Acta Odontologica Scandinavica, 2011; 69: 193–200

informa
healthcare

REVIEW ARTICLE

A dental look at the autistic patient through orofacial pain

FARES ZEIDÁN-CHULIÁ[1,2], ULVI K. GURSOY[3], EIJA KÖNÖNEN[3] & CARMEM GOTTFRIED[1,2]

[1]*Neuroglial Plasticity Laboratory at Department of Biochemistry, Postgraduate Program in Biological Sciences: Biochemistry, Institute of Basic Health Sciences,* [2]*Pervasive Developmental Disorders Program (ProTID), Clinical Hospital of Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil, and* [3]*Institute of Dentistry, University of Turku, Turku, Finland*

Abstract

Autism is a neurodevelopmental disorder characterized by impaired social interaction and restricted interests, compromised communication skills, and repetitive patterns of behavior. Both social and behavioral problems, which may include hyperactivity and quick frustration, may hinder the detection of other important pathologies such as orofacial pain. This is aggravated by the invasive nature of oral exploration, which may trigger violent and self-injurious responses, such as temper tantrums and/or head banging, which make the work of professionals extremely difficult during diagnoses, follow-up examinations, and dental treatments. In addition, mercury-containing amalgams used to treat dental caries (the most common form of acute orofacial pain) have been associated with higher rates of severe autism in children. The purpose of this review is to describe the current state of the art regarding the co-occurrence of orofacial pain and autism spectrum disorder, and how these conditions may interrelate clinically and neurobiologically.

Key Words: *Amalgam fillings, autism, behavioral symptoms, dental intervention, oral health*

Introduction

Autism is a complex neurodevelopmental disorder characterized by impaired social interaction and communication, repetitive patterns of behavior, and unusual stereotyped interests [1]. Owing to the variety and grade of its characteristic features and associated symptoms among patients, it is generally termed 'Autism Spectrum Disorder' (ASD). With the exception of Asperger's syndrome, ASD is related to different ranges of mental retardation. People with ASD show diverse medical and behavioral problems, which make the management of these patients extremely complicated. Behavioral features include hyperactivity and irritability, aggression, self-injury, lack of attention, and several fits of bad temper [2,3].

Orofacial pain may be difficult to diagnose in those who suffer from developmental disabilities, aberrant social interaction, and impaired communication skills. In the case of ASD patients, this limitation may act as one potential masking factor influencing the sudden aggravation of autistic patients' behavioral core symptoms, which dramatically affects the patient's quality of life. Therefore, this article will explore the possible bi-directional influence of orofacial pain on autistic behavior (and vice versa) as well as the clinical implications of such an interrelation.

Orofacial pain in the autistic scenario

In general, pain can be classified as neuropathic (e.g. in the case of herpes zoster virus infection), nociceptive (e.g. dental pain), or mixed (e.g. in cancer scenarios). Nociceptive pain is transmitted by physiological pathways through peripheral nerves to the central nervous system (CNS) in response to potentially tissue-damaging stimuli. In contrast, neuropathic pain results from a primary lesion or dysfunction in the nervous system, either central or peripheral [4].

Correspondence: Carmem Gottfried, MSc, PhD, Neuroglial Plasticity Laboratory, Department of Biochemistry, Institute of Basic Health Sciences, Federal University of Rio Grande do Sul, Rua Ramiro Barcelos, 2600-anexo-Bairro Santa Cecília 90035-003, Porto Alegre, RS, Brazil. Tel: +55 51 3308 5565. Fax: +55 51 3308 5540. E-mail: cgottfried@ufrgs.br

(Received 2 September 2010; accepted 25 November 2010)

