tourette's syndrome	Intranasal cocaine	3 times increase in vocal and motor tics including coprolalia, copropraxia, and new paranoid delusions	–

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Cardoso and Jankovic (1993)	31/F	None	Intranasal cocaine	Tenfold increase in head and hand tremor, cervical and axial dystonia	–
	30/M	Depression, paranoid schizophrenia	Intranasal cocaine	Generalized dystonia with axial involvement	–
Attig et al. (1994)	35/F	None	Intranasal and crack cocaine	Grunting, nostril-flaring, jerking of arms and head	–
Daniels et al. (1996)	49/M	Motor and vocal tics	Crack cocaine	Uncontrollable eye blinking	Within a day of abstinence, symptoms resolved
Opsoclonus-myoclonus					
Scharf (1989)	26/F	None	Intranasal cocaine	Myoclonic jerking of trunk, extremities, opsoclonus (conjugate, clockwise rotary)	Patient had an episode of isolated seizure with cocaine a few years ago
Elkardoudi-Pijnenburg and Van Vliet (1996)	29/M	Migraine and hypertension	Chronic heroin use, incidental cocaine misuse	Conjugated beats in all directions mimicking nystagmus, myoclonic jerks of the trunk	Patient was a chronic opioid user and cocaine use was incidental
Catatonia					
Gingrich et al. (1998)	36/F	None	Cocaine	Mutism, staring, slow purposeless hand gestures and resistance to movement	–
Anbarasan et al. (2011)	35/F	None	Crack cocaine vapor inhalation	Echolalia, speech latency, rigidity, gait ataxia, disorganized behaviour	A diagnosis of cocaine-induced leukoencephalopathy was made
Van Esch et al. (2019)	54/F	Psychosis	Cocaine and methadone	Disorganization, disorientation, confusion that progressed to rigidity, stupor, stupor, echolalia	–
Yeoh et al. (2022)	31 (mean)/4 M and 1 F	None	Cocaine, cannabis, and other substances were studied	Catatonia as described by the Bush-Francis catatonia rating scale	Cocaine and other stimulants caused acute onset catatonia

Reference	Age /Sex	Comorbidities	Cocaine route, mixture of drugs	Clinical manifestations	Notes
Srichawla et al. (2023)	51/M	None	Intranasal cocaine, alcohol	Rigidity in bilateral upper and lower extremities, high blood pressure, high fever suggestive of malignant catatonia	–
Mixture of movement disorders and different types of studies					
Dhopesh et al. (1997)	57 (mean) /M (50 individuals)	None	Cocaine, unknown route	UPDRS 0 to 1 in cocaine users. UPDRS scores range from 0 to 3 among controls	This study suggested chronic heavy use of cocaine did not result in parkinsonism. Fifty age-matched cases and controls were enrolled
Maat et al. (2008)	Age unspecified /M (106 individuals)	None	Cocaine, multiple routes	Dyskinesias, parkinsonism, and akathisia	UPDRS, Barnes Akathisia rating scale, and AIMS rating scales were used in the assessment of extrapyramidal symptoms
Kim et al. (2023)	40 (mean) /16 M and 5 F	None	Cocaine	Parkinsonism, dystonias, dyskinesias, and akathisias	Cocaine use was associated with increased risk of movement disorders with antipsychotic use

AIMS – abnormal involuntary movement scale; F – female; M – male; NA – not available/not applicable; UPDRS – unified Parkinson's disease rating scale

"crack dancing" even among users of cocaine. Cocaine-induced moderate to severe involuntary choreiform movements have also been reported, which were transient and improved after a short hospital stay. While phenotypically, the movements are indistinguishable from other movement disorders, the pathogenesis in cocaine-induced movement disorders involves excess dopamine in the synaptic cleft secondary to cocaine (Narula et al., 2017), and sensitization of the basal ganglia and change in the dopaminergic activity are hypotheses that explain the mechanism of these abnormal movements (Bartzokis et al., 1999).

Dystonia

Binge use of cocaine has resulted in acute dystonic reactions in patients who have not taken other drugs. However, individuals who are already on antidopaminergic

agents had worsened dystonic symptoms after cocaine use (Catalano et al., 1997). Cocaine withdrawal has been reported to cause generalized dystonia, vocalization, and posturing in young women who were treated with diphenhydramine (Millichap, 1989). Also, long-term use of cocaine can cause structural changes in the dopaminergic receptors in the basal ganglia, leading to persistent and severe spasmodic torticollis. Noteworthy, family history and other secondary causes of cervical dystonia should be revised before the diagnosis of cocaine-induced dystonia (Vinkers et al., 2010). Case reports describing orofacial dystonia involving the lips, jaw, tongue, and extrapyramidal motor tract dysfunction impacting speech secondary to cocaine use have been reported.

Tics

Cocaine-induced tics have been described in individuals who used cocaine chronically without pre-existing conditions or a family history of movement disorders. Case reports describe individuals who used cocaine and presented with grunting, head jerks, and flaring of the nostrils. Cocaine worsens pre-existing tics in individuals with Tourette syndrome, and new-onset tics were reported after high-dose cocaine use. The tics were complex and included vocal and motor components. In one of these cases, cerebrospinal fluid homovanillic acid levels were low which was a finding previously reported in similar cases. While abnormalities of cerebral blood flow were possibly confounding the findings, the absence of lateralization of tics favoured the hypothesis that cocaine was responsible (Pascual-Leone and Dhuna, 1990; Attig et al., 1994).

Dyskinesia

"Crack dancing" consists of self-limiting, choreoathetoid movements involving orofacial and limb musculature that may be associated with akathisia and can last up to several days. Prolonged cocaine use, even after abstinence, results in movement disorders such as dyskinesias. A case report describes a young female with twisting movements of her trunk, which emerged during periods of cocaine withdrawal and eventually became persistent. Rocking of the body, painful muscular spasms of the abdominal region, along with persistent truncal flexion were reported by the patient. She did not have pre-existing conditions, did not use neuroleptics, and denied family history, but reported polysubstance use. Interestingly, cocaine abusers had decreased cerebral blood flow in the frontal lobes in functional studies that were persistent even after a 90-day interval. Computed tomography also demonstrated cerebral atrophy in chronic cocaine users with a positive dose-response relationship. A characteristic stereotypical motor movement called "punding" has been described among cocaine users which involves the examination of objects or parts of the body with fascination, resembling obsessive-compulsive disorder patterns (Weiner et al., 2001).

Possibly one of the most visually dramatic movement disorders induced by cocaine is transient chorea and buccolingual dyskinesias, known in street slang as "crack dancing" or "boca torcida" by Hispanic addicts.

Parkinsonism

A case report of long-term intranasal and intravenous cocaine use resulting in parkinsonism has been described in the literature (Domingo and Martínez, 1997). A case report suggested genetic susceptibility to developing Parkinsonian features in individuals with chronic cocaine use. After 18 months of cocaine use, the individual described developed features of parkinsonism, and the dopamine transporter study was asymmetric, consistent with phenotypic findings. His genetic makeup revealed leucine-rich repeat kinase-2 gene homozygosity. The phenotypic and genotypic features were no longer present after the individual was abstinent from cocaine (Illés et al., 2019).

Alpha-synuclein overexpression in dopaminergic neurons has been described in cocaine users. Hyperechogenicity of the substantia nigra on ultrasound has been found in individuals with Parkinson's disease and also among chronic cocaine users indicating similar underlying pathology (Cenci et al., 2022). Although cocaine and Parkinson's disease have depleted dopamine, chronic use of cocaine was not found to result in Parkinsonian features in other studies. Interestingly, cocaine users had excess iron accumulation in their globus pallidus, indicating iron dysregulation resulting in free radical-mediated damage (Dhopesh et al., 1997; Ball et al., 2019).

Parkinsonism is rarely described as a result of cocaine use, and, in fact, inhaled cocaine has been reported to ameliorate Parkinsonian "off" periods in self-medicating patients without triggering dyskinesias (Di Rocco et al., 2006).

Opsoclonus-myoclonus

Popularly known as "dancing eye-dancing feet", opsoclonus-myoclonus secondary to cocaine use has been reported in the literature. Continuous intermittent nystagmus beats in a circumductive fashion were noted on physical examination, along with myoclonic jerks and ataxia. Elkardoudi-Pijnenburg and Van Vliet (1996) reported a case where after a few weeks of hospital stay, the opsoclonus improved, and his symptoms were completely resolved after four months. Previous reports have demonstrated similar findings with intranasal cocaine use. Opsoclonus is generally thought to occur secondary to loss of inhibition of ocular saccades. Several differential diagnoses should be excluded, including viral illness, tumours, toxins, poisons, and autoimmune etiologies, and the exact pathogenesis remains unclear (Scharf, 1989).

Tremors

Cocaine is reported to cause hand tremors, among other movement disorders. The nigrostriatal and mesolimbic tracts are the primary dopaminergic systems that are downregulated, resulting in tremors. Interestingly, individuals who were abstinent from

cocaine displayed resting tremors and slow reaction time in the study. Confounding factors such as anxiety, alcohol, and nicotine were studied, but no significant relationship was established. Cocaine is hypothesized to dysregulate the metabolism of glucose in the basal ganglia and alter receptor binding in the striatum in controlled studies demonstrating a link between cocaine and Parkinsonian features such as tremors (Bauer, 1996).

Stuttering

Linazasoro and Van Blercom (2007) reported an interesting observation on cocaine and stuttering. They describe a case report of a 30-year-old male with developmental stuttering and mild facial dyskinesias whose symptoms resolved for a few hours without re-emergence when he used cocaine. This finding was surprising because multiple case reports indicate that cocaine can induce new tics or worsen existing tics. It was conjectured that this phenomenon is secondary to a relatively low dopamine state due to a complex interaction between the neurotransmitters.

Future studies

Reporting cocaine use in a standardized format by healthcare professionals can prove useful in understanding the impact on society, and thereby, the need for allocation of budget by policymakers. Risks of developing movement disorders in particular conditions can be studied, and this knowledge can be implemented as a preventative care measure for affected populations. Studying the effects of cocaine on the dopaminergic system can provide insights into the neurobiology of stimulant use in general. Moreover, it can provide reliable information on targeting future therapeutics against addiction.

Understanding the intricacies of movement disorders and their response to substances can be useful in developing strategies to reduce movement disorder disease burden. Imaging modalities and biomarkers are essential for supporting understanding of neurological pathologies and research is needed to identify imaging findings and biomarkers that can support diagnosis and thereby initiation of treatment promptly. Longitudinal studies, while complicated because of the nature of the study, should be undertaken to improve understanding of the long-term use of cocaine.

Experiences of patients and their families of movement disorders secondary to cocaine should be recorded and reported so information is available to discuss prognostication and encourage abstinence among subjects. Studies assessing the understanding of drug use and associated complications among the general population can help guide resources toward educating the community as a whole. Animal models can help enhance our understanding of interactions of the brain and chemicals.

Limitations

Cocaine use disorder is underreported due to perceived social stigma and legal consequences, which limits the data gathered to perform a thorough analysis of the literature. Cocaine use disorder commonly occurs in conjunction with opioid use disorder and alcohol use disorder, among others, and even contaminants, which results in confounding data.

Case reports and case series, which lack control groups and randomization, are core data sources for this review. The quality of individual reports and studies will vary significantly, which translates to the quality of the literature review as concrete conclusions cannot be drawn. As a case in point, multiple case reports omit the route and quantity of cocaine use, which is important information to assess a dose-response relationship. Timelines of case reports and series are varied, and updates in research could have been missed. Ethical concerns arise in experimenting with substances to study their effects in animal and human subjects, which results in relying on data obtained from illicit consumption.

Conlusion

Cocaine use, acutely or chronically, can result in a wide array of movement disorders. This literature review provides insights into our understanding of mechanisms underlying cocaine-induced movement disorders. Also, it highlights the knowledge gaps that need to be filled through dedicated research, paving the way to potential therapeutic modalities in the hope of reducing the disease burden. Studying the effects of a widely used substance on the dopaminergic system will result in an enhanced understanding of neurobiology, which can be used in understanding, preventing, and developing therapeutic strategies for other movement disorders. It will add another reason to restrict the use of substances in medical care and research.

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Rheumatoid Arthritis and Osteoarthritis in Adult Women: A Functional Approach to the Stomatognathic System

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Received April 11, 2023; Accepted July 28, 2024.

Key words: Rheumatoid arthritis – Osteoarthritis – Masticatory muscles – Electromyography – Bite force – Mandibular mobility

Abstract: Rheumatoid arthritis and osteoarthritis both affect the articular cartilage, and are characterized by signs and symptoms that can affect the functions of the human body. This cross-sectional observational study evaluated electromyographic activity in the masseter and temporalis muscles, molar bite force, and mandibular mobility in adult women with rheumatoid arthritis or osteoarthritis. A total of 42 women were distributed into 3 groups: rheumatoid arthritis group (ARG, n=14); osteoarthritis group (OAG, n=14); and a healthy control group (CG, n=14). Electromyography was used to evaluate mandibular tasks at rest, right and left laterality, protrusion, and dental clenching during maximum voluntary contraction, with and without parafilm, and a dynamometer was used to analyse the right and left molar bite forces. A digital caliper was used to measure the range of mandibular movement for maximum mouth opening, right and left laterality, and protrusion. Statistical analyses were performed, including analysis of variance and Tukey's test ($P<0.05$).

This study was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP and Instituto Nacional de Tecnologia – Medicina Translacional (INCT.TM).

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https://doi.org/10.14712/23362936.2024.20

Electromyography showed no significant differences between the groups when evaluating the masticatory muscles during the mandibular tasks. Significant difference was observed between the ARG and CG, however, in the maximum right (P=0.007) and left (P=0.02) molar bite forces. Significant difference was observed in the maximum mouth opening of the ARG and OAG groups compared with that of the CG (P=0.009), suggesting that adult women with rheumatoid arthritis or osteoarthritis experience functional alterations in the stomatognathic system, particularly in molar bite force and maximum mouth opening.

Introduction

Rheumatoid arthritis and osteoarthritis are both chronic diseases that affect the musculoskeletal system, particularly the joint cartilage, of individuals with a family history, often involving the temporomandibular joints and structures that comprise the stomatognathic system (Bruno et al., 2022).

Rheumatoid arthritis is an inflammatory disease that results in functional damage to cartilage and bones (Smolen et al., 2016; Palinkas et al., 2018). It is one of the most common autoimmune diseases, affecting approximately 1% of the world's population. In the United States, approximately 1.28–1.36 million adults are affected (Hunter et al., 2017). Individuals with rheumatoid arthritis experience joint pain and stiffness, with morning stiffness lasting more than an hour being an important clinical characteristic related to the disease's inflammatory etiology (Aletaha and Smolen, 2018).

Osteoarthritis is the most commonly diagnosed joint disease in the world, with an age-associated increase in incidence and prevalence (Mandl, 2019), characterized by the degeneration of joint cartilage, which causes a decrease in joint spaces, friction between bones, pain, edema, and functional disability (Musumeci et al., 2015). It is the most frequent disease of the musculoskeletal system, and can affect at multiple joints with cartilage at any time (Fernández-Torres et al., 2017; Vina and Kwoh, 2018).

Functional analyses of the stomatognathic system in individuals with chronic degenerative diseases are performed using internationally recognized assessments, such as gnathodynamometry, range of mandibular movements, and masticatory performance, to obtain accurate diagnoses and more effective treatment results (Zhao and Monahan, 2007; Righetti et al., 2020; Gonçalves et al., 2022). Therefore, studies which aim to demonstrate the influence of chronic degenerative diseases on the stomatognathic system are relevant, because they aim to verify changes in the performance patterns relating to masticatory mechanics, as well as possible influences on the effectiveness of rehabilitation treatments in different areas of health. The null hypothesis of the present study was that adult women with rheumatoid arthritis or osteoarthritis do not present with functional changes in the stomatognathic system.

Material and Methods

The protocol for the present cross-sectional observational study was approved by the ethics committee of the Faculty of Dentistry of Ribeirão Preto, University of São Paulo, Brazil (Process # 67983717.2.0000.5419). Written informed consent was obtained from all the women who participated in the study.

Convenience sample selection

In the initial phase of the present study, 174 adult women from the cities of Ribeirão Preto, Batatais, and Bebedouro in the State of São Paulo, Brazil were recruited and evaluated – 102 with a diagnosis of rheumatoid arthritis, 72 with a diagnosis of osteoarthritis. Based on the established exclusion criteria, 88 women with rheumatoid arthritis and 58 with osteoarthritis were excluded from the present study.

In total, 42 women, 40–70 years of age, participated in the present study. The patients were divided into the following three groups: rheumatoid arthritis group (ARG, n=14); osteoarthritis group (OAG, n=14); and a group of health controls (CG, n=14). For the ARG group, the mean age was 52.3 ± 11.2 years, and the mean body mass index (BMI) was 31.1 ± 4.64 kg/m^2; for the OAG group, the mean age and BMI were 54 ± 6.8 years and 27.3 ± 3.93 kg/m^2, respectively; and for the CG group, the mean age and BMI were 50.2 ± 9.5 years and 27.2 ± 3.88 kg/m^2, respectively. For the group constitution, pairing by age and BMI was considered. BMI was calculated in kilograms and meters, as follows: BMI = weight in kilograms/(height in meters) × (height in meters).

