Phenotypic analysis of discordant monozygotic twins for pain-related temporomandibular joint disorder. Case report

Análise fenotípica de gêmeas monozigóticas discordantes para disfunção temporomandibular dolorosa. Relato de caso

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ABSTRACT

BACKGROUND AND OBJECTIVES: The design of research with monozygotic twins discordant for the disease has emerged as a powerful tool for the detection of phenotypic risk factors. The aim of this study is to report a clinical case of monozygotic twins discordant for pain-related temporomandibular joint disorder (TMD) from a cognitive-behavioral-emotional phenotypic analysis, from the comparison of clinical variables of pain, history of exposure to painful procedures in early childhood, and coping with pain.

CASE REPORT: TMD-Twin presented a diagnosis of painful (myofascial pain with referral) and joint (disk displacement with reduction) TMD according to the criteria of the DC/TMD. Control-Twin did not show TMD, however she presented other chronic pains. TMD-Twin showed reduced pressure pain threshold, hyperalgesia in trigeminal and extra-trigeminal regions compared to the Control-Twin. TMD-Twin was more exposed to painful procedures and emotional events due to congenital heart problems. Both had central sensitization based on the Central Sensitization Inventory, although TMD-Twin had more catastrophic thoughts about pain. TMD-Twin presented an internal locus of control.

CONCLUSION: Both monozygotic twins presented a chronic pain phenotype, although they were discordant with the TMD-related pain. The main differences were the lower pressure pain threshold and higher hyperalgesia locally presented by TMD-Twin. The internal locus of control indicates greater pain sensitivity, with better coping of the painful experience for the TMD-Twin. One possible explanation for this clinical condition can be that painful experiences in early childhood have shaped a phenotype of greater sensitivity with better coping and resilience to the painful condition.

Keywords: Chronic pain, Facial pain, Monozygotic twin, Temporomandibular joint disorders, Central nervous system sensitization.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O desenho da pesquisa com gêmeos monozigóticos discordantes para a doença surgiu como uma ferramenta poderosa para a detecção de fatores de risco fenotípicos. O objetivo deste estudo foi relatar um caso clínico de gêmeas monozigóticas discordantes para disfunção temporomandibular (DTM) dolorosa a partir de análise fenotípica cognitivo-comportamental-emocional entre elas, por meio de comparação de variáveis clínicas de dor, histórico de exposição a procedimentos dolorosos na primeira infância e enfrentamento de dor (autoeficácia e *locus* de controle).

RELATO DOCASO: A gêmea-DTM apresentou diagnóstico de DTM dolorosa (dor miofascial com referência) e articular (deslocamento do disco com redução) segundo os critérios do DC/TMD. A gêmea-controle não apresentou DTM, contudo apresentou manifestação clínica de outras dores crônicas. A gêmea-DTM apresentou limiar de dor à pressão reduzido, hiperalgesia em regiões trigeminais/extra-trigeminais quando comparados à gêmea-controle, que na primeira infância foi mais exposta a procedimentos dolorosos devido a problemas cardíacos congênitos. Ambas apresentaram sensibilização central de acordo com o Inventário de Sensibilização Central, embora a gêmea-DTM apresentou mais pensamentos catastróficos sobre a dor. A gêmea-DTM apresentou *locus* de controle interno.

CONCLUSÃO: Ambas as gêmeas apresentaram fenótipo de dor crônica, apesar do fato de serem discordantes para a DTM. Dentre as avaliações, as que mais diferiram entre o par foram o baixo limiar de dor à pressão e hiperalgesia local presentes na gêmea com DTM. O *Iocus* de controle interno associado à maior sensibilidade indicou melhor enfrentamento da experiência dolorosa para a gêmea-DTM. Uma possível explicação para esta manifes-

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tação clínica está pautada na hipótese de que experiências dolorosas na primeira infância vivenciadas por ela tenham moldado um fenótipo de maior sensibilidade com melhor enfrentamento e resiliência frente à condição dolorosa.
Descritores: Dor crônica, Dor facial, Gêmeos monozigóticos, Síndrome da disfunção da articulação temporomandibular, Sensibilização do sistema nervoso central.