ISSN 0001-6357 print/ISSN 1502-3850 online
DOI: 10.3109/00016357.2010.549505

Orofacial pain is constituted by any symptom resulting from a diverse number of diseases and disorders that would lead to a sensation of discomfort or pain felt in the region of the face, mouth, nose, ears, eyes, head, and neck [5,6] (Figure 1). Its prevalence among the general population varies from 17% to 26% and it is chronic in 7–11% of these cases [7,8]. Although neuropathic orofacial pain is usually evaluated by a multidisciplinary team of neurologists, dentists, neurosurgeons, psychologists, and other healthcare professionals [4,9], it is often labeled as a 'psychopathology' whenever the etiology remains obscure [10]. It is most likely that, in any other pathological scenarios (e.g. autism) where the communication channel between healthcare professionals and patients is compromised, orofacial pain either remains undiagnosed or is tagged as 'idiopathic' in a high percentage of cases; however, this is not the only problem. Loss of teeth, a common dental event also in the autistic scenario, may be accompanied by impaired oral motor functions. Epidemiologic studies keep on revealing, among the populations of many countries, high rates of temporomandibular disorders, toothaches, headaches, and some other conditions associated with orofacial pain [11,12]. In general, the impairment of oral motor functions could potentially be aggravated by the typical seizures, stereotyped movements, and anxiety scenarios commonly present in autism [13,14], and this may synergistically influence the prevalence of orofacial pain among autistic patients and their general oral health status.

From autism to orofacial pain: the many types of orofacial motor disorders

The term 'orofacial motor disorder' (OMD) refers to a spectrum of movement aberrations, both hyper- and