Women with chronic degenerative diseases were diagnosed by rheumatologists after evaluating clinical signs and symptoms, imaging, and laboratory tests (da Mota et al., 2011). A clinical intake form was used to collect personal information, such as the general and oral health history, existence of additional uncompensated systemic diseases, and parafunctional habits. The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) were used to rule out temporomandibular disorders (Yap et al., 2023). The DC/TMD was applied to the patients in all three groups as a diagnostic criterion for temporomandibular dysfunction.

The exclusion criteria were as follows: absence of the first permanent molars, upper or lower; dental restoration with a risk of fracture; presence of temporomandibular disorder; orthodontic, speech therapy, or otorhinolaryngological treatment; use of medications that could interfere with muscle activity; physical or emotional indisposition to perform the tests; and clinical history of psychiatric or neurological disorders.

The post hoc sample calculation was performed using G*Power software, version 3.1.9.7 (Franz Faul, Kiel University, Kiel, Germany) to ensure that a representative sample was used. For the post hoc sample calculation, the values obtained for the maximum right bite force from the ARG (153 ± 27) and OAG (211 ± 27) groups, with an error of 5%, were considered. According to the analysis protocol issued

by the software, the effect size was 2.23 and the test power was 99%. The intra-examiner reliability was assessed by calculating the intraclass coefficient (ICC), and the reliability was considered acceptable for electromyographic activity (EMG) (ICC = 0.936).

Electromyographic analysis of mandibular tasks

The EMG evaluation of the masseter and temporalis muscles was performed by a single trained professional using the TrignoTM Wireless EMG System (Delsys, Inc., Natick, Massachusetts, USA). The electromyographic recording allowed us to evaluate the EMG of the masticatory muscles during the following mandibular tasks: rest (4 s); right (10 s) and left laterality (10 s); protrusion (10 s), and dental clenching in maximum voluntary contraction with (4 s) and without (4 s) an inert material. The inert material (Parafilm; Pechiney Plastic Packaging, Batavia, IL, USA) consisted of a folded sheet of paraffin (18×17×4 mm, 245 mg) placed between the permanent molars (upper and lower) on both sides of the dental arch (Siéssere et al., 2009).

To obtain EMG data, surface electrodes were installed in the belly regions of the masseter and temporalis muscles on both sides of the mouth using the maximum voluntary contraction maneuver and digital palpation, which is considered the best point for investigation (Hermens et al., 2000). Superficial aseptic cleaning was performed using 70% isopropyl alcohol before fixing the electrodes, in order to reduce the electrical impedance of the biological tissues (Di Palma et al., 2017).

EMG data were acquired in a calm environment, with the patients sitting erectly on a chair, and breathing lightly and slowly. The head was positioned in the Frankfurt plane, the hands were lightly supported on the anterior region of the thighs, and the feet were placed on the ground.

Molar bite force analysis

An IDDK model digital dynamometer (Kratos Equipamentos Industriais Ltda., Cotia, São Paulo, Brazil) was used to measure the maximum bite force, adjusted for the oral cavity to avoid condylar displacement or muscle distension. The dynamometer contained two rods with two Teflon disks at their ends, to which the bite force was applied, which was recorded in Newtons (N) (Palinkas et al., 2010; Gomes et al., 2022).

The patients were seated erectly on a comfortable chair with their feet flat on the floor and their hands rested on the anterior region of their thighs. To ensure sanitary conditions, the device's rods were aseptically cleaned with 70% isopropyl alcohol prior to each collection, in addition to being covered with disposable latex finger cots.

The rods were positioned over the region of the first permanent molar, which provides the greatest occlusal force (Regalo et al., 2008). The patients were asked to bite the device with their maximum effort three times, with a two-minute rest period between recordings, and alternating between the right and left sides (Bonjardim

et al., 2009). All patients were instructed in advance to perform the tests by squeezing the device between their teeth before obtaining official records to ensure the reliability of the procedure.

Analysis of the range of mandibular movements

The amplitude of the patients' mandibular movements, in millimeters, was evaluated based on the mean value obtained from three measurements using a digital caliper (Mitutoyo®, Suzano, São Paulo, Brazil) during the mandibular tasks of maximum mouth opening, right and left laterality, and protrusion. Before each evaluation, the procedure was explained to the patients, and for reference standardization, dental midlines were adopted, along with the deviations. The equipment was positioned at the incisal and mesial regions of the upper and lower central incisors (Mazzetto et al., 2017).

Statistical analysis

The raw EMG data were used to determine the values for amplitude, using the root mean square (RMS) in microvolts (μV) per second. To allow for comparison, the RMS value obtained during the tooth clenching at maximum voluntary contraction was used to normalize the data obtained during the mandibular tasks. Statistical analyses were performed using GraphPad Prism software (GraphPad Software Inc., version 5.0, California, USA). The results were compared using analysis of variance (ANOVA), with a significance level of 5% and a confidence interval of 95%, and a post hoc comparison was performed using Tukey's test.

Results

Table 1 shows the normalized electromyographic activity of the masseter and temporalis muscles during mandibular tasks for the rheumatoid arthritis (ARG), osteoarthritis (OAG), and control (CG) groups. There were no significant differences in the normalized EMG of the masticatory muscles between the groups. Clinical analysis showed that the ARG group showed higher normalized EMG values during rest, right and left laterality, and protrusion in the temporal and right masseter muscles, and lower values in dental clenching in maximum voluntary contraction with parafilm compared to the OAG and CG groups for all masticatory muscles.

In the analysis of the maximum molar bite force, the ARG group showed less force on the right (P=0.007) and left (P=0.02) sides compared to the OAG and CG groups, with a significant difference when compared with the CG group. The OAG group presented a lower bite force than the CG group on both sides; however, the difference was not significant (Table 2).

Table 3 shows the range of mandibular movements in the ARG, OAG, and CG groups. A significant difference was observed for the maximum mouth opening

among the three groups (P=0.009), although no significant differences were observed for right and left laterality or protrusion between the groups.

Discussion

The null hypothesis of the present study, that adult women with rheumatoid arthritis or osteoarthritis do not present with functional changes in the stomatognathic

Table 1 – Differences in mean values (standard error) of normalized EMG data between groups

Mandibular task Muscles	Groups			P-value
	ARG mean ± standard error	OAG mean ± standard error	CG mean ± standard error	
Rest				
RM	0.20 ± 0.03	0.14 ± 0.04	0.12 ± 0.02	0.23
LM	0.21 ± 0.07	0.21 ± 0.05	0.13 ± 0.02	0.43
RT	0.34 ± 0.06	0.27 ± 0.06	0.20 ± 0.05	0.24
LT	0.24 ± 0.03	0.21 ± 0.04	0.19 ± 0.04	0.60
Protrusion				
RM	0.39 ± 0.07	0.21 ± 0.06	0.23 ± 0.04	0.08
LM	0.33 ± 0.10	0.28 ± 0.07	0.24 ± 0.06	0.71
RT	0.51 ± 0.18	0.24 ± 0.05	0.18 ± 0.03	0.09
LT	0.27 ± 0.05	0.21 ± 0.04	0.17 ± 0.04	0.47
Right laterality				
RM	0.25 ± 0.06	0.12 ± 0.03	0.13 ± 0.03	0.06
LM	0.23 ± 0.06	0.23 ± 0.05	0.22 ± 0.04	0.99
RT	0.39 ± 0.06	0.24 ± 0.05	0.26 ± 0.04	0.99
LT	0.20 ± 0.04	0.19 ± 0.03	0.15 ± 0.03	0.45
Left laterality				
RM	0.20 ± 0.03	0.14 ± 0.04	0.21 ± 0.04	0.06
LM	0.22 ± 0.07	0.18 ± 0.05	0.14 ± 0.03	0.06
RT	0.40 ± 0.12	0.24 ± 0.05	0.22 ± 0.05	0.23
LT	0.29 ± 0.06	0.23 ± 0.05	0.23 ± 0.03	0.71
MVC/parafilm				
RM	0.83 ± 0.12	1.40 ± 0.32	1.09 ± 0.25	0.27
LM	0.78 ± 0.11	1.53 ± 0.38	1.09 ± 0.25	0.06
RT	0.85 ± 0.14	1.15 ± 0.34	1.22 ± 0.38	0.68
LT	0.71 ± 0.11	1.11 ± 0.27	1.27 ± 0.49	0.47

EMG – electromyographic activity; ARG – rheumatoid arthritis; OAG – osteoarthritis; CG – without the diseases, control; RM – right masseter; LM – left masseter; RT – right temporalis; LT – left temporalis; MVC – maximum voluntary contraction. Significant difference, ANOVA and Tukey's post-test (i.e., P<0.05)

Table 2 – Differences in mean values (standard error) of molar bite force data between groups

Molar bite force (N)	Groups			P-value
	ARG mean ± standard error	OAG mean ± standard error	CG mean ± standard error	
Right	153 ± 27[a]	211 ± 27	260 ± 12[b]	0.007
Left	149 ± 33[a]	217 ± 24	252 ± 17[b]	0.020

ARG – rheumatoid arthritis; OAG – osteoarthritis; CG – without the diseases, control; N – newtons.
Significant difference, ANOVA and Tukey's post-test ([a] and [b] – difference between groups) (i.e., P<0.05)

Table 3 – Differences in mean values (standard error) of range of mandibular movements data between groups

Mandibular tasks (mm)	Groups			P-value
	ARG mean ± standard error	OAG mean ± standard error	CG mean ± standard error	
Maximum mouth opening	36.4 ± 1.7[a]	36.7 ± 1.7[a]	43.0 ± 1.6[b]	0.009
Protrusion	6.2 ± 1.0	5.2 ± 0.6	6.7 ± 0.6	0.360
Right laterality	7.6 ± 0.9	7.8 ± 0.8	9.3 ± 0.8	0.220
Left laterality	8.7 ± 1.2	9.5 ± 0.8	8.9 ± 0.7	0.360

ARG – rheumatoid arthritis; OAG – osteoarthritis; CG – without the diseases, control; mm – millimeters.
Significant difference, ANOVA and Tukey's post-test ([a] and [b] – difference between groups) (i.e., P<0.05)

system, was rejected, based on the results found for the various methodologies used, which demonstrated that this specific population does, in fact, present with changes in the functionality of the stomatognathic system, particularly in the molar bite force and maximum mouth opening. The present study used a variety of internationally standardized techniques to accurately assess the stomatognathic system of the study population, including evaluations of the masticatory muscles, bite force, and range of mandibular movements.

At rest, it was possible to observe a record of normalized EMG activity of both the masseter and temporalis muscles in all groups, as reported in the literature (Palinkas et al., 2013; Gonçalves et al., 2018). This finding is expected because it is necessary to recruit muscle fibers in both muscles to maintain this postural condition. Although there was no significant difference between the groups, there was greater EMG activation of the temporalis muscles in relation to the masseters in all groups, which is consistent with the literature (Cecílio et al., 2010).

When evaluating protrusion, no significant differences were observed between the three groups; however, higher normalized means of the EMG data from the right temporal muscle were observed in relation to the right masseter muscle in the ARG

and OAG groups. This finding differs from the typical pattern of EMG activation, in which greater activity of the masseter muscle is expected compared to the temporalis muscle (Cecílio et al., 2010). In the control group, however, the pattern was as expected, with greater activity in the masseter than the temporalis muscles.

In evaluating right and left laterality, the typical pattern of behaviour is that the temporalis muscle is more active on the same side to which the mandible is projected (working side), while the masseter muscle is more active on the opposite side, to which the mandible extends (balance side) (Blanksma et al., 1995). The results of the present study showed that in this mandibular task, the results were in line with what is expected for right laterality in the OAG and CG groups, based on the relevant literature, except for the right masseter muscle in the ARG group. On the left side, the normalized means of the EMG data for the ARG and OAG groups were the opposite of the expected pattern, which was thought to be the result of systemic compensation when performing the requested function, in turn recruiting more muscle fibers contralaterally.

Although no significant differences were found in the tooth-clenching task at maximum voluntary contraction, the activity of the masseter muscle in the OAG group tended to dominate at greater clenching intensities, which is in agreement with the relevant literature (Mioche et al., 1999).

Bite force is used to understand a wide range of factors of the masticatory system (Jansen van Vuuren et al., 2020), including the maximum load performance in the region of the first molars, which determines the efficiency of this system (Regalo et al., 2008; Pepato et al., 2014). Bite force is a fundamental factor in masticatory tasks, and depends on muscle volume, activity, and coordination, as well as mandibular mobility, as all these factors are important in the of fractionation food (van der Bilt et al., 2006).

The results of the present study showed weaker left molar bite forces, with a significant difference between the ARG and CG groups. The importance of evaluating the functional and parafunctional mandibular loads that oral diseases and dysfunctions are partially related to these loads (Hattori et al., 2009).

Bite force is produced by muscle coactivation, predominantly the masseter, medial pterygoid, and temporalis muscles (Peck, 2016). Since the generation of potential force in these muscles closer to the mandible is related to the size of the cross-section and the length of the muscle, it is important to correlate degenerative diseases that affect the musculoskeletal components and the impaired ability to apply forces to cut and grind food.

Mandibular range of motion requires neuromuscular control of the masticatory muscles, since, for the execution of masticatory activity, a combination of muscle activities is necessary for the mandible to move and exert enough force to cut or crush food (van der Bilt et al., 2006). In the present study, lower means of maximum mouth opening were observed, identifying a significant difference in the ARG and OAG in relation to the CG. Therefore, the assessment of mandibular mobility is an

integral part of dental examinations (Türp et al., 2020), especially in patients with chronic degenerative diseases.

The process of aging involves significant changes in several physiological functions, which decrease the body's ability to maintain homeostasis, increasing an individual's predisposition to disease and, consequently, death. The skeletal muscles are particularly affected by aging, especially with regard to the decrease in muscle mass and strength, which is characterized by sarcopenia (Scicchitano et al., 2018).

Although sarcopenia is frequently observed, it is one of the main determinants of several adverse effects of aging, such as frailty, disability, and limitations in the activities of daily life, all of which affect quality of life (Azzolino et al., 2019). It is important to emphasize that sarcopenia involves the entire body, affecting both the masticatory muscles and maximum molar bite force (Fan et al., 2022).

The relationship between oral disease and sarcopenia can be observed by the common presentation of inflammation and oxidative stress, which are related to biological and environmental factors. Poor oral health affects food selection, which is directly related to nutrient intake, in turn resulting in malnutrition, frailty, and sarcopenia (Azzolino et al., 2019).

Although the present study did not evaluate for the presence of sarcopenia, the patients were diagnosed with a chronic degenerative disease (rheumatoid arthritis or osteoarthritis), which is correlated with aging and oxidative stress (Phull et al., 2018; Brance et al., 2021). The role of oxidative stress in the pathophysiology of aging is complex, involving the agglutination of reactive oxygen species and a reduction in antioxidant mechanisms (Scicchitano et al., 2018). Furthermore, previous studies have suggested that the interaction between oxidative stress, chronic inflammation, and mitochondrial dysfunction can affect the balance between protein synthesis and protein breakdown, inducing apoptosis, in addition to causing atrophy and loss of fibers in aging skeletal muscles (Nishikawa et al., 2021).

Therefore, changes related to the aging process that affect joint tissues predispose patients to rheumatoid arthritis and osteoarthritis. The reduction in muscle mass and increase in fat mass that occur with aging result in an increased joint load, with a subsequent increase in the production of adipokines and cytokines, resulting in low-grade systemic inflammation. Additionally, elevated levels of reactive oxygen species can contribute to osteoarthritis by promoting oxidative stress (Loeser et al., 2016).

In contrast, oxidative stress has been shown to be a potential contributor to the initiation and establishment of a pro-inflammatory milieu in individuals with rheumatoid arthritis, which is defined as a high-grade condition (da Fonseca et al., 2019). These findings corroborate the results of the present study, as both diseases have potential effects on the components of the stomatognathic system, which was more evident when analysing ARG in relation to OAG and CG.

The present study has some limitations. Of note, the presence of osteoarthritis or rheumatoid arthritis in the temporomandibular joints was not evaluated, nor was the status of unilateral or bilateral involvement. In the case of rheumatoid

arthritis, magnetic resonance imaging (MRI) should be used as part of the diagnostic process, as it is the only test capable of detecting bone marrow edema, which is a good predictor of disease progression. Additionally, MRI is a safe and appropriate tool for monitoring responses to the treatment of synovial and erosive progression (Barile et al., 2017). For osteoarthritis, the most recommended diagnostic method is computed tomography (Haj-Mirzaian et al., 2020). This study utilized a women-only sample; therefore, it is recommended to investigate and verify the results in men patients to achieve a comprehensive understanding of the findings.

Conclusion

The results of the present study suggest that adult women with chronic degenerative diseases of the joint cartilage (rheumatoid arthritis or osteoarthritis) undergo functional changes in the stomatognathic system, with an emphasis on changes to the maximum molar bite force and maximum mouth opening range.

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 Prague Medical Report / Vol. 125 (2024) No. 3, p. 232–238

A Rare Case of Neuromyelitis Optica Spectrum Disorder Secondary to Primary Sjögren's Syndrome in an Older Woman

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Received March 28, 2024; Accepted July 28, 2024.