INTRODUCTION

Temporomandibular disorder (TMD) can be understood as an orofacial musculoskeletal pain syndrome, which mainly affects women. It is characterized by orofacial signs and symptoms, usually easy to manage and/or self-resolving. However, a portion of the population develops an imbalance in the endogenous pain modulation system, resulting in challenging management. In these cases, the association of multisystem alterations, changes in behavior, emotional status, and social interactions are frequently observed[1-3]. Therefore, TMD symptoms must be understood as a complex and specific individual response, with individualized signs and symptoms, which can be amplified or attenuated, depending on the genetic composition and epigenetic factors[4-7].
Studies about twins have played an essential role in estimating the hereditary fraction of hundreds of phenotypic characteristics and pathological conditions. The design of research with monozygotic twins (MZ) discordant for the disease has emerged as a powerful tool for the detection of phenotypic risk factors, as it allows for the reduction of a range of unknown confounding factors, typically found in population studies, especially concerning research with epigenetics[8]. MZ twins share a common genotype, whereas the most are not identical. Several types of phenotypic disagreement can be observed, such as differences in disease susceptibility and a wide range of anthropomorphic characteristics. There are several possible explanations for these observations, but one of them is the existence of epigenetic differences[9,10].
Considering the complexity of factors involved in the manifestation of TMD, the aim of this article is to report a clinical case of MZ twins discordant for pain-related TMD from the cognitive-behavioral-emotional phenotypic analysis between them, the comparison of clinical pain variables, history of exposure to painful procedures in early childhood and coping with pain (self-efficacy and locus control).

CASE REPORT

This case report is part of a research approved by the Ethics Research Committee of the Faculty of Philosophy, Sciences and Letters – Ribeirão Preto (São Paulo University) under CAAE protocol 98129918.6.0000.5407. CaRe (Case Report) guideline was used to prepare this manuscript and guarantee accuracy, transparency, and usefulness of case reports[11].

Patient information
Twins 1 and 2, 20 years old, monozygotic identical, university students, single, living in the same family from birth to the present time.

Primary concerns/symptoms and clinical findings
Twin 1 presented a diagnosis of painful (myofascial pain with referral) and joint (disk displacement with reduction) TMD according to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD – Brazilian Portuguese version)[12]. In addition, she reported a history of recurrent otitis and difficulties in speech development, however she did not suffer any injury in the TMJ region during childbirth.
Twin 2 did not present TMD according to the same clinical evaluation protocol, but reported a painful condition for approximately 10 years, including the paranasal sinuses, temples close to the eyes, the frontal region of the head, and trapezius muscles. She also reported to having restless legs syndrome and polycystic ovary.

Timeline
Twin 1 (TMD-twin) reported she had a congenital heart condition, and due to this, during her early childhood, she underwent three cardiac surgeries. In addition, she had a low birth weight and was kept in the incubator for two months. Such health conditions exposed her to more painful procedures (surgeries, sutures, venous access, injections, among others) and salient emotional events (incubator, hospitalization, among others) than Twin 2 (control-twin).