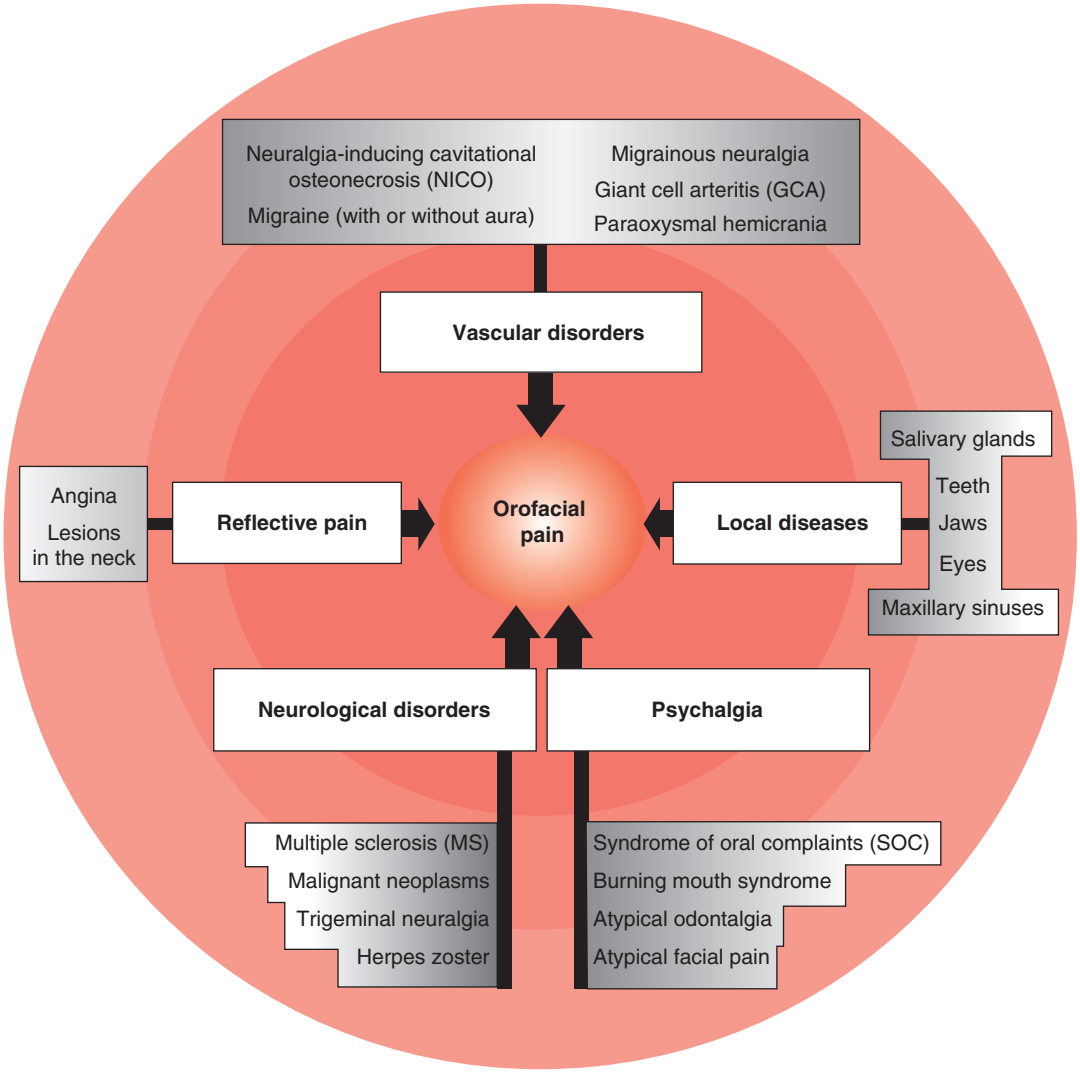

Figure 1. Revisiting the potential causes of orofacial pain. The diagram represents a number of different diseases and disorders that can potentially give rise to orofacial pain [5,6]. The multifactorial etiology of orofacial pain and the complex nature of facial structures make its diagnosis and therapeutic evaluation extremely complicated.

hypoactive, involving the muscles of the orofacial complex that are innervated by cranial nerves V, VII, and XII. OMDs generally present as localized problems that specifically affect the masticatory system, but they are actually driven by alterations in the functionality of the CNS [15]. In any case, dentists should be able to recognize and get involved in the management of such problems because OMDs can cause pain and dysfunction of the jaw, and may interfere with routine dental care of patients [15].

Bruxism

Awake bruxism is generally defined as the awareness of jaw clenching, and is mainly associated with reactions to stress and nervous tics. The pathophysiology of bruxism is still unclear. However, the most compelling hypothesis describes bruxism as a neuromotor dysregulation disorder that affects ≈10–20% of the population [16,17]. Although bruxism has widely been explained to cause pain by overloading the musculoskeletal tissue, additional experimental models may be required in order to better comprehend such a relationship [18]. The treatment options for bruxism, which include the use of splints or behavioral modification techniques, are limited in children with autism due to their poor mental skills (with the exception of Asperger's syndrome) and communication difficulties. In addition, obsessive routines, repetitive and self-injurious behaviors, and unpredictable body movements are symptoms that can potentially interfere with daily oral hygiene and professional dental care in a child with autism [16].

Dystonia

Dystonia is a syndrome of abnormal involuntary muscle movements due to sustained muscle contractions, which generates twisting, repetitive patterned movements, and/or aberrant postures [15]. Oromandibular dystonia is a form of focal dystonia that affects the orofacial region and involves the jaw openers (lateral pterygoids and anterior digastrics), tongue muscles, facial muscles (especially the orbicularis oris and buccinator), and platysma [19].

Dyskinesia

Orofacial dyskinesia is constituted by a group of repetitive, involuntary, and stereotypical movements of the tongue, lips, and, occasionally, the jaw of the patient [20,21]. This is either of spontaneous origin or induced by medication (tardive) [22]. From time to time, edentulous orodyskinesia can be confused with drug-induced oral tardive dyskinesia due to the similarities of their abnormal movements localized in the tongue, lips, and jaw. This may result in a misdiagnosis and, furthermore, inappropriate care [23].

Both dystonia and dyskinesia can lead to increased tooth wear [24] which, in the case of ASD patients, may be exaggerated by the typical seizures or anxiety scenarios associated with this neurodevelopmental syndrome [14].

Drug-induced dystonic extrapyramidal reactions

Age is a determinant of the kind of pharmacological response obtained with any psychotropic treatment, which differs between children, adolescents, and adults. Commonly used neuroleptics in children and adolescents may lead to some unwanted side effects, which include extrapyramidal symptoms, sedation, and withdrawal dyskinesias [25]. Diverse novel antipsychotics have been developed in order to decrease such side effects and, eventually, have demonstrated a relatively low risk of parallel extrapyramidal effects [26]. For instance, the atypical neuroleptic risperidone showed both efficacy and safety for the treatment of different behavioral aspects of autism, including irritability, hyperactivity, aggression, and stereotypy [27].