Key words: Aging – Neuromyelitis optica spectrum disorder – Primary Sjögren's syndrome

Abstract: Primary Sjögren's syndrome is an autoimmune disorder that is characterized by lymphocytic infiltration of salivary and lacrimal glands. The extra-glandular manifestations might be arthritis, myalgia, glomerulonephritis, skin rashes, and neurologic involvement. One of the uncommon neurologic manifestations is neuromyelitis optica spectrum disorder (NMOSD). In the present case, an older woman is reported that was diagnosed with NMOSD secondary to keratoconjunctivitis sicca, which is rare in geriatric practice.

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https://doi.org/10.14712/23362936.2024.21

Introduction

Primary Sjögren's syndrome (PSS) is an autoimmune disorder, most commonly presenting with dry mouth and eyes, that is characterized by lymphocytic infiltration of the exocrine glands. There are also extra-glandular involvements such as arthritis, myalgia, glomerulonephritis due to mixed cryoglobulinemia and amyloidosis, skin rashes, interstitial pneumonitis and gastrointestinal manifestations (Fox, 2011). The prevalence of neurologic manifestations in PSS is estimated to range from 8 to 49% (Margaretten, 2017). Neurological involvements of PSS vary widely and are divided into peripheral and central nervous system manifestations. While peripheral neuropathies can be seen as sensory, sensorimotor, autonomic or cranial neuropathy, central nervous system involvement might be present in different spectrums including focal cerebral lesions, multiple sclerosis-like involvement, aseptic meningitis or encephalitis, ataxia due to cerebellar involvement, cognitive dysfunction and depression (Margaretten, 2017). Neuromyelitis optica spectrum disorder (NMOSD) is frequently seen in the third and fourth decades. NMOSD cases seen after the age of 50 are defined as late onset, while NMOSD cases seen after the age of 70 are defined as very late onset. Very late onset NMOSD are extremely rare (Hu et al., 2022). The frequency of NMOSD in patients with PSS is also very rare. As far as we know, the co-existence of NMOSD and Sjögren's syndrome has been reported in an older patient (Shahmohammadi et al., 2019).

In this case report, an older woman with NMOSD after PSS will be presented.

Case report

A 74-year-old female patient was admitted to our outpatient geriatric clinic with complaints of dry mouth, stinging and burning in the eyes, and numbness in the hands bilaterally. The patient, who had known diagnoses of hypertension and diabetes mellitus, applied to the rheumatology department at another center about four years ago due to dry mouth and dry eyes. Lymphocytic infiltration was detected in the minor salivary gland biopsy. Positive for ANA titer (+++; cytoplasmic pattern) and negative for rheumatoid factor (RF), anti-SSa, anti-SSb were measured simultaneously. She was diagnosed with PSS at four years ago. The patient was followed up without medicine during this period. Then, two years ago, she was admitted to the neurology department due to dizziness and widespread paresthesia throughout the whole body. On neurologic examination glove-sock-shaped sensory deficit, dysdiadochokinesia and cerebellar dysmetria in addition to bilateral paresthesia were detected. No acute pathology was detected on cranial imaging. The spinal magnetic resonance imaging of the patient showed an edematous appearance in the spinal cord at the cervical and thoracic levels, and staining lesions showing long segment involvement in the spinal cord (Figure 1). In the patient

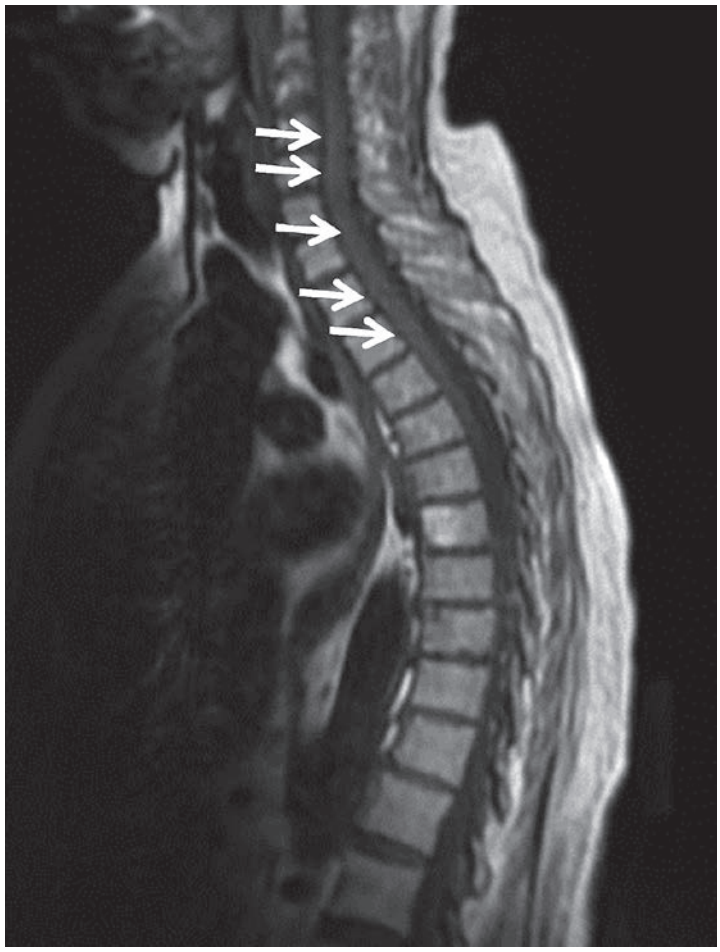

Figure 1 – Cervical and thoracal T2 magnetic resonance image demonstrates edema and longitudinally extending hyperintensity in the cervico-thoracal junction indicating acute myelitis.

who had no signs of optic neuritis, transverse myelitis was primarily considered. Cerebrospinal fluid assessment revealed high protein levels. Serum anti-NMO (neuromyelitis optica) antibody was detected positive. Multiple sclerosis was not considered in the differential diagnosis because the clinical course was not primarily relapsing-remitting, no oligoclonal bands were seen in the cerebrospinal fluid sample, no multiple lesions were found in the spinal MRI (magnetic resonance imaging), and NMO-specific antibody positivity. In addition, since there was no history of infection or immunization before the neurological symptoms, the diagnosis of myelin oligodendrocyte glycoprotein antibody associated disease was excluded. Additionally, since the symptoms develop in a chronic process, acute myelopathies were excluded. She was started on high dose intravenous methylprednisolone (1 gram daily for three consecutive days) for the treatment of acute attacks. When no significant clinical response was observed, intravenous immunoglobulin (1 g/kg daily for five

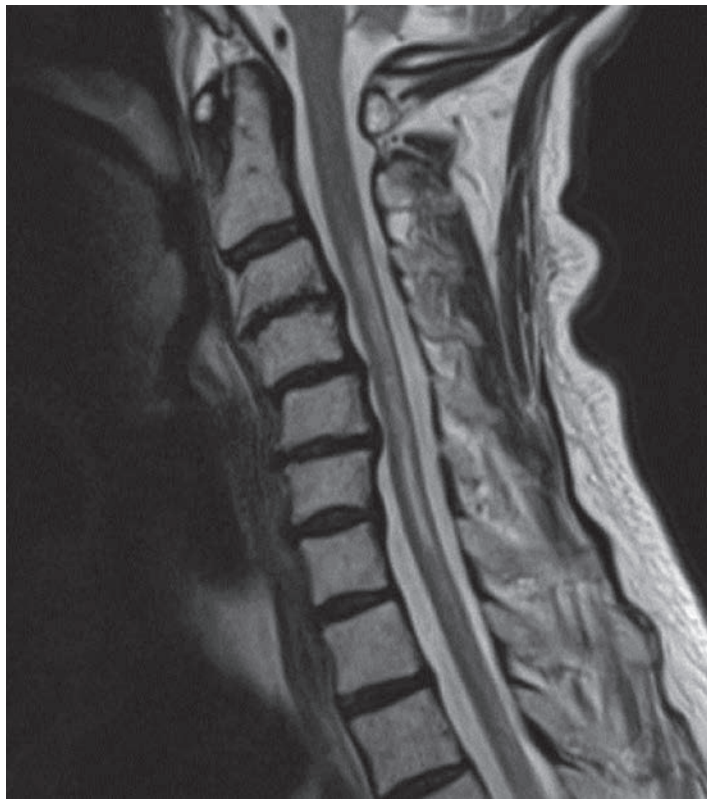

Figure 2 – Cervical and thoracal T2 magnetic resonance image (2 years later) revealed bright longitudinal lesions indicative for sequale of demyelinisation and chronic transverse myelitis.

consecutive days) was applied as second-line treatment. There was no need for plasma exchange for the patient, who received a clinical response after intravenous immunoglobulin treatment, and maintenance treatment was planned as rituximab. During the follow-up, her neurological complaints not sicca symptoms regressed, and no myelitis recurrence was observed and her control MRI only showed some chronic alterations (Figure 2). She has suffered from dry mouth and dry eyes started again for six months ago and were admitted to our geriatric clinic. In comprehensive geriatric assessment, she had forgetfulness, which did not affect her daily life activities, recurrent falls in a year, polypharmacy and widespread body pain. The medications were recorded as lercanidipine 20 mg/day, nebivolol 5 mg/day, olmesartan 20 mg/day, levothyroxine sodium 50 mg/day, sitagliptin 100 mg/day, gliclazide 60 mg/day, gabapentin 600 mg/day, esomeprazole 40 mg/day. In physical examination, there was orthostatic hypotension, minimal paresthesia and no disorientation on neurological examination. Cerebellar examination was normal. Schirmer test was bilaterally less than 5 mm of strip wetting in 5 minutes. Laboratory tests revealed anemia (hemoglobin level: 10.8 g/dl), increased erythrocyte sedimentation rate (66 mm/h), and estimated glomerular filtration rate according

to MDRD (Modification of Diet in Renal Disease) was 23 ml/min/1.73 m^2. Vitamin B12 and 25-hydroxyvitamin D levels were normal. Treatment and recommendations were made for polypharmacy and orthostatic hypotension, and the patient was referred to the rheumatology department with a diagnosis of PSS. Azathioprine treatment was started due to the risk of NMOSD relapse, and pilocarpine treatment was also performed due to severe dry mouth. She is followed up in our geriatric outpatient clinic in terms of geriatric syndromes. This case report, which is very rare in geriatric practice, is made to contribute to the literature.

Discussion

Dry mouth is one of the common symptoms in older adults. In community-dwelling elderly, the reported prevalence ranges from 17 to 40% (Liu et al., 2012). The most common cause of dry mouth in geriatric practice is medication-related. Xerostomia may develop especially due to polypharmacy and antipsychotic, antimuscarinic, antihistamine, sedative or opioid analgesic drugs that have anticholinergic burden (Prado-Mel et al., 2022). In addition, dry mouth is a problem that can affect malnutrition, dysphagia dental problems, oral hygiene disorders and daily living activities in elderly individuals (Barbe, 2018). Other causes of dry mouth in the elderly including a history of radiation to the head and neck area, psychiatric problems, and Parkinson's disease (Barbe, 2018). Dry eye can also be related to anticholinergic medication in elderly individuals, and it frequently develops after surgery or due to age-related vision problems (Prado-Mel et al., 2022). PSS, which is known to present with dry mouth and dry eyes, is generally seen in middle-aged women. Elderly-onset Sjögren's syndrome (Eo-SS) is a rare condition (Fulvio et al., 2023).

The average prevalence of neurological involvement in PSS is 20% (Margaretten, 2017). Neurological presentation in PSS is quite broad. It may be asymptomatic, such as white matter changes may be detected incidentally on cranial imaging. They may also present with clinically evident neurological symptoms and findings. While peripheral neuropathy is the most common, multiple sclerosis-like lesions, encephalitis, cognitive dysfunction, ischemic stroke and psychiatric symptoms can be listed (Margaretten, 2017). In general, the underlying mechanisms are immune-mediated vasculopathy, vasculitis or demyelination (Alexander, 1993). NMOSD is extremely rare in association with Sjögren's syndrome. NMOSD has been differentiated from MS (multiple sclerosis) soon after the discovery of a highly specific serum autoantibody (NMO-IgG) which targets aquaporin-4: the main channel regulating water transport in CNS (central nervous system). The spectrum embraces five subgroups: idiopathic NMOSD (previously known as Devic disease) optic neuritis or longitudinally myelitis associated with systemic autoimmune disease; optic neuritis or longitudinally myelitis associated with brain

lesions; Asian optic-spinal MS and limited forms of NMO (Jarius et al., 2023). The common clinical features of NMOSD are ocular pain with impaired vision, severe symmetrical paraplegia, sensory loss and bladder dysfunction. In the present case, bilateral paresthesia without optic neuritis occurred. NMOSD usually affects women in their third and fourth decades. As in our case, NMOSD cases with an onset age over 70 years are known as very old onset NMOSD and are very rare (Hu et al., 2022). Additionally, the co-existence of NMOSD and PSS is mostly associated with anti-SSa/SSb positivity (Berkowitz and Samuels, 2014); however, there are cases also without anti-SSa/SSb positivity (Akaishi et al., 2021). In our case, SSa/SSb antibodies were observed as negative, which differs from the literature in this respect.

When NMOSD develops in patients diagnosed with PSS, treatment should be started as soon as possible. IV pulse methylprednisolone treatment should be started as the first choice. Plasmapheresis should be considered in cases unresponsive to steroids. Azathioprine, rituximab or mycophenolate mofetil should be planned for maintenance treatment (McCoy and Baer, 2017). Our patient responded to IV pulse steroids and rituximab was started as maintenance treatment. Although her symptoms including dry mouth and dry eyes regressed during the treatment, sicca symptoms started again because she gave up the treatment for an unknown reason. Our patient was referred to the rheumatology department with a maintenance immunosuppressive treatment plan in case of a recurrency of NMOSD. He continued to be followed up in the geriatric outpatient clinic in terms of geriatric syndromes.

Conclusion

A very rare case of NMOSD secondary to PSS has been reported in geriatric practice. Although the anticholinergic burden effect is often considered in older adults who are admitted to the hospital with dry mouth and dry eyes. When the patients are evaluated within the framework of comprehensive geriatric assessment, there may be an underlying rheumatological disease such as PSS. Even though elderly individuals are rarely seen in NMOSD regardless of its etiology, it may be associated with PSS. Moreover, it should be kept in mind that sicca symptoms may flare up again when treatment is stopped the maintenance treatment for NMOSD.

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Use of Marsupialization as a Definitive Treatment for Large-sized Dentigerous Cysts in a Patient with Mucopolysaccharidosis Type I

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Received March 11, 2024; Accepted July 28, 2024.

Key words: Mucopolysaccharidosis type I – Dental retentions – Dentigerous cyst – Marsupialization

Abstract: The correct diagnosis is fundamental for the appropriate treatment to be employed in a particular pathology. The best treatment is not the one that solves only local problems, fragmenting the patient, and therefore, it is necessary to integrate the entire systemic condition of the individual before initiating any local treatment. This context inevitably requires dentistry to participate in a multidisciplinary approach, where the role of the dentist is expanded in concepts that encompass ethics, human dignity, and professional valorization. This article describes a clinical case of a patient with mucopolysaccharidosis type I, whose treatment of cystic lesions present in the mandible was exclusively performed through marsupialisation. The objective of this study is to demonstrate, within the complexity of this rare syndrome, the difficulties of diagnosis and the need for evaluation of the patient beyond the limits of the oral cavity, as well as to report two cases of large dentigerous cysts, surgically treated conservatively through marsupialisation, without the need for re-approach for enucleation and without recurrences over a 20-year period.

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https://doi.org/10.14712/23362936.2024.22

Introduction

The triad of pathology-semiology-diagnosis is true and indispensable, given that the goal of diagnosis can only be achieved through it (Castro et al., 1995). Thus, the work carried out by the professional with the patient in collecting clinical data that will compose not only the symptomatic picture of the disease but also its entire physical and psychological panorama, past and present, needs to be done in a detailed manner. In dentistry, for the diagnosis of oral clinical alterations, it is no different; semiotic maneuvers are necessary and indispensable (Tommasi, 1989).

Thus, the diagnosis should include a systematic and organized general assessment of the patient. In this context, it is important to remember that the oral cavity and the maxillofacial region can be the initial site of manifestation of rare diseases (Tommasi, 1989). Tommasi (1989) affirm that the dentist has the ethical responsibility to base their professional practice on continually updated knowledge, which allows them to better interpret the pathologies they encounter and to provide effective prevention and appropriate treatment for them.

Mucopolysaccharidoses (MPS) represent a typical example of the complexity of the human body and the challenge that professionals face regarding a comprehensive and systematic patient assessment (Zhou et al., 2020). According to Murahovschi (2013), MPS are a group of diseases characterised by excessive urinary excretion of acid mucopolysaccharides and accumulation of tissue material. Clinically, it can be recognized as a disease with abnormal phenotype, classified into 7 types and 13 subtypes based on their genetic, clinical, and biochemical characteristics (Nagpal et al., 2022). The first case of MPS was described by Charles Hunter in 1917, and two years later, MPS I was described by the same author. The prevalence of different types of MPS varies across continents, suggesting an association with geographical regions and ethnicity (Zhou et al., 2020). The estimated occurrence of this syndrome is 1 in 25,000 births (Hampe et al., 2020). It is an autosomal recessive disease, except for MPS II, which is transmitted as an X-linked recessive disorder (Ribeiro et al., 2015; Nagpal et al., 2022).