Diagnostic assessment and methods
The twins were evaluated according to:
• Oral Behavior Checklist - Brazilian Portuguese version[1,13]: scores sum for both was high, totaling 29 for the twin with pain-related TMD and 32 for the control-twin (Table 1). According to the total scores, both twins presented possible awake bruxism.
• Pressure pain threshold (PPT) in trigeminal areas (anterior temporalis, masseter, and TMJ) and extra-trigeminal areas (trapezius, lateral epicondyle, and knee) were compared bilaterally (IDDK digital compression algometer™, Kratos, Cotia, São Paulo, Brazil): TMD-twin had lower PPT for all areas evaluated compared to the control-twin, that is, more sensitivity to pain in trigeminal and extra trigeminal areas (Figure 1).
• Presence of hyperalgesia was also analyzed with the same algometer. A constant compression (5 seconds) of 1.5 kg/f in each trigeminal point and 2 kg/f in each extra-trigeminal point was applied. A score representing the perceived intensity of pain felt was requested (VAS - zero to 10). TMD-twin reported greater pain intensity during the exam, especially in the trigeminal areas and in the trapezius, region compared to the control-twin, indicating a higher level of hyperalgesia[14] (Figure 2).
• Brief Pain Inventory (BPI - Reduced Version, in Portuguese[15]): the scores are represented by the mean of the values assigned in each dimension of perception (Table 2).
• Locus of Control Pain Scale - Form C (PLOC-C, Portuguese version[16]): it was observed that the TMD-twin had a higher internal locus of control and in other people (relatives, friends) than the control-twin, with the same locus of control being equal between them at random and other health professionals (Table 2).

Table 1. Oral Behavior Checklist: scores for each item and total sum for the twins

	Items – Oral Behavior Checklist																					Total
Scores	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	Total
TMD	4	0	0	3	0	0	0	3	0	0	4	0	4	0	0	0	4	4	0	3	0	29
Control	3	3	0	1	4	3	1	2	0	4	4	2	2	0	2	0	4	1	2	2	1	32

TMD = Temporomandibular Disorder.

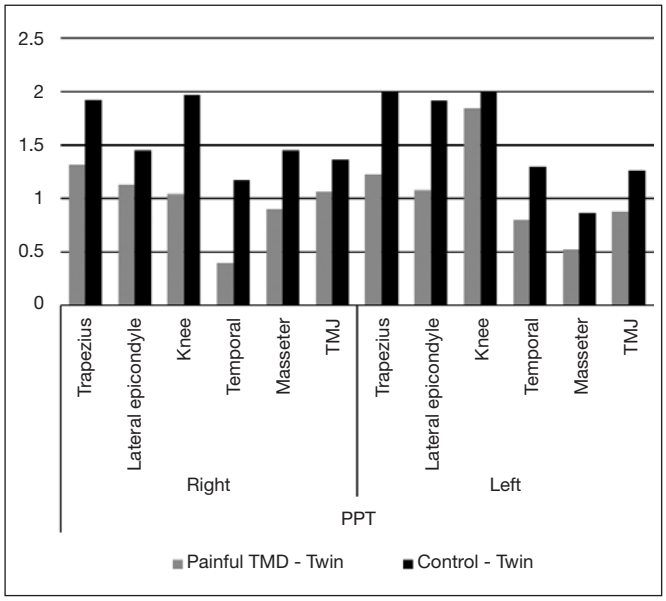

Figure 1. Pressure pain threshold for trigeminal and extra-trigeminal areas in the comparison between the twins

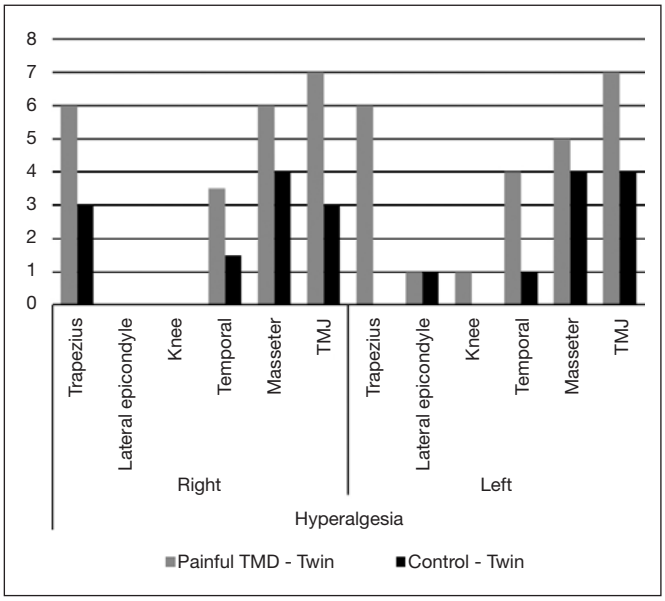

Figure 2. Evaluation of hyperalgesia for trigeminal and extra-trigeminal areas in the comparison between the twins