A neurobiological link between autism and orofacial pain?

Pain can be classified according to the mechanisms that are actually involved in it. Currently, the proposed mechanism-based classification has four main categories: nociceptive pain, functional pain, inflammatory pain (tissue injury), and neuropathic pain (nervous injury) [18,28]. The International Association for the Study of Pain® (IASP) has classified >50 fairly localized pain syndromes in the craniofacial region, including trigeminal neuralgia, post-herpetic neuralgia, odontalgia, and migraine. A complete list was published by the IASP in the mid-1980s [29].

Neuralgia (the word is derived from the Greek words *neuron*, meaning nerve, and *algos*, meaning pain) can affect people of different ages, though it rarely occurs in children. It can be triggered by a great variety of events, including tooth decay, eye strain, or shingles (an infection caused by the herpes zoster virus) [9]. The most common type of neuralgia (trigeminal neuralgia) gives rise to a brief, searing pain along the trigeminal nerve but its actual cause has not conclusively been established. Two trigeminal nerves exist: one supplying sensation to the right side of the face and the other to the left. Sensory innervations of the mouth, face, and scalp depend on the trigeminal nerve, and diseases affecting the nerve can cause orofacial pain, sensory loss, or both [7,9]. Usually, the pain only affects one side of the face, being felt either on the skin or in the mouth and teeth.

Interestingly, researchers started to associate certain cellular events concerning neuron–glial interaction with the biological basis of persistent pain [30].

For example, Okada-Ogawa et al. [31] demonstrated the involvement of astroglia (in the medullary dorsal horn) in trigeminal neuropathic pain-associated mechanisms, and Guo and colleagues [32] reported both the activation and hypertrophy of astroglia, together with elevated levels of glial fibrillary acidic protein and connexin 43, in a trigeminal model of inflammatory hyperalgesia. Moreover, *in vivo* studies have also shown that even dental extraction is sufficient to trigger neuroplastic changes as a response likely associated with the modified oral scenario [33].

Glia secrete growth factors, such as brain-derived neurotrophic factor (BDNF) and basic fibroblast growth factor, for protecting neurons that can additionally enhance pain [34]. This could be of extreme importance, since BDNF and other neurotrophins have been found to be elevated in the blood of autistic patients. Indeed, the literature strongly suggests hyperactivity of this growth factor as one of the possible etiologic factors of the autism-associated neurobiological aberrancies [35–37]. In any case, due to the different putative origins of this pain (neurological, vascular, or dental), patients can be misdiagnosed and receive dental treatment when they actually suffer from trigeminal neuralgia. This situation may be more common than it seems, since the professional consulted (i.e. a physician or dentist) is usually chosen in order to get the most plausible diagnosis [38], and orofacial pain is the main reason why patients seek a dental consultation [39].

From orofacial pain to autism: exploring the amalgam-based dental treatment

The most common form of acute orofacial pain is due to dental caries [40]. The management of dental caries includes the removal of infected hard tissues of the tooth and their replacement with filling materials, such as amalgam, composites, or glass-ionomer cements. There have been great improvements in the properties of composite materials and national regulations have limited the use of amalgam in Scandinavian countries during the last decade; however, amalgam is still the filling material of choice for posterior restorations in most countries of the world due to its handling and adequate mechanical properties [41].

Dental amalgam is a mercury-based material (50%), mixed with silver (35%), tin (9%), copper (6%), and zinc (trace amounts) [42]. Amalgam is classified as an intermetallic compound and is unstable, which means that mercury vapor leaks from amalgam over time. The amount of mercury absorbed from one dental amalgam filling ranges from 2 to 17 μg per day [43]. The amount of mercury release may increase in subjects who use chewing gum or are affected by bruxism, such as autistic patients [43]. In subjects with amalgam fillings, the mercury level in blood or urine is two to five times higher than in those without amalgam fillings, and the concentration of mercury in body tissues is two to 12 times higher in comparison with subjects without amalgam fillings [44–46]. Placental, fetal, and infant mercury burden is highly associated with the number of amalgam fillings of the mother [46–48], and mercury levels in amniotic fluid [49] and breast milk [50] correlate significantly with the number of maternal amalgam fillings.