The metabolic alteration through lysosomal degradation of mucopolysaccharides present in this rare genetic disease is reflected in significant changes in many tissues of the body, including bones, cartilage, and connective tissues. In general, MPS is caused by the deficiency or absence of a specific enzyme necessary to break down mucopolysaccharides, leading to the accumulation of these molecules in body tissues. The symptoms and severity of MPS can vary widely depending on the type of the disease and the degree of enzyme deficiency (Hampe et al., 2020; Zhou et al., 2020; Nagpal et al., 2022).

The etiology of mucopolysaccharidosis type I is related to the lack or relative deficiency of the enzyme α-L-iduronidase, and the symptoms mainly include alterations in physical appearance, growth delay, bone deformities, short stature, facial abnormalities, and umbilical and inguinal hernias. Additionally, there are

typically associated health problems such as respiratory infections, cardiac and hepatic issues, neurological problems, and delayed cognitive development (Ribeiro et al., 2015; Hampe et al., 2020; Zhou et al., 2020).

Regarding diagnosis, unfortunately, in most cases, it is established when irreversible characteristics of the disease are already present. The treatment of MPS mainly involves managing symptoms and complications, and the prognosis depends on the type and severity of the disease. In general, the most severe forms of MPS can lead to a reduced life expectancy, while milder forms may not alter the life expectancy of affected patients. However, most people with MPS face significant challenges and require ongoing medical support and care throughout their lives (Turra and Schwartz, 2009; Hampe et al., 2020).

Regarding the buccomaxillofacial complex, MPS can cause gingival alterations such as fibrosis and hyperplasia, as well as malocclusions, dental retentions, and the development of cysts and tumours (Sharma et al., 2012; Sabry et al., 2018; Torres et al., 2018; Zhou et al., 2020). This paper describes a clinical case of a patient with MPS type I with significant physical impairment and multiple maxillofacial manifestations. Among them, dental retentions and large dentigerous cysts were observed. Marsupialization was successfully instituted as the sole treatment for the patient's dentigerous cysts, and no recurrence was observed over a period of 20 years.

Case report

A 13-year-old male patient of Caucasian descent, presented to the surgery clinic at UNIFAL-MG with a complaint of swelling on the face that had started 3 years ago. Initially, it was possible to observe physical growth deficiency, lip incompetence, stiffness in the hand joints, and skeletal and thoracic deformity (Figure 1A and B). The patient did not present mental retardation. Corneal opacification was already observed. In the medical history, bronchitis, asthma, and adenoid hypertrophy were recorded.

During the extraoral clinical examination, no lymph node enlargement in the head and neck region was observed, with only volumetric increase on the left side of the face, near the mandibular body and ramus. Additionally, widened head and nose, dilated nostrils, prominent supraorbital ridges, round cheeks, and thick lips were observed (Figure 1C). Upon intraoral clinical examination, gingival hyperplasia, open bite, delayed eruption, and ectopic positioning of some teeth were detected (Figure 2). Panoramic and occlusal radiographs revealed extensive unilocular radiolucent lesions causing expansion in the basal cortical bone of the left mandible, involvement of retained teeth in the right mandible, displaced tooth germs (17, 18, 27, 28, 37, 38, 47, and 48), presence of a supernumerary tooth located in the maxillary midline, maxillary sinuses with irregular contours due to tooth displacements, and significant condylar resorption (Figure 3).

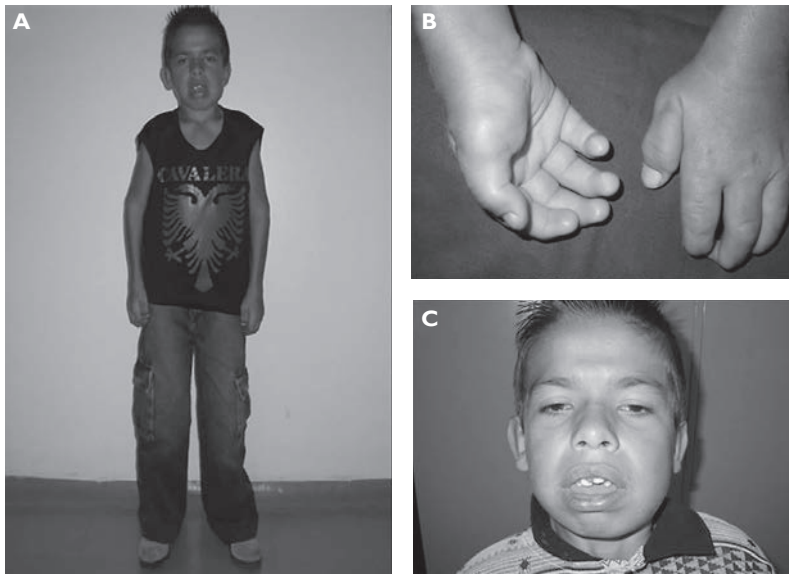

Figure 1 – Physical growth deficiency, skeletal and chest deformity, changes in the joints of hands (A and B); lip incompetence, enlarged head and nose, dilated nostrils, prominent supraorbital region, thick cheeks and lips (C).

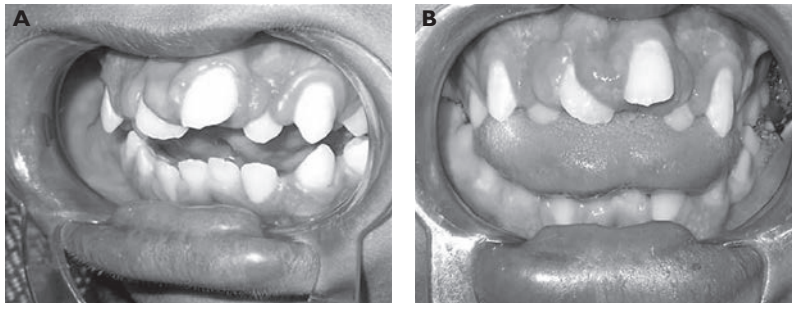

Figure 2 – Intraoral photograph showing gingival hyperplasia, anterior open bite with tongue interposition, macroglossia, delayed eruption, and ectopic positioning of dental elements (A and B).

Based on the clinical examination, medical history, and radiographic findings, three diagnostic hypotheses were suggested: cleidocranial dysostosis, Gorlin-Goltz syndrome, and MPS. The latter was supported by medical documentation provided by the patient, indicating the possibility of this pathology.

The treatment plan for the oral lesions involved marsupialization due to the possibility of pathological fracture of the mandible. Initially, the left side was addressed. After local anesthesia, a puncture was performed, with positive aspiration of a transparent yellow fluid. Subsequently, an elliptical incision was made in the area

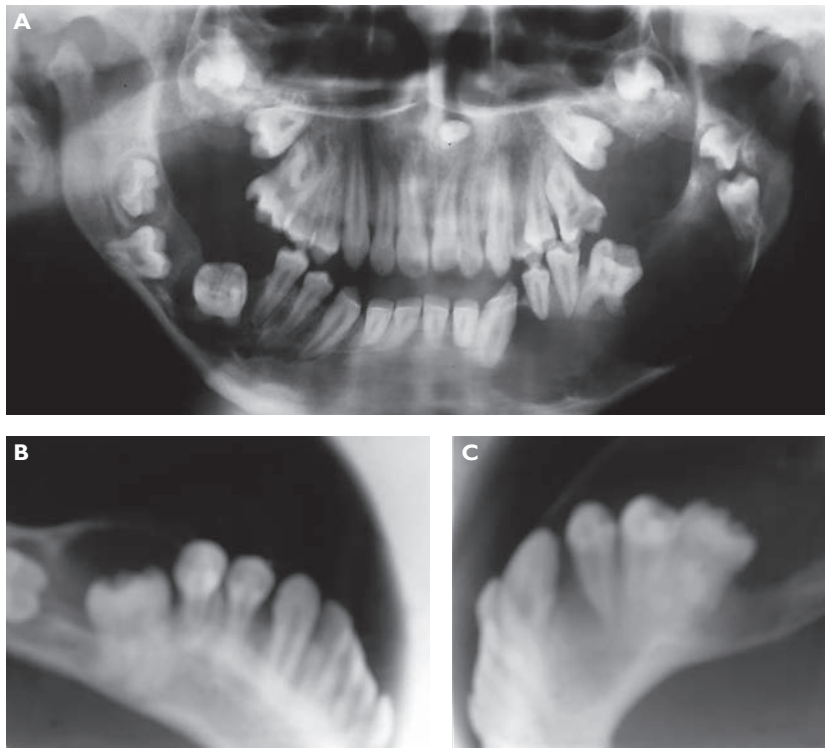

Figure 3 – Panoramic radiographs (A) showing extensive unilocular radiolucent lesions in the mandible bilaterally, involving tooth 46 on the right, retained teeth, supernumerary teeth in the midline, and marked condylar resorption (A). Occlusal radiographs showing expansion caused by the cystic lesion in the basal cortical bone of the right mandible (B) and left mandible (C).

in question, followed by tissue dissection that allowed direct access to the cystic cavity. The specimen was sent for histopathological examination, and a semi-rigid latex drain was installed (Figure 4). The patient and their guardian were instructed to irrigate with saline solution three times a day. After 10 days, with epithelialization of the fistulous tract observed, the latex drain was removed, and the patient and guardian were instructed to maintain cavity hygiene as previously described. The histopathological result revealed the presence of a dentigerous odontogenic cyst. Surgery on the right side of the mandible was then scheduled. The incision of the fibrous gingiva allowed access to the radiolucent lesion in the region of tooth 46 for drain installation to permit decompression of the cystic cavity. The patient and guardian were again instructed on the same postoperative cavity hygiene care as in the previous procedure. The drain was removed after 10 days.

The patient attended clinical and radiographic follow-up until the postoperative period of 1 year and 6 months, during which significant bone formation was observed in the region of the cystic lesions (Figure 5). After this period, the patient

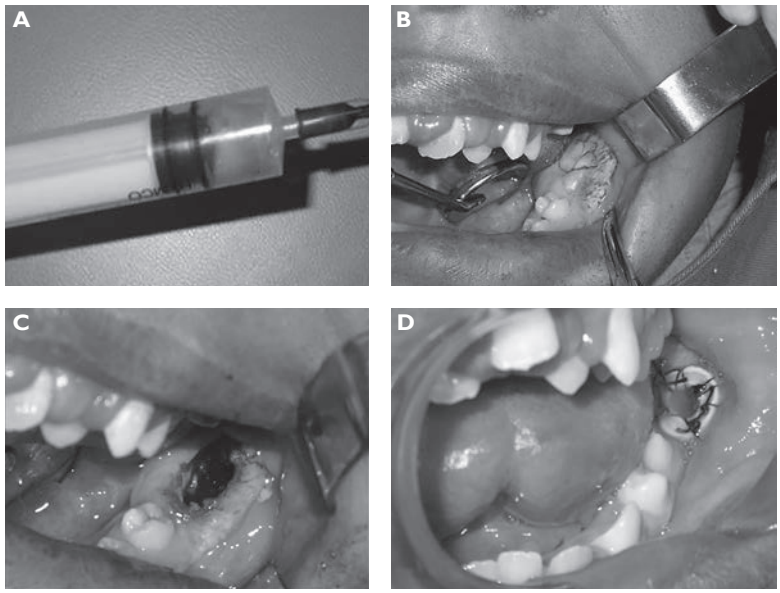

Figure 4 – Images showing the surgical technique of marsupialization. Positive aspiration of the lesion with return of a transparent yellow fluid (A); elliptical incision over the mandibular ridge (B); excision of part of the cystic capsule for incisional biopsy and tissue dissection to access the cystic cavity (C); semi-rigid latex drain in position (D).

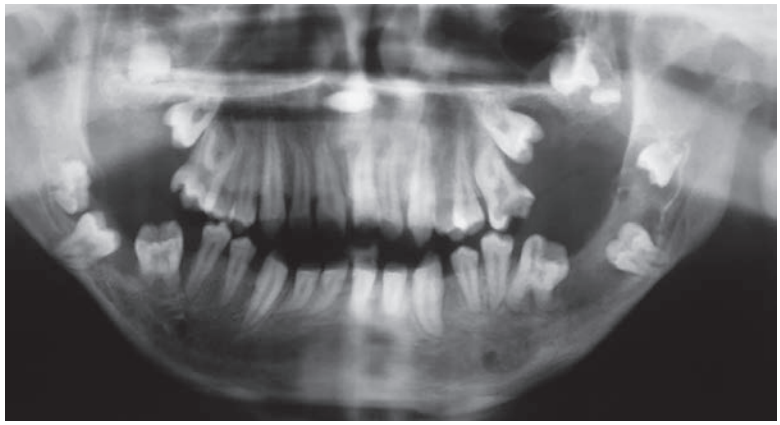

Figure 5 – Panoramic radiograph taken 18 months postoperatively showing significant bone formation in the region of the cystic lesions.

did not attend further follow-up appointments, returning recently, after 20 years, with the main complaint of malocclusion. Upon extraoral clinical examination, in addition to the evolution of the body changes already observed in childhood, significant opacification associated with blindness in the right eye and reduced

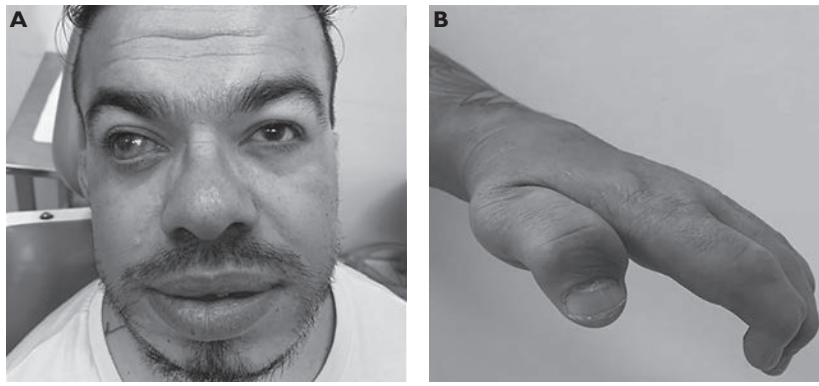

Figure 6 – Extrabuccal photos showing the evolution of the body changes already observed in childhood (A and B); ocular involvement with significant corneal opacity associated with blindness in the right eye (A).

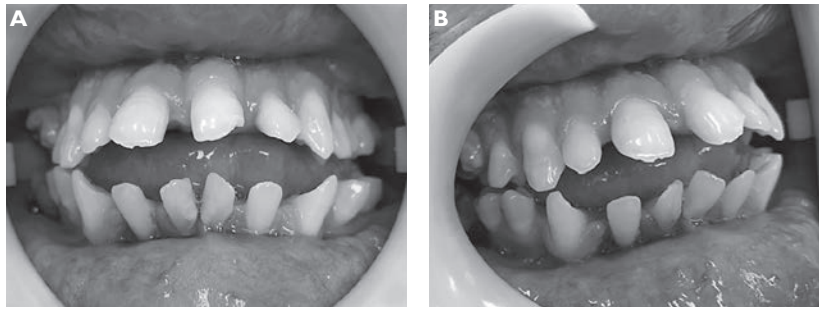

Figure 7 – Intraoral photos showing anterior open bite with significant vestibular inclination of the anterior teeth, macroglossia, and tartar accumulation (A and B).

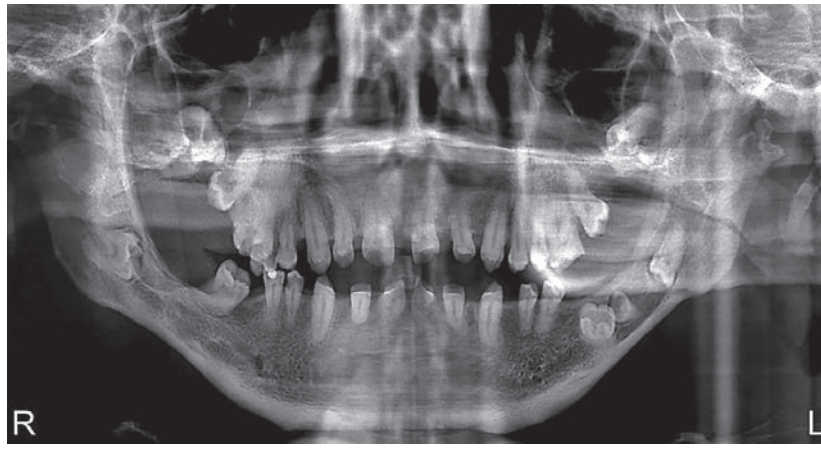

Figure 8 – Panoramic radiograph after 20 years from the first visit showing retained teeth and absence of recurrent cystic lesions.