Table 2. Cognitive-behavioral-emotional characterization of each twin sister investigated according to assessment protocols

Instruments		TMD-twin	Control-twin
OBC*	Total score of orofacial behaviors	29	32
BPI†	Sensorial perception	1.5	3
	Interferencial perception	6	2.43
	Total	7.5	5.43
BP-CSI‡	A (total score)	45	52
	B (number of diagnoses)	3	5
Pain maps	Number of painful areas in the craniocephalic region	6	7
PLOC-C§	Internal control locus	13	9
	Random control locus	10	10
	Other people – control locus	7	5
	Other professional – control locus	9	9
PCS‖	Rumination	10	7
	Magnification	5	6
	Helplessness	13	7
	Total	28	20
MAAS¶	Level mindfulness	47	26

*OBC = Oral Behavior Checklist; †BPI = Brief Pain Inventory; ‡BP-CSI = Central Sensitization Inventory; §PLOC-C = Locus of Control Pain Scale-Form C; ‖PCS = Pain Catastrophizing Scale; ¶MAAS = Mindful Attention Awareness Scale.

• Central Sensitization Questionnaire (Brazilian Portuguese Central Sensitization Inventory - BP-CSI)[17]: TMD-Twin had a score of 45 and the Control-Twin of 52 (Table 2). The number of painful sites in trigeminal regions was counted, marked with an "X" on a pain map of the cranioencephalic complex. TMD--Twin scored 6 points, and the Control-Twin scored 7 points, differing their location (Table 2).

• Pain Catastrophizing Scale (PCS)[18]: TMD-Twin had higher catastrophizing levels, considered as a high-risk factor for chronic pain and rumination, as well as helplessness, than the control-twin (Table 2).

• Mindful Attention Awareness Scale (MAAS) - Brazilian version[19]: it was observed that the trait of mindfulness was higher in the TMD-Twin (Table 2).

Diagnostic challenges and diagnosis (including other diagnoses considered)

At first, the DC/TMD instrument allowed the confirmation of TMD in one of the twins and not in the control. The initial expectation was that the control did not present any painful condition or phenotype of pain. However, despite the absence of TMD diagnosis, the control-twin presented chronic pain from primary headache. This was a challenge for understanding how different diagnoses of chronic pain could manifest phenotypically in each of the twins, considering that both have the same genotype.

DISCUSSION

Identical (monozygotic) twins have always intrigued researchers since they have the same genotype at birth, and they develop different phenotypes throughout their lives, becoming completely different individuals. In the last decade, several studies with discordant monozygotic twins have been published, as with this methodology, it is possible to establish a case-control study design in which a series of variables are controlled, as they are shared between the siblings: genetic material, social environment (if raised by the same family), age, gender, among many others[20-22].

TMD-twin had greater pain sensitivity (lower PPT) and hyperalgesia in trigeminal and extra-trigeminal areas when compared to the control-twin, indicating a picture of generalized chronic pain[3]. These findings point to the fact that the nociceptive experience goes beyond inherited genetic components and is modulated by a series of biopsychosocial variables, such as attention, assessment with cognitive and emotional meaning attribution of perceived sensations, the role of the disease in relation to social norms and expectations and behavior, often maladaptive[2]. Reduced PPT and hyperalgesia were also identified in regions not affected by painful TMD, indicating a lack of modulation and descending pain control. Added to this, scores for the CSI questionnaire for both suggest central sensitization of the pain system, which justifies the presence of pain referred to palpation found in the TMD-twin.