The first report on the association between mercury and autism was published in the early 1990s; it was suggested that organic mercury is a human behavioral teratogen, being related to seizure disorders, childhood schizophrenia, early-onset emotional disturbances, and autism [51]. In 2000, the National Research Council of the US National Academy explained the mechanism behind the above-mentioned hypothesis by stating that the developing nervous system is a sensitive target organ for low-dose mercury exposure [52]. Later, other researchers reported that mercury exposure can cause immune, sensory, neurological, motor, and behavioral dysfunctions [53–55].

Evidence on the relationship between prenatal mercury exposure from maternal amalgam and the severity of autism is still limited. To the best of our knowledge, the only clinical study has been performed by Geier et al. [56], who reported that pregnant women exposed to mercury from six or more dental amalgam fillings during their pregnancy were significantly (3.2-fold) more likely to have children with severe autism rather than (mild) ASD than mothers with five or fewer amalgam restorations. The major challenge involved in performing new studies in this area is to limit the confounding variables, namely other sources of mercury exposure. In general, there are four main accepted sources of mercury coming into contact with humans, i.e. pollution, fish products, mercury-containing vaccinations, and amalgam restorations (Figure 2). Mercury can also be found in different concentrations in bleaching creams, toothpastes, lens solutions, antiseptics, and immunotherapy solutions [55–57].

With the limited information concerning amalgam hazards, it has been suggested that the mercury in dental fillings can be considered safe [58]. However, this may not be true, since the link between mercury exposure and autism also includes the subject's susceptibility. It has been proposed that when an infant or fetus has genetic or biochemical susceptibility, i.e. a decreased ability to remove mercury after exposure, can autism develop [53,55].

According to Echeverria et al. [59], coproporphyrinogen oxidase polymorphism alters the impact of mercury on cognitive mood scores. Furthermore, a quarter of the US population is polymorphic for this genotype. Another reason for the acceptance of amalgam as a safe filling material is because it does not