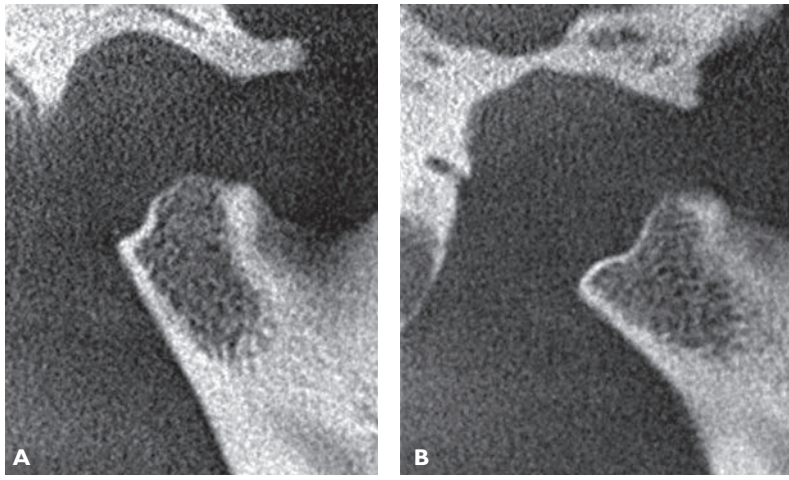

Figure 9 – Sagittal section of computed tomography scan of the right (A) and left (B) TMJ (temporomandibular joints) showing severe reabsorption.

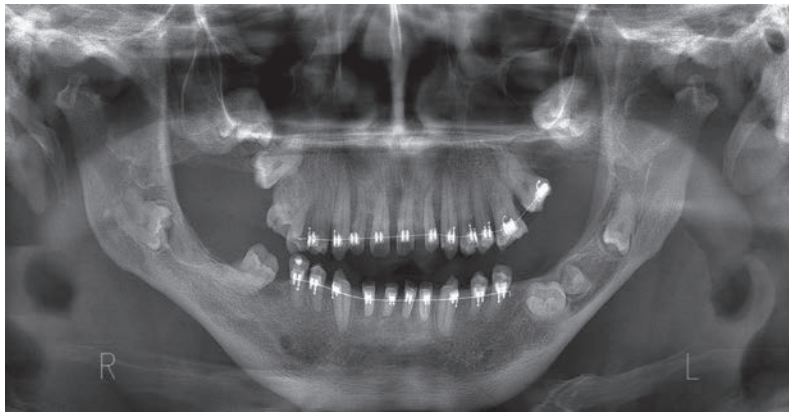

Figure 10 – Panoramic radiograph after 20 years from the first visit showing retained teeth, absence of recurrent cystic lesions and orthodontic treatment in progress.

left visual acuity was observed (Figure 6). Upon intraoral physical examination, anterior open bite with significant anterior teeth vestibular inclination, macroglossia, and tartar accumulation were observed (Figure 7). Current radiographs show dental retentions but the absence of associated cystic lesions (Figure 8) and in the computerized tomography of the TMJs (temporomandibular joints), severe resorption oh the condyles was observed (Figure 9). This situation demonstrates that isolated marsupialization was, in this case, sufficient as the definitive treatment for two large dentigerous cysts. The patient underwent periodontal treatment and is undergoing orthodontic treatment for malocclusion correction (Figure 10: panoramic

radiograph with the orhodontic treatment in progress). Regarding this, dental inclination is largely due to macroglossia. It is known that macroglossia is preferably treated through partial glossectomy. However, the patient in question has a history of serious complications due to intubation for general anesthesia due to tracheal stenosis. Therefore, the application of botulinum toxin was proposed to reduce tongue muscle tone and consequently muscular force. This procedure is being planned and will be performed soon.

Discussion

The lack or relative deficiency of the α-L-iduronidase enzyme in MPS I is caused by a mutation in the IDUA gene located on chromosome 4p.16 (Bay et al., 2021; Nagpal et al., 2022). This enzymatic deficiency alters the metabolism of mucopolysaccharides, resulting in the accumulation of glycosaminoglycans (GAGs) and dermatan and heparan sulfates in organs and tissues. GAGs constitute the main component of the extracellular matrix and are responsible for cell-cell and cell-matrix adhesion. Additionally, they provide structural stability for cartilaginous structures such as heart valves and joints (Tatapudi et al., 2011; Hampe et al., 2020). The incidence of MPS I varies from 1 to 3 in 100,000 live births (Carvajal Gavilanes et al., 2023). Patients with a severe phenotype of the disease, if left untreated, have a low life expectancy, with death commonly occurring in the first decade of life. Prevention of severe cardiac and respiratory compromise, as well as cognitive impairment, can only be achieved through early diagnosis. However, early diagnosis is challenging as the initial manifestations of the disease are nonspecific (Hampe et al., 2020; Zhou et al., 2020; Bay et al., 2021).

Three subtypes of MPS I have been proposed, differing in the severity of the disease, ranging from mild (Scheie syndrome), moderate (Hurler-Scheie syndrome), to severe (Hurler syndrome or MPS-IH). However, in 2008, the guidelines on MPS I were revised and updated, so that now the disease is classified into two broader groups. These are severe MPS I (Hurler syndrome) and attenuated MPS I (Scheie syndrome and Hurler-Scheie syndrome) (Grupo de Trabajo de Enfermedades poco frecuentes, 2008). The severe form of the disease is caused by the absence or extremely low levels of the α-L-iduronidase enzyme, associated with genotypes with deletions and nonsense mutations (Hampe et al., 2020). This paper describes a clinical case of a patient with attenuated MPS I, whose characteristics and symptoms are suggestive of Hurler-Scheie syndrome.

Diagnosing MPS in general unfortunately occurs when irreversible characteristics of the disease are already present (Zhou et al., 2020). In countries like Brazil, the diagnosis is often delayed (Ribeiro et al., 2015). According to Vieira et al. (2008), there is an average of 4.8 years between the onset of symptoms and the diagnosis of the disease. Thus, methods that can achieve early diagnosis, in the asymptomatic

phase, are important to improve the quality of life and survival of patients affected by the disease. Radiographs, for example, can reveal kyphosis of the lumbar vertebrae, which is the first sign of the disease, especially in MPS IV. Additionally, computed tomography (CT) and magnetic resonance imaging (MRI) of the skull can show early neurological changes characteristic of MPS types I, II, and III. For definitive diagnosis and determination of the MPS subtype, new approaches involve urine and blood tests for GAGs, genetic testing, and enzymatic assays (Zhou et al., 2020; Bay et al., 2021). However, initially, the most important aspect is the observation of the family medical history, as it is a hereditary disease. A positive family history, the presence of signs and symptoms, as well as the order of their appearance, are important for establishing the diagnostic hypothesis of MPS (Torres et al., 2018; Zhou et al., 2020). Torres et al. (2018) described a clinical case of a patient diagnosed with MPS II even during the intrauterine period. Early diagnosis was possible due to a family history of MPS with severe phenotype. For the patient in question, initiating treatment in the first months of life managed to attenuate the manifestation of the disease (Torres et al., 2018).

In this context, it is important for healthcare professionals to be aware of the characteristics, signs, and symptoms of MPS in order to facilitate early diagnosis. Early symptoms observed before six months of age include frequent rhinitis, hernias, hepatosplenomegaly, thoracolumbar kyphosis, thin and non-elastic skin, and early closure of facial sutures. Additionally, specific facial characteristics are observed, including enlarged head and nose, dilated nostrils, prominent supraorbital ridges, round cheeks, thick lips, macroglossia, and dental alterations (Ribeiro et al., 2015; Torres et al., 2018; Hampe et al., 2020). In the patient of the present clinical case, all the facial characteristics listed above were identified, along with malocclusion, delayed eruption of some teeth, dental retentions, and mandibular cysts. Torres et al. (2018), described a case of a patient with MPS II who also presented multiple maxillofacial manifestations, including delayed tooth eruption, dental retentions, and macroglossia. Sharma et al. (2012), reported a clinical case of severe MPS I (Hurler syndrome), in which the patient also had mandibular cysts, similar to the present clinical case.

The skeletal and soft tissue alterations present in patients with MPS I are due to the accumulation of GAGs in these tissues and may predispose to upper airway obstruction. Regarding skeletal changes, nasal dysmorphism, shortened neck, abnormalities in cervical vertebrae, and mandibular hypoplasia can be mentioned. As for soft tissue alterations, enlargement of the tongue, adenoids, and tonsils can narrow the airway passage. This situation leads to noisy breathing, apnea, and recurrent respiratory infections (Ribeiro et al., 2015; Torres et al., 2018; Hampe et al., 2020). In the case of the present clinical case, the patient has a medical history of adenoid hypertrophy and respiratory diseases (bronchitis and asthma). It is worth noting that initially, respiratory symptoms are more pronounced in the upper airways, but as the disease progresses, bronchotracheal involvement may occur. This

is because GAG deposition causes deformity and narrowing of the tracheal lumen. In severe cases, this situation can lead to death (Hampe et al., 2020). In the present clinical case, there is a history of difficulties in intubating the patient for general anesthesia due to tracheal stenosis. Therefore, partial glossectomy for the treatment of macroglossia was not performed, as it requires intubation and general anesthesia. Instead, the injection of botulinum toxin into the tongue was proposed to reduce tongue tone and volume and thus control tongue protrusion. This procedure is being scheduled. In this context, it is important to note that the application of botulinum toxin to the tongue has been reported by several authors in the treatment of involuntary tongue protrusion resulting from oromandibular dystonia (Charles et al., 1997; Yoshida, 2019; Hassell and Charles, 2020).

After 6 months of age, other symptoms of MPS may become evident, such as visual and hearing impairment, cardiac alterations, more pronounced musculoskeletal defects, and psychomotor retardation (Ribeiro et al., 2015; Hampe et al., 2020). In the initial contact with the patient in the present study, at the age of 13, there was slight corneal opacification, but no impairment of visual acuity. However, when he returned as an adult, after 20 years, marked corneal opacification associated with blindness in the right eye and decreased visual acuity in the left eye was observed. The ocular changes resulting from MPS I are caused by the accumulation of GAGs in ocular tissues and include glaucoma, abnormalities in eye movement, changes in the retina, optic nerve atrophy, exophthalmos, and corneal opacification (Hampe et al., 2020; Nagpal et al., 2022). The latter is the most common ocular alteration in MPS (Nagpal et al., 2022).

Among all manifestations of MPS I, skeletal changes, collectively referred to as multiple dysostosis, are the most frequent and disabling alteration. The most prominent skeletal changes include thoracolumbar kyphosis and growth restriction. However, other skeletal alterations may also be present, such as: enlarged skull, flattening of vertebral bodies, hypoplasia of the odontoid process in the C2 vertebra, paddle-shaped ribs, short and widened clavicles, bullet-shaped phalanges, enlarged skull, and J-shaped sella turcica. In addition to structural skeletal changes, MPS I can cause decreased bone density predisposing to fractures (Hampe et al., 2020). The patient in the present clinical case already presented many skeletal alterations since the first appointment. He had growth restriction, enlarged skull, changes in the hands with stiffening of the joints, malformation of the thorax, and condylar resorption. The bone changes progressed as the patient aged but without significant impairment of his ambulation and mobility.

After the first year of life, cognitive changes may appear, especially in severe MPS I (Hurler syndrome). In these patients, cognitive development slows down at 6–9 months of age, seems to plateau in the second year of life, and may progress to decline thereafter if appropriate treatment is not instituted (Hampe et al., 2020). The patient in the present clinical case did not show signs of cognitive impairment in adolescence or adulthood. Therefore, the MPS I in this patient is certainly the

attenuated form of the disease. This is because most patients with Hurler syndrome die in the first decade of life due to progressive neurological impairment associated with cardiorespiratory failure (Tatapudi et al., 2011). In contrast, patients with the attenuated disease form can reach adulthood, although they also present systemic changes. Patients with Scheie syndrome have a higher life expectancy than those with Hurler-Scheie syndrome and Hurler syndrome (Zhou et al., 2020).

In the attenuated forms of MPS I, the clinical presentation may be limited to growth restriction, corneal opacification, mild facial features, hepatosplenomegaly, and micrognathia. In this attenuated variant of the disease, skeletal changes in the hands and spine may not be severe. However, due to airway narrowing and macroglossia, respiratory infections are almost always recurrent (Ribeiro et al., 2015; Hampe et al., 2020). The described condition is observed in the patient of the current article. However, it is important to note that in the attenuated form, although milder, the symptoms of the disease appear later, making early diagnosis more challenging than in the severe form of the disease. Assadeck et al. (2019) reported a series of three cases of attenuated MPS I (Hurler-Scheie syndrome) from the same family, in which babies were considered normal at birth. The first signs appeared slowly after the second year of life, and the diagnosis was only established when the patients were 12 years old, the same age range as the patient in the present clinical case. The timing of diagnosis in these patients suggests, once again, an attenuated form of MPS I, characterized by late symptoms, a longer life expectancy, and mild or absent neurological changes (Assadeck et al., 2019).

Regarding the treatment of MPS, it mainly involves managing the symptoms and complications of the disease to slow its progression and improve the patient's quality of life. Enzyme replacement therapy and hematopoietic stem cell transplantation are the mainstays of treatment, but it is worth noting that they are not effective for all cases (Sharma et al., 2012; Torres et al., 2018; Zhou et al., 2020). Therefore, treatment also includes palliative care, orthopedic surgeries to correct bone deformities, respiratory therapy, and physiotherapy. Overall, therapies are aimed at improving quality of life and reducing disease complications (Hampe et al., 2020). Torres et al. (2018) describe a clinical case of a 7-year-old patient who was diagnosed with MPS II in utero and was treated with hematopoietic stem cell transplantation at 70 days of age. This study highlights the importance of early diagnosis and treatment in attenuating the disease manifestation (Torres et al., 2018). It is worth noting that there is a promising treatment option still in development called gene therapy, which is targeted at treating the corneal opacification associated with MPS. However, knowledge about gene therapy is limited to animal studies, so more human studies are needed for a better understanding of its effects and applications (Nagpal et al., 2022).

Regarding the facial characteristics, in the present article, the patient exhibited coarse facial features such as cranial enlargement, prominent supraorbital ridges, widened nose, rounded cheeks, thick lips, and incompetent lips. Upon intraoral

examination, malocclusion with anterior open bite associated with macroglossia was observed. Tatapudi et al. (2011) described a case of a 15-year-old adolescent with MPS I (Hurler-Scheie syndrome), who also had anterior open bite associated with macroglossia, among other facial characteristics observed in the present clinical case. According to a cross-sectional study conducted by Turra and Schwartz (2009), in which 78 patients with different types of MPS were evaluated for alterations in the structures and function of the stomatognathic system, teeth and the tongue were the most affected structures; while swallowing and chewing were the most compromised functions. The authors of the mentioned study emphasize that the high frequency of alterations in the structures of the stomatognathic system in MPS leads to changes in its functions. These, in turn, can exacerbate structural alterations (Turra and Schwartz, 2009).

Among the dental alterations observed in patients with MPS I, abscesses, cavities, enamel defects, retained teeth, agenesis, and cysts can be mentioned (Tavares et al., 2004; Sharma et al., 2012; Ribeiro et al., 2015; Sabry et al., 2018; Torres et al., 2018; Carneiro et al., 2021). Regarding dental development, according to Tavares et al. (2004), delayed tooth eruption, inclusion of permanent teeth, hyperplasia of dental follicles, and several teeth associated with a single follicle, leading to a rosette-like radiographic image, can be observed. This characteristic is only reported in cases of MPS. Additionally, other authors, as in the present study, also highlight the association of macroglossia with anterior open bite. This results from the excessive pressure of the enlarged tongue due to the deposition of GAGS on the anterior teeth (Tatapudi et al., 2011; Sharma et al., 2012). However, in the case of MPS I, it is important to remember that mandibular hypoplasia associated with pronounced condylar resorption is also frequently present and influences the development of anterior open bites (Koehne et al., 2018). In the present study, pronounced condylar resorption was observed, with condyles already showing signs of flattening and concavities.

Ribeiro et al. (2015) conducted a multicenter study in which they evaluated the orofacial manifestations of 26 patients with different types of MPS. The authors observed that facial manifestations such as deficiency of the midface, anterior open bite, convex profile, macroglossia, gingival hyperplasia, and diastemas are frequently observed characteristics in MPS in general and do not allow differentiation between its subtypes. However, enamel hypoplasia was significantly more associated with MPS IV ($p=0.043$) (Ribeiro et al., 2015). On the other hand, another study evaluated maxillomandibular structural differences (width and height) in patients with different types of MPS and found that the mandible in MPS I is smaller than in MPS II and III and compared to the disease-free population, and such a finding is due to the progressive condylar resorption present in MPS I patients (Koehne et al., 2018). In the present clinical case, at the age of 13, during the initial assessment, significant condylar resorption was already observable, which worsened over time as shown in the panoramic radiograph taken at 33 years old, where little condylar remains with a

concave surface. Such radiographic characteristic was quite common in MPS I patients in a previous study (Koehne et al., 2018). Another cross-sectional study evaluated the craniofacial characteristics of MPS patients through anthropometric and lateral cephalometric measurements and observed a prevalence of the dolichofacial profile, as well as an increase in the lower anterior face, pronounced incisor inclination, reduced upper airway space, and lip incompetence ($p<0.05$) (Carneiro et al., 2023). It is important to note that facial abnormalities in MPS not only affect aesthetics and social life but can also alter vital functions such as eating and breathing. The latter is directly affected by maxillomandibular hypoplasia (Koehne et al., 2018).