Complementarily, the painful TMD-twin had a total BPI and interferential pain perception score with higher values than the control-twin, but with a lower level of pain sensory perception, representing a cognitive interpretation of the pain experience perhaps indicating greater resilience acquired by previous painful experiences. Perhaps, in this case, the difference was the exposure to several painful procedures in early childhood to which the TMD-twin was submitted. In this case, it is interesting to note that sensory intensity of pain was inversed to the perception of interference in the twins' lives. The one with greater sensory perception (control-twin) scored less perception of interference, and the one with less sensory perception had a greater perception of pain interference in daily activities (TMD-twin), corroborating the concept of multidimensionality of the painful experience.

It was observed that the TMD-twin had more catastrophic thoughts related to rumination and helplessness, with scores that suggest a high risk for painful chronicity. The rumination factor seems to be related to the subject's excessive attention to the painful event and the helplessness factor related to a self-assessment of inability to deal with this threat value. Magnification, on the other hand, with a high score for the control-twin according to the 75th percentile previously established, concerns the magnitude of importance attributed to the possible risks of worsening the condition, reiterating the idea that she is also a chronic pain patient, although it is not manifesting in the stomatognathic system[23,24].

Locus of pain control was similar between the twins, differing mainly in the locus of internal control dimension, higher for the TMD-twin. This demonstrates internal accountability to deal with the pain greater than the control-twin. Perhaps the more pronounced mindfulness trait can contribute to a more autonomous and optimistic coping with managing one's own body, while it can also lead to thoughts fixed on the painful state and its expectation of improvement or worsening, related to catastrophizing of pain. It is possible that the increase or decrease in pain is also related to attention, depending on where the focus is directed. In this case, mindfulness-based intervention would contribute by providing training in non-judgment and equanimity of attention to different bodily sensations, for example[25,26].

Knowing the levels of the mindfulness trait in people with painful TMD can elucidate, at least in part, the level of awareness about thoughts and behaviors and internal processes resulting from the presence of pain. Furthermore, it also brings a positive perspective to the management of chronic painful TMD, contemplating the biopsychosocial model, with neurophysiological and epigenetic results[18,19]. A higher level of mindfulness trait was observed in the TMD-twin, where the rumination factor seems to be related to the subject's excessive attention to the painful event and the helplessness factor related to a self-assessment of inability to deal with the threat value, both presented by her as well[18,27].

With a broader view, this multisystem deregulation of the organism leads to its internal imbalance, that is, to illness, in which the perception of pain, accompanied by the attribution of cognitive and emotional meaning, is the main motivation for seeking professional help[27]. On the other hand, this professional help has its role well-performed when the gaze turns to pain control and to alleviating the suffering of those who seek it, to alleviate primary symptoms and prevent the consequences of unrelieved pain, since a delay in healing can depress the immune system[28,29].

The strengths of this case are related to the possibility of applying specific instruments to analyze a cognitive-behavior-emotional model linked to chronic pain conditions. But there were limitations related to the absence of genetics and epigenetics analyses, which could clarify specific characteristics in the DNA of each twin.

CONCLUSION

This case report shows that although the twins are discordant for painful TMD, the control-twin also has a chronic pain phenotype, based on this cognitive-behavioral-emotional analysis. Among the assessments performed, the greater difference between the pair were the pressure pain threshold and hyperalgesia of trigeminal and extra-trigeminal regions, and the locus of internal control, which indicates greater pain sensitivity, with better coping of the painful experience for the TMD-twin. The genetic and epigenetic analysis could highlight other specificities of these manifestations. This study hypothesizes that exposure to painful experiences in early childhood has made the TMD-Twin more sensitized and molded her coping of the pain experience of TMD.

AUTHORS' CONTRIBUTIONS

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Data Collection, Research, Methodology, Writing - Review and Editing
Melissa de Oliveira Melchior
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