Carneiro et al. (2021) conducted research on dental and maxillofacial alterations in MPS patients by evaluating panoramic radiographs and observed that various conditions such as supernumerary teeth, conoid teeth, retained teeth, root dilaceration, periapical and furcation lesions, condylar hypoplasia, and dentigerous cysts are more prevalent in MPS patients compared to the general population. However, in the literature review conducted in this study, few reports of dentigerous cysts in MPS I patients were observed. Sabry et al. (2018), on the other hand, described a situation similar to the present clinical case, in which a dentigerous cyst associated with the impacted tooth 37 was treated exclusively by marsupialization in an MPS II patient. In this work, as in the present study, enucleation was not necessary, as complete resolution of the cyst was achieved after 12 months of follow-up (Sabry et al., 2018). This scenario, of a syndrome with so many maxillofacial manifestations, poses a significant challenge for the dentist and highlights the importance of understanding MPS characteristics. This is because the contribution of the dentist can be crucial for the diagnosis of the disease. Furthermore, most alterations of the stomatognathic system in MPS require monitoring and treatment (Sharma et al., 2012; Ribeiro et al., 2015; Carneiro et al., 2021).

In the case of the patient in the present study, the presence of extensive radiolucent lesions involving the angle and body of the left mandible and tooth 46 on the right side, as well as the possibility of a pathological fracture of the mandible, determined the choice of appropriate surgical treatment, with marsupialization of the cystic lesions being proposed and performed. The marsupialization procedure involves creating a surgical window in the cyst wall, emptying the cystic content, maintaining continuity between the cyst and the oral cavity to decrease intracystic pressure, reduce the size of the lesion, and promote bone filling (Ellis, 1996; Sharma et al., 2012). Normally, future surgical intervention is needed for enucleation. However, in the present clinical case, despite the large extent of the cysts, isolated marsupialization allowed for the eruption of tooth 46 and the disappearance of the cysts without any sign of recurrence after 20 years postoperatively. Sharma et al. (2012) and Sabry et al. (2018) also employed marsupialization alone as the technique of choice for the treatment of extensive mandibular dentigerous cysts

involving the lower first molars in an MPS patient. This is because the technique is more conservative, allows for cyst regression and gradual bone tissue formation, and the teeth involved in the lesion can be preserved (Sharma et al., 2012; Sabry et al., 2018). The disadvantage of marsupialization is the need to educate the patient and/or caregiver about the importance of hygiene care and follow-up visits to keep the drain patent, and after its removal, the fistula, so that cystic decompression occurs effectively, and the technique is successful. The main complications associated with marsupialization are recurrent infections, especially due to poor hygiene, and early closure of the fistula, which requires re-intervention (Sabry et al., 2018). In the present clinical case, the patient and their caregivers were committed to hygiene care and follow-up visits for a period of 18 months, ensuring good progress in the case.

In dentistry, regardless of the type of lesion present, it is crucial to integrate local treatment, essential for improving the patient's quality of life, with their systemic conditions, achieved through a comprehensive clinical examination, refined knowledge, and a multidisciplinary approach (Tommasi, 1989). In the reported case, the patient not only presented with retained teeth, malocclusion, macroglossia, and intraosseous cystic lesions. He is an individual with a rare syndrome, still incurable, which typically brings significant systemic complications and may require modifications in the treatment plan. However, it is possible to treat these oral conditions, providing the patient with better oral health and survival conditions.

Conclusion

For a correct diagnosis in dentistry, it is essential to consider the patient as a whole and, whenever necessary, resort to a multidisciplinary approach to institute appropriate and comprehensive treatment for the patient and promote health. MPS is a rare syndrome with a difficult diagnosis that causes significant systemic alterations. Therefore, it requires multidisciplinary and intensive patient care, including the need for a dentist on the team due to the pronounced maxillofacial involvement. In this article, the clinical case of a patient with the attenuated form of MPS I was described, yet still presenting multiple manifestations of the disease. Among these, two large dentigerous cysts in the mandible were successfully treated exclusively by marsupialization, without the need for a second intervention for enucleation.

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A Rare Case of Primary Vulval Amelanotic Melanoma Involving the Urethra

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Received June 7, 2024; Accepted July 28, 2024.

Key words: Amelanotic melanoma – AM – PVAM – Amelanotic melanoma vulva – Vulval melanoma – Gynecologic tumor – Vulvar cancer – Diagnostic procedure – CT – MRI

Abstract: A 60-year-old woman came to the Emergency Department complaining of a vaginal formation. The urologist suspected a urethral caruncle: the patient was discharged with vaginal oestrogen cream to relieve symptoms and a follow-up was suggested. After two months the patient returned to the Emergency Department since the mass was increasing in volume and complaining of dysuria and haematuria. Ultrasound, contrast-enhanced computed tomography, and contrast-enhanced magnetic resonance revealed a mass arising from the mucosa and involving the vulva and the urethra, suspicious of malignancy. We present a challenging diagnosis of an infiltrative and rapidly progressive primary vulval amelanotic melanoma with a complete imaging evaluation and a confirmed histological diagnosis.

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https://doi.org/10.14712/23362936.2024.23

Introduction

Cancers of the vulva and vagina are uncommon neoplasms, with vulval cancers being more common than vaginal cancers; the most common subtype being squamous cell carcinoma (Gong et al., 2019).

Melanomas are even rarer tumours responsible for a diagnostic challenge. Primary vaginal amelanotic melanoma (PVAM) is a rare not pigmented subtype of melanoma that accounts for 0.4–27% of all cases. Patients with red hair, type I skin, freckles, a lack of nevi on the back, a sun-sensitive phenotype, or a history of AMs (amelanotic melanomas) are more prone to acquire them: the male/female ratio ranges between 0.5 and 4. Since tumour cells lack melanin colour, PVAM may resemble other frequent vaginal cancers with a better prognosis, creating a diagnostic challenge (Weinberg and Gomez-Martinez, 2019).

The most important prognostic factors include tumour size, depth of invasion, metastasis status of lymph nodes, and distal metastasis status (Muinonen-Martin et al., 2018).

Surgery is the mainstay of melanoma treatment: the resection might be extensive, but the recurrence is possible and frequent. Radiotherapy can be used as a neoadjuvant or adjuvant treatment to increase local control rates, while chemotherapy can shrink large masses before surgery (Pye et al., 2023).

This case report describes the imaging examination, especially CT (computed tomography) scans, and MRI (magnetic resonance imaging) in the diagnostic process of an unaware patient who experienced pain and vaginal discomfort.

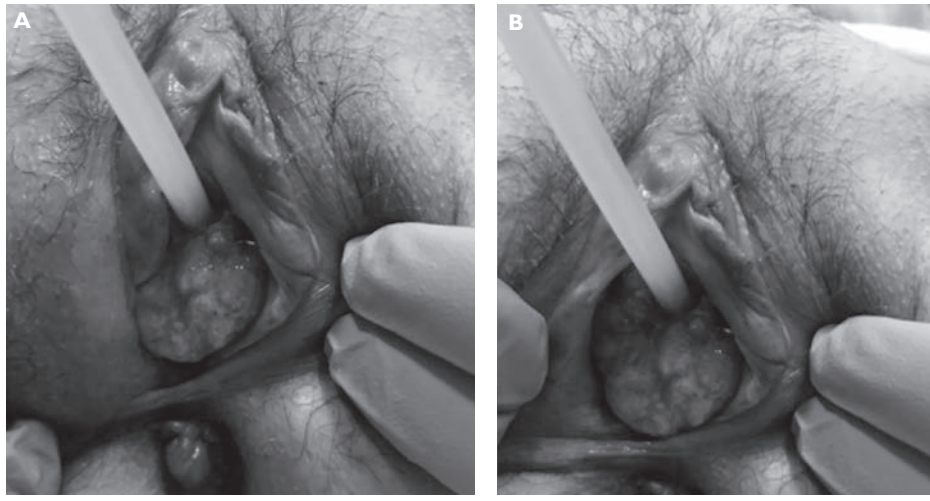

Figure 1 – Macroscopic image showing the vulvar formation with a round morphology, hard consistency, non-homogeneous colour, and appearance, not mobile, without superficial ulcerations.

Case report

A 60-year-old woman attended the Emergency Department with a spherical, growing formation between her vulva and urethra. The urologist suspected a urethral caruncle, so she returned home with a vaginal oestrogen lotion to relieve the discomfort; a follow-up was scheduled. Two months later, the mass had suddenly enlarged, causing her pain, embarrassment, dysuria, and haematuria, motivating her to return to the Emergency Department for a clinical examination (Figure 1).

The physician requested further imaging investigations (CT and MRI) to suspect a malignancy motivated by the high growth rate and the little mobility to the fascial plane.

An abdomen CT with contrast medium administration was performed to better localize the lesion and for staging (Figure 2).

A pelvic MRI with contrast medium administration was scheduled for the next day to characterize the lesion better and evaluate the local infiltration (Figure 3).

A few days following the MRI, the patient underwent a histological sample, which confirmed the suspicion: vulval amelanotic melanoma, a quickly progressing malignancy (Figure 4).

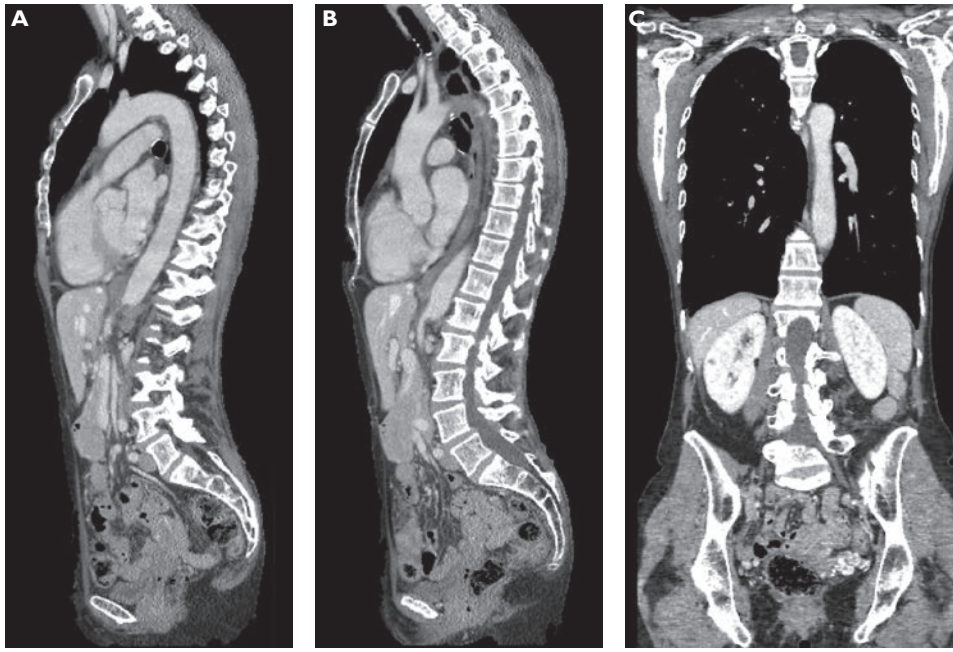

Figure 2 – Subsequent computed tomography scans in the sagittal (A and B) and coronal (C) planes in the venous phase showed a lesion of the vaginal pertaining with ill-defined margins and inhomogeneous contrast-enhancement without clear planes of cleavage with the surrounding perineal muscles; no distant secondary lesions were evident.

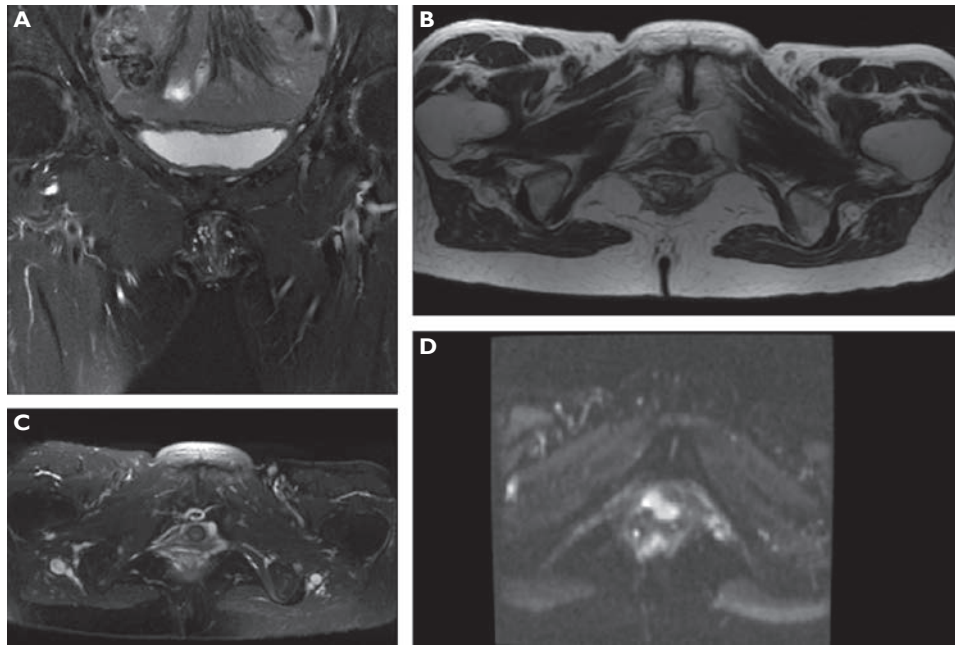

Figure 3 – Magnetic resonance imaging sequences: A) coronal T2 PROP fat-suppressed; B) axial T2; C) axial T1 fat-suppressed after contrasting medium administration; D) axial DWI (diffusion-weighted imaging) at high b-values with a small FOV (field of view). Examination revealed a lobulated, homogeneous lesion with intermediate SI (signal intensity) and maximum diameter of about 3.2 cm originating from the anterior wall of the vagina and extending and infiltrating the urethral meatus posteriorly and the levator muscles of the anus laterally.

Tumour cells were immunohistochemically categorized as positive for HMB-45, S-100, Melan-A, SOX-10, and p16. They also tested negative for cytokeratin's AE1-AE3, CD45 (LCA), and CD79a. Fontana-Masson staining did not detect melanin pigments (Wechter et al., 2004).

Immediately afterward the patient was started on radiotherapy and chemotherapy, to reduce the size of the tumour and promote survival. The patient underwent extensive surgery and had an MRI to evaluate the effects (Figure 5).

The patient is currently on immunotherapy and close follow-up. The early treatment of urethral melanoma is essential due to the tendency to early metastasis.

Discussion

Malignant melanoma is an aggressive, infamous malignancy with a wide variety of morphological and immune-histochemical expressions, frequently leading to an

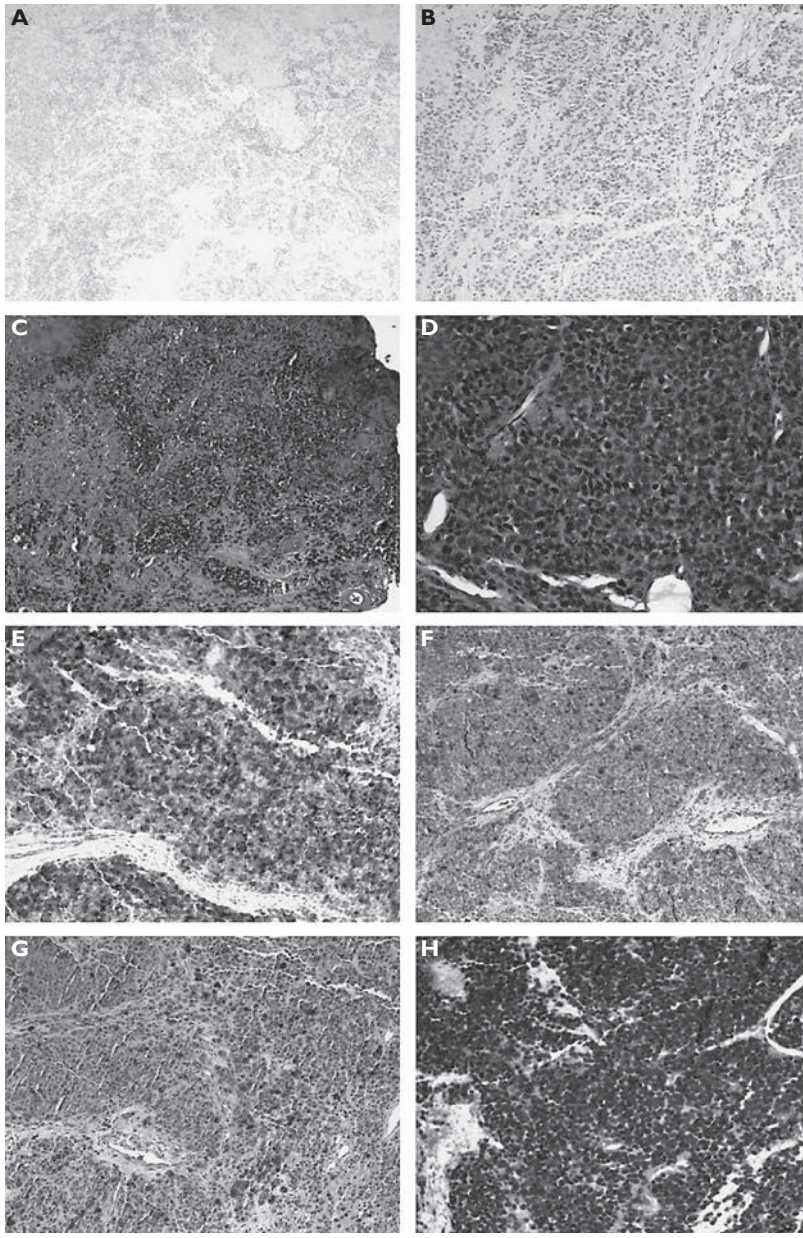

Figure 4 – Histological examination: A) cytokeratin 20 (CK 20) (4×); B) cytokeratin AE1/AE3 (CK) (10×); C) stained by haematoxylin-eosin (HE) (10×); D) stained by HE (20×); E) the antibody HMB45 (10×); F) the protein Melan-A (10×); G) proteins S100 (10×); H) gene SOX10 (10×). Sheets and nests of large pleomorphic epithelioid malignant melanocytic cells with prominent nucleoli and several atypical mitotic figures from the tumour. Melanin production can be focally present. Immunoreactivity for Melan-A, HMB45, S100, and SOX10 and negativity for CKAE1/AE3, CK8/18, CK20, p63, and GATA3 allows the differential diagnosis with high-grade urothelial carcinoma and confirms the diagnosis of melanoma.

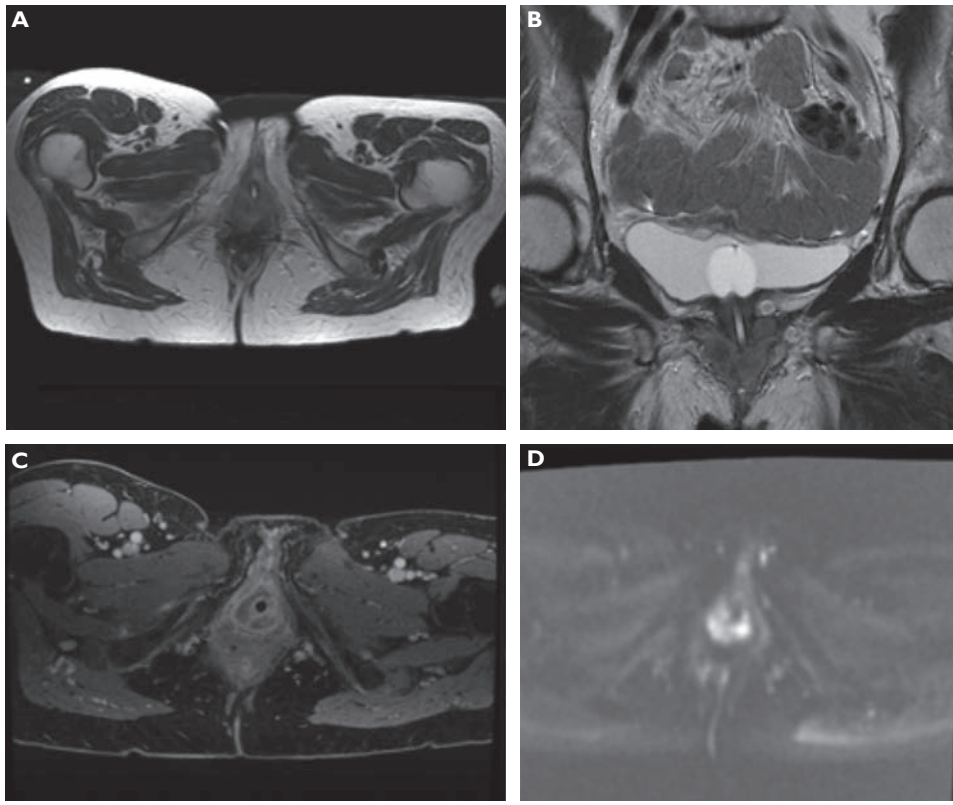

Figure 5 – Magnetic resonance imaging sequences: A) axial T2; B) coronal T2; C) axial T1 fat-suppressed performed after contrasting medium administration; D) axial DWI (diffusion-weighted imaging) at high b-values. Examination revealed an increase in the size of the known vaginal lesion; there were no substantial variations of the intensity-contrastographic characteristics and the infiltrative appearance on the urethral meatus and the levator ani muscles.

incorrect diagnosis. Amelanotic melanoma, with its diverse clinical presentations, lack of pigmentation, and various histological findings, has earned a reputation as a master masquerade within the melanoma group.

Amelanocytic melanoma of the vulva is a rare form characterized by a lack of pigmentation (amelanotic precisely). Typically, melanoma is associated with skin pigmentation due to melanin, which gives the lesion a dark or black colour. However, amelanocytic melanoma can present as a whitish, reddish, or the same shade as the surrounding skin, making its diagnosis more complex (Osama et al., 2022).

Amelanocytic melanoma in the vulva with infiltration of the urethra represents an even rarer condition that is difficult to diagnose, as in this case. It is paramount to emphasize that diagnosing amelanotic melanoma requires careful evaluation through

clinical examination, imaging, and histological and immunochemical examinations. It is crucial to include amelanotic melanoma in the differential diagnosis of cutaneous lesions of the vulva, as it can often be confused with other nonmelanocytic skin neoplasms or urological conditions such as an of a urethral caruncle (Maetzold and Takacs, 2022).

Suspicious symptoms of gynecological oncology include frequent bleeding after sexual intercourse, atypical vaginal discharge, dyspareunia, constipation, and persistent pelvic pain. Rapid and comprehensive diagnostics are necessary for vulvar melanoma, which spreads locally and mostly through the lymphatic system. Prognostic factors for carcinoma vulvar include tumour size, depth of invasion, lymph node status, and distal metastases (Filippetti and Pitocco, 2015).

A skin biopsy and immunochemical examination of tumour cells can help confirm the diagnosis of amelanotic melanoma. Melanoma staging, which includes the amount of infiltration into the urethra, is critical for treatment planning and determining the risk of metastatic metastasis. The disease's stage determines the treatment of amelanotic vulval melanoma and may include surgery, targeted medicines, immunotherapy, and chemotherapy. The patient must be followed by a multidisciplinary team consisting of a urologist, oncologist, and radiologist who can assure regular disease monitoring and targeted customized treatment (Oiso et al., 2010).

The diagnosis involves a thorough clinical and laboratory evaluation and CT and MRI scans with contrast medium. CT scans are effective for characterization and local staging. In contrast, MRI scanning is appropriate for identifying local infiltration given the rapid progression of these neoplasms necessitates surgical therapy, affecting prognosis and follow-up (Patil et al., 2021).

Amelanocytic melanoma of the vulva, particularly when associated with external urethral invasion, is an uncommon but hazardous condition that necessitates early detection and a comprehensive treatment strategy. Educating healthcare providers and patients on the importance of preventing, diagnosing, and treating cutaneous melanoma, especially amelanotic melanoma is critical.

Conclusion

This case emphasizes the necessity of detecting non-pigmented nodules on the vulva of older ladies as possibly malignant melanoma, and that a combination of diagnostic imaging and immunohistochemistry stains may be effective in determining the stage of the melanosomes in melanoma cells. Vulvar melanoma is a sporadic and aggressive tumour, even more so in its amelanotic variant. First- and second-level imaging examinations are useful in the characterization and oncologic staging, treatment, and follow-up.

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 Prague Medical Report / Vol. 125 (2024) No. 3, p. 264–272

Cerebral Arterial and Venous Air Embolism Following Removal of Percutaneous Sheath Introducer

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Received July 12, 2022; Accepted July 28, 2024.

Key words: Cerebral air embolism – Arterial air embolism – Venous air embolism – Central line – Sheath introducer

Abstract: Cerebral air embolism after removal of central venous catheter (CVC) is a rare complication but can lead to fatal outcomes. We report a rare case of both cerebral venous and arterial embolism occurring in a patient with underlying scleroderma-related interstitial lung disease (SSc-ILD) and pulmonary hypertension following removal of percutaneous introducer sheath for pulmonary artery catheterization. We discuss the mechanisms, pathophysiology, management and prevention of cerebral air embolism.

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https://doi.org/10.14712/23362936.2024.24

Introduction

Central venous catheters are used extensively in critical care for hemodynamic monitoring, medication administration, hemodialysis and transvenous pacing. Cerebral air embolism is a rare, but potentially fatal complication of central venous catheterization. Venous air emboli can paradoxically enter the arterial circulation through a patent foramen ovale leading to cerebral air embolism and cause neurological compromise. We report a case of cerebral arterial and venous air embolism that occurred after removal of central venous catheter in a patient with interstitial lung disease secondary to systemic sclerosis and severe pulmonary hypertension. In addition, we discuss methods to prevent air embolism related to central venous catheterization.

Case report

A 57-year-old male with a history of interstitial lung disease (ILD) secondary to systemic sclerosis presented to the pulmonary clinic with progressive dyspnea. He had been on supplemental oxygen at 2 liters per minute, but his requirements had been rapidly increasing over the past few weeks. He denied any fever, chills, productive cough or chest pain. Due to worsening hypoxia, he was admitted for further workup. He was on high flow nasal cannula at 20 liters per minute in the medical intensive care unit. Computed tomography (CT) of the chest showed a pattern consistent with usual interstitial pneumonia with lower lobe predominant bilateral reticular opacities in the posterobasilar distribution, volume loss, traction bronchiectasis and honeycombing. No consolidations, effusions or ground glass opacities were noted. Transthoracic echocardiography showed dilated right ventricle with depressed systolic and diastolic function, abnormal septal motion, elevated right ventricular systolic pressure at 84 mm Hg. No interatrial shunting was visualized on colour Doppler. Right heart catheterization was done at bedside which showed mean pulmonary artery pressure of 43 mm Hg, pulmonary capillary wedge pressure 10 mm Hg, cardiac output 3.8 liters per minute, cardiac index 1.9 l/min/m^2, systemic vascular resistance 2803 dynes×s/cm^5 (35 Wood units), pulmonary vascular resistance 695 dynes×s/cm^5 (8.7 Wood units) which was consistent with severe group 1 pulmonary hypertension.

Patient was started on ambrisentan and tadalafil in addition to prednisone and mycophenolate for ILD. He responded well to therapy with symptomatic improvement and decrease in oxygen needs to 2 liters per minute. The patient was prepared for discharge with removal of Swan Ganz catheter. He was placed in supine position in bed as he did not tolerate the Trendelenburg position. The patient was instructed to hum as the sheath introducer was pulled out. A sterile gauze dressing was applied and taped in place. The patient was alert and conversant

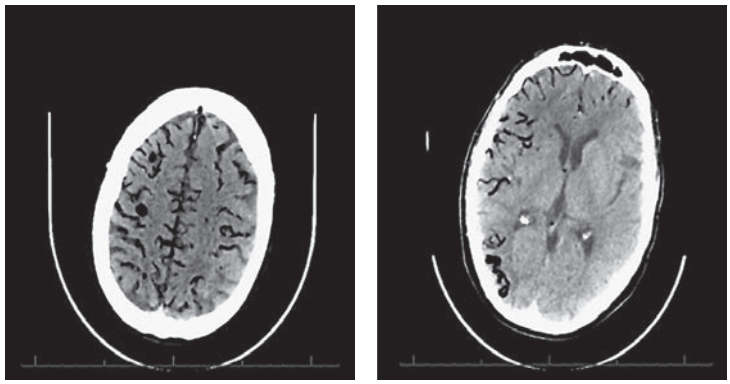

Figure 1 – Computed tomography of head showing extensive air in the vascular territory overlying both cerebral hemispheres. Gas is seen predominantly within the cerebral veins, superior sagittal sinus and right cavernous sinus. Several pockets of gas are seen in the right frontal region which may represent gas within focally dilated cerebral veins or adjacent sulci.

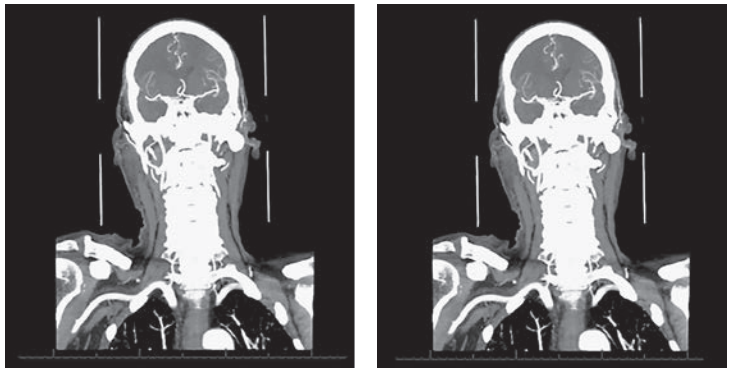

Figure 2 – Computed tomography angiography of head and neck (maximum intensity projection images) showing decreased arterial density in the upper right cerebral arteries and, to a lesser extent, upper left cerebral arteries indicating decreased perfusion. This would suggest air within distal small arteries.

at the time being assisted into the chair. Within a few minutes, he was noted to be unresponsive with horizontal nystagmus and generalized tonic clinic seizure activity. CT of the head was done immediately afterwards showing air within the cerebral veins, superior sagittal sinus and right cavernous sinus (Figure 1). CT angiography of the head showed decreased arterial density in the upper cerebral arteries (right > left), suggestive of air within distal small arteries (Figure 2). Patient was placed on 100% oxygen in Trendelenburg position. Bedside echocardiogram showed dilated right ventricle (RV), normal left ventricular ejection fraction with small amount of bubble artifact in the left atrium and left ventricle. Despite supportive measures, patient did not improve and passed 12 hours after the insult. Autopsy

showed multifocal subacute microinfarcts in occipital lobe and cerebellum, focal subarachnoid hemorrhage in the occipital region, and hypoxic ischemic changes in the hippocampus, cerebellum, and occipital lobe.

Discussion

Air embolism is an uncommon, but potentially lethal complication that occurs as a consequence of air entry into the vasculature. The reported incidence rate is 0.03–2% (Nagai et al., 2014). It can be classified into venous and arterial air embolism. Venous air embolism occurs when air enters the systemic venous circulation and travels to the right ventricle and pulmonary circulation causing interference with gas exchange, pulmonary hypertension, right ventricular strain, cardiac arrhythmias, and eventually cardiac failure (Muth and Shank, 2000). Arterial air embolism occurs when air enters the arterial circulation. It is a more serious occurrence and can cause ischemia in any organ with poor collateral circulation. The most common etiologies of air embolism include surgery, trauma, vascular interventions, barotrauma from mechanical ventilation (Muth and Shank, 2000) or as a result of paradoxical embolism.

Air embolism can occur during central venous catheter (CVC) insertion, manipulation, or removal. During catheter insertion, venous air embolism may occur from failure to occlude the needle hub and/or catheter, fracture or detachment of catheter connections (Inamasu et al., 2001). The risk is increased if the patient is hypovolemic with reduced central venous pressure (CVP). Increased negative intrathoracic pressure due to deep inspiration or upright positioning of the patient reduces CVP to below atmospheric pressure putting patient at risk for air entering very rapidly into the venous circulation (Pronovost et al., 2004).

Air embolization may lead to three outcomes: delivery to pulmonary circulation, to the systemic circulation via anatomic right to left shunts, or retrograde ascension to the cerebral venous system. Migration of emboli to the pulmonary circulation causes rise in pulmonary arterial pressure and increased resistance to right ventricular outflow which in turn causes diminished pulmonary venous return. This causes decreased left ventricular preload, diminished cardiac output and, ultimately, systemic cardiovascular collapse (Durant et al., 1947).

Paradoxical air emboli, such as cerebral arterial air emboli, are caused when air that has entered the venous circulation manages to enter the systemic arterial circulation and causes end-artery obstruction. The mechanisms by which this can occur can be broadly divided into intracardiac or intrapulmonary right-to-left shunts. Intracardiac shunts include passage of air via patent foramen ovale, atrial or ventricular septal defects. Elevated pulmonary arterial pressure due to venous air embolism may lead to an elevated right atrial pressure exceeding the left atrial pressure, causing right-to-left shunt of air through a patent foramen ovale, septal

defect or functional right-to-left shunt due to severe pulmonary hypertension. Intrapulmonary shunting of air bubbles can occur through pulmonary arteriovenous malformations. In some cases, venous gas may enter the arterial circulation by overwhelming the ability of the pulmonary circulation to filter out gas emboli. Animal studies suggest that a large bolus of gas (20 ml or more) or small continuous amounts (11 ml per minute) introduced into the venous system may generate intraarterial bubbles (Muth and Shank, 2000).

Cerebral venous air embolism can also result from retrograde flow of air against the direction of blood flow as it enters the venous circulation. Gas bubbles rise in blood due to their lower specific gravity (Chuang et al., 2019). This depends on bubble size, central vein diameter, cardiac output and position of patient's head above the heart. In veins above the level of the heart, atmospheric pressure is higher allowing air to enter the bloodstream and rise against gravity causing cerebral venous occlusion and infarction that does not follow typical arterial vascular distribution (Schlimp et al., 2014). Experimental studies have shown that retrograde venous air emboli can occur in certain settings, such as the patient being either supine or at least at an angle of 45 degrees to the horizontal plane, venous valve insufficiency, and increased right sided cardiac pressures (Schlimp et al., 2005; Fracasso et al., 2011).

Cerebral arterial embolism typically involves the migration of gas to small arteries, average diameter 30–60 micrometers. The emboli cause pathologic changes by obstructing end-arterial flow causing distal ischemia and cytotoxic edema. The surface of the bubble mechanically irritates the arterial endothelium and also generates an inflammatory foreign body response resulting in vasogenic edema and greater perfusion impairment (Mathieu et al., 2006).

Heckmann et al. (2000) studied cerebral embolism as a complication of CVC and found that subclavian vein puncture access was more likely to result in cerebral air embolism. This is possibly because the site of skin penetration is slightly higher than with internal jugular catheters hence air is more likely to entrain due to the increased pressure gradient between the atmosphere and the venous system of the neck (Heckmann et al., 2000). The overall mortality rate was 23% in these patients (Heckmann et al., 2000).

The rate and volume of air introduced also plays a role in the effect of the air embolus. Large, rapid boluses of air are more likely to result in complications than slow infusions of small amounts of air. The estimated fatal dose is 300–500 ml of air introduced at 100 ml/s (Ordway, 1974). This can occur through a 14-gauge catheter with a pressure gradient of 5 cm H_2O (Ordway, 1974). In canine models, gas entering the venous system at a rate more than 0.3 ml/kg per minute overwhelms the ability of the lungs to filter and results in arterial air emboli and tissue ischemia (Orebaugh, 1992).

Introducer catheters are large bore intravenous catheters that are combined with a valve side-port apparatus, which allows for penetration by a multi-lumen or pulmonary artery catheter (PAC). Hemostasis valve is an integral part of the

introducer sheath and is designed to prevent fluid from the inside lumen of the catheter from leaking when there is positive intraluminal pressure and to prevent air from entering the catheter when there is negative intraluminal pressure. Introducer sheath self-sealing valves maintain competence with pressure changes under simulated *in vivo* pressure conditions of up to –30 cm water pressure (MacGregor et al., 1998). It is recommended that an obturator cap be used over the valve to prevent air embolism when the catheter is not in use. This cap seals the external surface of the valve apparatus using an O-ring located on the external surface of the side port-valve assembly. The obturator also penetrates through the valve itself to provide the mechanical seal. Introducer valves that are penetrated with a PAC or other catheter must be observed closely for leakage of fluid around the PAC. This implies a faulty valve that may entrain air at low pressures. Data demonstrates that in the absence of visible leakage, the least amount of pressure required to entrain air was –125 mm Hg (MacGregor et al., 1998). The maximum negative intrathoracic pressure that can be generated in humans remains unclear however studies using maximal inspiratory pressures at the mouth have ranged from approximately –50 to –150 mm Hg, and esophageal transducer experiments during a sniff test have shown maximal transdiaphragmatic pressures in healthy adults to range from –82 to –204 cm H_2O (–61 to –152 mm Hg) (Black and Hyatt, 1969; Leech et al., 1983; Wilson et al., 1984).

Diagnosis requires a high degree of suspicion, particularly in case of neurologic symptoms around the insertion, use or removal of a CVC. Computed tomography of the head or magnetic resonance imaging done immediately after reveals the presence of air in the cerebral vasculature, but may be false negative if there is a delay in imaging (Caulfield et al., 2006). Bedside echocardiogram with agitated saline injection is helpful to differentiate between intracardiac shunt or intrapulmonary shunt.

Treatment is supportive. The patient is placed in the Trendelenburg position on the left, known as Durant's maneuver (Heckmann et al., 2000). This keeps air trapped in the heart away from the right ventricular outflow tract and may help in reducing the blockage of the vasculature. Oxygen therapy is recommended but it remains unclear whether hyperbaric oxygen therapy has any role (Heckmann et al., 2000).

Aspiration of air during venous air embolism may be required in case of an "air lock" in the right ventricular outflow tract. Multilumen or Swan Ganz catheters have been shown to be ineffective in aspirating air, with success rates between 6 and 16% (Bedford et al., 1981; Colley and Artru, 1987, 1989; Bowdle and Artru, 1988; Hanna et al., 1991; Artru, 1992). This may be related to the narrow luminal diameter, but offers the highest chance of success when there is already a catheter near the right atrium or ventricle. The best available device that has been studied is the Bunegin-Albin multiorifice catheter with success rates ranging from 30–60% (Colley and Artru, 1987, 1989; Bowdle and Artru, 1988). It has been reported that in a case

of venous air embolism, the withdrawal of 15 ml of air percutaneously from the right heart resulted in prompt hemodynamic improvement (Stallworth et al., 1950). Typically, 15–20 ml of air may be aspirated using this technique. Currently no data is available to support emergent catheter insertion for air aspiration during acute hemodynamic compromise in the setting of venous air embolism.

Prevention is the best treatment. It is imperative to correct dehydration before the procedure to increase CVP for decreasing the gradient that is necessary for air embolism to occur. During CVC placement, ensuring occlusion of needle hub and catheter (Pronovost et al., 2004), keeping connections secure when not in use prevents air embolism from the catheter (Opeskin et al., 1998). CVC removal must always be done in supine or Trendelenburg position with Valsalva maneuver to increase CVP. An impermeable dressing consisting of petrolatum gauze, sterile gauze and transparent dressing should be applied after removal (Hsiung and Swanson, 2000) and pressure should be held to the site for 1 to 5 minutes (Thielen and Nyquist, 1991), preferable longer in order to close off any patent catheter tracts.

In our patient, cerebral air embolism occurred likely due to two mechanisms. A large volume of air entrainment into the venous circulation through a dysfunctional one-way valve in the sheath introducer for pulmonary artery catheter led to a paradoxical air embolus through a functional right-to-left intracardiac shunt due to severe pulmonary hypertension (Eisenmenger physiology). There was also retrograde flow of air through the internal jugular vein to the cerebral venous vasculature as demonstrated in cranial imaging studies.

Conclusion

Cerebral air embolism is an exceptionally rare complication of central venous catheterization and can be associated with high mortality. A high clinical suspicion must be present in any patients exhibiting neurologic symptoms surrounding CVC insertion, manipulation or removal. Prevention and prompt diagnosis may decrease morbidity and mortality.

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Ruptured Liver Abscess Post Severe COVID-19 Infection: A Case Report

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Received April 16, 2023; Accepted July 28, 2024.

Key words: SARS-CoV2 – COVID-19 – Vaccination – Liver abscess

Abstract: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) caused imminent acute infection of respiratory tract known as Coronavirus disease 2019 (COVID-19). Complications of hepatobiliary system especially liver often found in post-acute COVID-19 patients. However, there are only few studies specifically discussing about liver abscess in patients who had history of contracted COVID-19. We present a case of a 54-years-old gentleman with no previous medical illness and no history of vaccination, who was presented with ruptured liver abscess post COVID-19 infection Category 4 (symptomatic with lung infection and the need of oxygen supplementation). Percutaneous drainage was performed to drain the abscess and collections.

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https://doi.org/10.14712/23362936.2024.25

Introduction

SARS-CoV2 is classified in Coronaviridae family, a single-stranded RNA virus. Angiotensin-converting enzyme 2 (ACE2) receptor became the main target of SARS-CoV2 (Nardo et al., 2021). ACE2 receptors also exist in other organs, such as the liver, heart, kidneys, pancreas and nerve sheaths (Li et al., 2020a; Skok et al., 2021). Liver abnormalities in post-infected SARS-CoV2 patients were shown in the other studies. Hepatocytes and cholangiocytes, which also contain the virus-specific ACE2 receptors, are directly susceptible to SARS-CoV-2 infection. According to expression profiling, cholangiocytes express ACE2 twenty times more than hepatocytes do. Compromised hepatic transaminases, as a sign of liver involvement, can result from direct injury of these cells (Yang et al., 2020).

Case report

A 54-year-old man developed sudden onset of the right hypochondriac and epigastric pain on day 22 post-COVID-19 infection Category 4. The nature of pain was described as colicky and radiated to the back, associated with vomiting and also loss of appetite. He did not have a history of liver disease or other systemic illnesses. He was not vaccinated with the COVID-19 vaccine prior to the infection. Initially, he was admitted to Covid Center Hospital before being transferred to our center for further management. During the transfer, the patient required respiratory support to maintain the oxygen requirement. He also completed the steroid regime for COVID-19 treatment for two weeks before the transfer.

On examination, there was tenderness at the right hypochondriac and epigastric region. Complete blood count showed a high total white count (29.2×10^9/l). In contrast, other biochemistry profiles, such as liver function test, showed elevation in aminotransferase enzymes and hypoalbuminemia features which were albumin 22 g/l, total bilirubin 42 umol/l, alkaline phosphatase (ALP) 4.37 ukat/l, alanine transaminase (ALT) 2.76 ukat/l, and aspartate transaminase (AST) 0.65 ukat/l. The C-reactive protein (CRP) also was on the higher side (151.0 mg/l).

Ultrasound of the hepatobiliary system revealed an ill-defined heterogenous hypoechoic lesion at segment V of the liver measuring 4×11.2×9.8 cm with a liquefied area within. A heterogeneous hypoechoic lesion was also present at left subphrenic region measuring approximately 6.0×16.6 cm. There was also the presence of echogenic and internal debris within with minimal peri splenic free fluid (Figure 1).

Further evaluation with a 4-phase liver CT (computed tomography) revealed a ruptured liver abscess with multiple loculated collections. There was a well-defined lobulated hypodense lesion with no significant enhancement in the right lobe of the liver, measuring approximately 11×9×10.4 cm (Figure 2). The lesion continued with

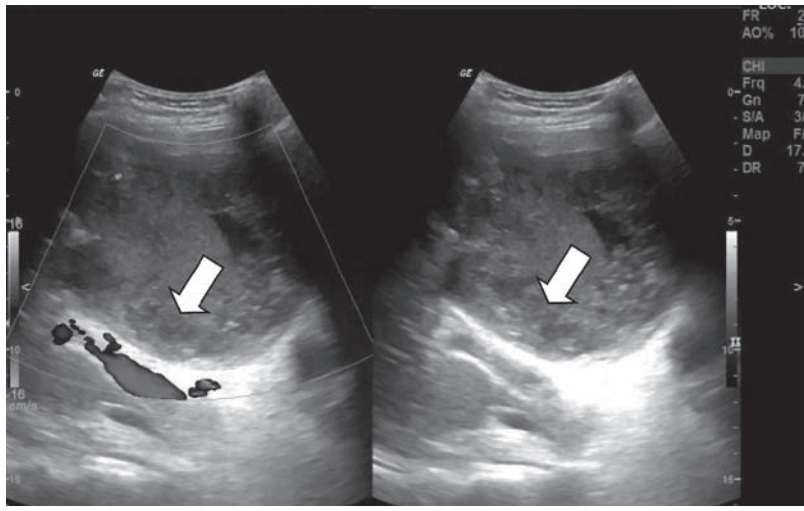

Figure 1 – Ultrasound hepatobiliary-hypoechoic lesion at segment V (arrows). Presence of echogenic and internal debris within with minimal peri splenic free fluid.

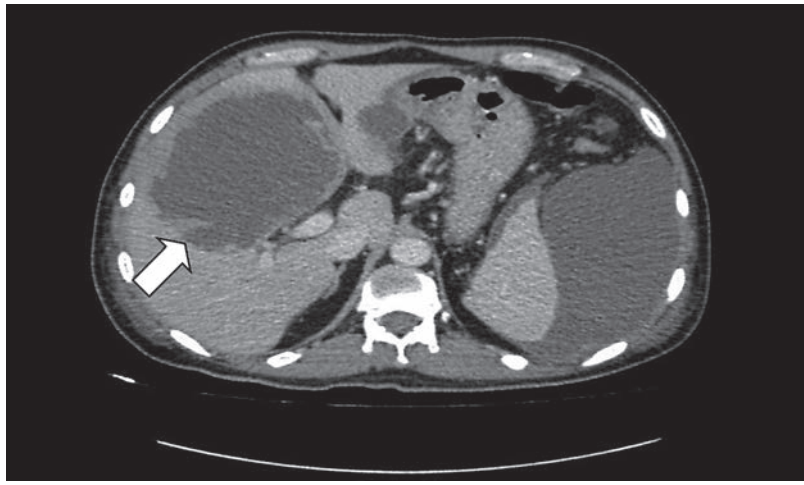

Figure 2 – Computed tomography liver 4 phases revealed a well-defined lobulated hypodense lesion with no significant enhancement in the right lobe of the liver measuring approximately 11×9×10.4 cm (arrow).

an elongated loculated collection between the stomach and duodenum (D1 and D2) and the left lobe of the liver, measuring about 2.8 cm in maximum thickness. There was also a loculated collection at the hepatorenal region. At the left hypochondrium, the subcapsular splenic collection at the superolateral aspect of the spleen extended to the subphrenic region, measuring about 13.5×9.6×14 cm.

Given the patient's symptoms and ongoing infection in the setting of post-COVID-19 infection, percutaneous drainage under ultrasound guidance was done. About 800 ml thick, exudative and yellowish pus was drained out during the procedure. An immediate start of intravenous meropenem during his stay in the ward was indicated. Neither pus nor blood cultures showed any growth. No acid-fast bacteria (AFB) were seen in direct smears. A serial hepatobiliary ultrasound done post-drainage showed improvement in terms of the reduced size of the collections and resolution of the left subphrenic collection. The patient was discharged after two weeks. He was well during the follow-up at the surgical outpatient clinic.

Discussion

Previous studies showed that severely ill patients with COVID-19 tended to develop gastrointestinal complications and had higher percentages for liver function derangements combined with low serum albumin level (Tian and Ye, 2020). This patient presented with a sudden onset of abdominal pain 22 days after the confirmed COVID-19 Category 4. There was clear evidence of elevation in aminotransferase enzymes and hypoalbuminemia with a raised total white count and CRP level.

Direct cytotoxicity of SARS-CoV2 virus by viral replication resulted in liver damage. This situation resulted in a hypoxic state brought on by respiratory failure, coagulopathy-induced vascular alterations, endothelial tissue inflammation, drug-induced liver damage and a history of liver disease exacerbations. Hypoxia and inflammation, which are frequent in severe COVID-19 instances, are crucial in the process of hepatocellular ACE2 expression (Nardo et al., 2021). The dysfunction of cholangiocytes, which can result in impaired bile production, inflammation, fibrosis, and liver dysfunction, might increase the expression of ACE2 in liver tissue, which may be one of the mechanisms of liver damage brought on by SARS-CoV2 infection (Banales et al., 2019). The SARS-CoV-2 induces direct damage to the biliary ducts by binding to ACE2 on cholangiocytes (Zhang et al., 2020). The other mechanisms of liver damage include hyperinflammation seen with cytokine storm and hypoxia-associated metabolic derangements (Li et al., 2020b). As our patient had been previously diagnosed with severe COVID-19 infection, hypoxia and inflammation led to extrapulmonary SARS-CoV2 dissemination that contributed to the liver abscess formation as there was a significantly raised ACE2 expression in the liver tissue.

It was proposed that possible factors behind the development of liver abscesses include suppression of immunity by COVID-19 infection itself and usage of steroids (Sahney et al., 2022). For our patient, we postulated that the predisposition to develop the liver abscess might have been related to COVID-19 itself and could have been accentuated by the previous use of steroids during their treatment for the severe infection of COVID-19.

As this patient did not have any medical illnesses and symptoms of liver abscess disease prior to COVID-19 infection, there was no available imaging for him. The very first imaging was done when the patient complained of the sudden onset of abdominal pain, as mentioned in the case report. Radiology images revealed a ruptured liver abscess with multiple loculated collections. Percutaneous drainage under ultrasound guidance was performed. No AFBs were seen in direct smear. We thus concluded that the patient was not diagnosed with extrapulmonary tuberculosis (TB). No microbes were found in the pus culture, as mentioned in the other case report of a COVID-19 patient with liver abscess (Dhadiala and Whatkar, 2021). As this was the first episode of abdominal symptoms, we concluded that this patient did not have any pre-existing liver abscess before their COVID-19 infection based on the symptoms' onset. The radiology images also showed evidence of ruptured liver abscess even though no common microbes were found in the cultures or smears. We hypothesized the liver abscess in our patient was associated directly with the COVID-19 infection according to these factors.

In our case, the core management focused on combination of drainage and targeted antibiotic therapy. As there are studies regarding liver abscess in post-COVID-19 patients still lacking, precautions for COVID-19 infection should still be taken. Our case report outlined the prompt diagnosis, pathophysiology, and approach to liver abscess after COVID-19 infection.

Conclusion

Due to the extremely small number of reported clinical cases, the pathophysiology and optimal management of liver abscess after COVID-19 have not been determined. As reported in our case, the pathophysiology of liver abscess after COVID-19 infection may result from the development of liver necrosis due to a specific interaction of the SARS-CoV2 with the liver parenchyma through ACE2 expression. Understanding the pathophysiology processes can guide the novel treatment of the disease in the future.

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Published by the First Faculty of Medicine, Charles University, Karolinum Press,
Ovocný trh 560/5, 116 36 Praha 1 – Staré Město, Czech Republic, www.karolinum.cz

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Published as quarterly journal. Typeset and printed by Karolinum Press.
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ISSN 1214-6994 (Print)
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