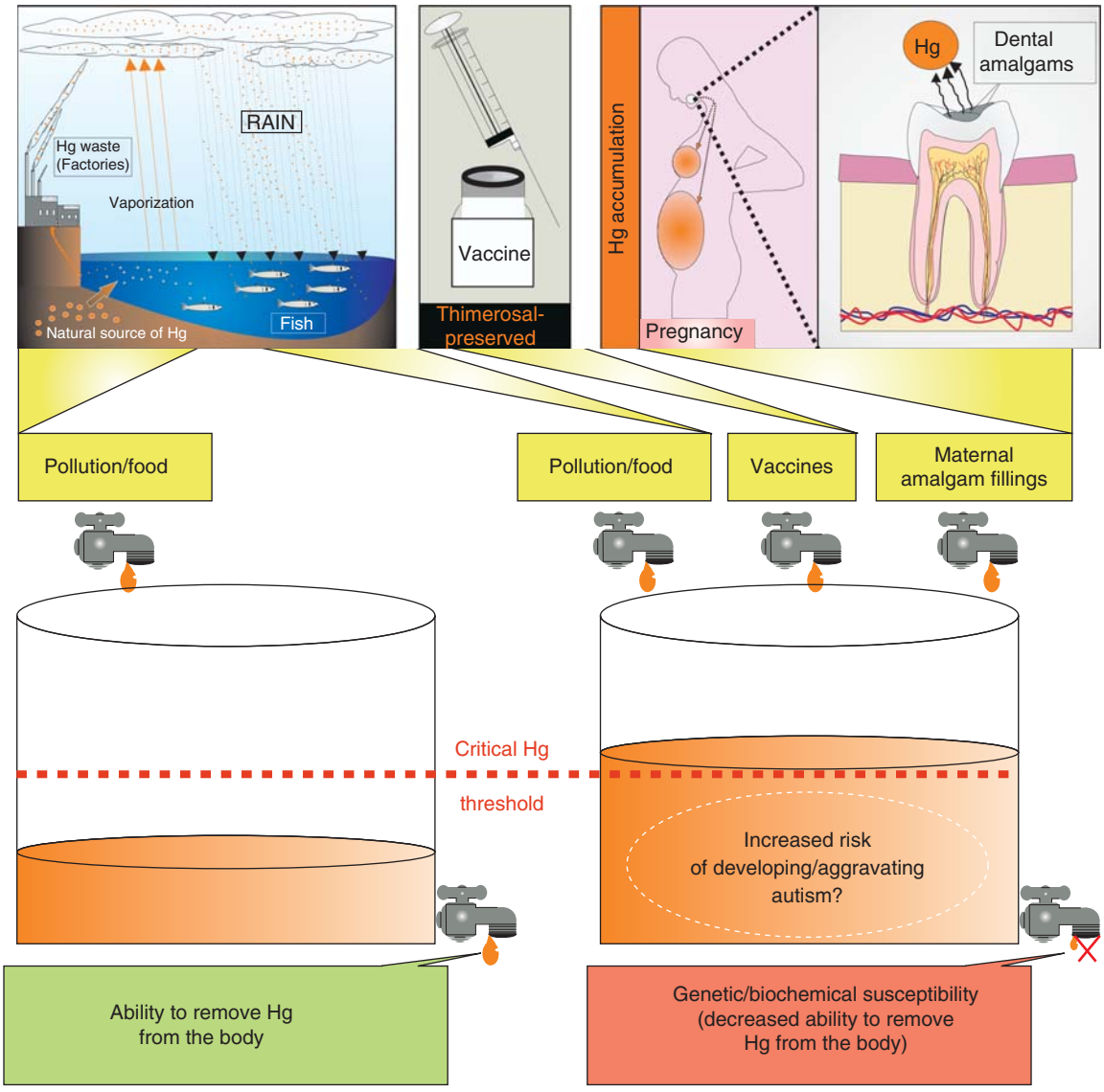

Figure 2. Cumulative mercury (Hg) exposure-based hypothesis for the development and/or aggravation of autism. There seems to be a positive correlation between the number of maternal amalgam fillings and the levels of Hg detected in both breast milk and amniotic fluid during pregnancy [47–50]. Moreover, having ≥6 amalgam fillings correlates positively with the child's probability of later being diagnosed with severe autism [56]. Therefore, it is possible that accumulated doses of Hg from different sources (e.g. pollution, maternal fish consumption, vaccinations, and dental amalgams) during infant development, together with a decreased ability to remove mercury from the body [59], could actually increase the probability of developing and/or aggravating autism among children [53,55].

raise the total blood mercury level above the safety limit (5.8 μg/l) by itself [58]. However, it must be kept in mind that accumulative doses of mercury from different sources, such as pollution, maternal fish consumption, vaccinations, and dental amalgams during infant development, may easily exceed the safety limit (Figure 2). In contrast to urine mercury levels, where the mercury falls to baseline values within weeks, mercury can stay in the brain and the CNS for up to 20 years [60]. Therefore, it is useful to consider the statement of the US Public Health Service and American Academy of Pediatrics, in which it was clearly stated that "all government agencies have to work rapidly toward reducing children's exposure to mercury from all sources" [55].

The 'challenge' of oral health interventions for autistic people

Behavioral problems, including hyperactivity and quick frustration, can definitively complicate the oral health care of patients with autism [61,62]. The invasive nature of oral care triggers violent undesired responses and self-injurious behavior, such as head banging or temper tantrums [13]. Moreover, damaging oral habits, e.g. picking at the gingiva, lip biting, and bruxism, are usually present in these patients [16]. They may exhibit abnormal responses and a higher sensitivity to various sensory stimuli, such as sound, touch, and bright colors [63]. Nevertheless, reactions vary depending on the patient

Table I. Autism-associated behavioral obstacles during oral healthcare interventions.

Management problem	Symptoms	Selected references
Behavioral	Anxiety, combative behavior, hyperactivity, quick frustration	[2]
Unusual responses to stimuli	Sound, bright colors, touch	[63]
Aversions	Oral, touch	[63]
Damaging oral habits	Bruxism, lip biting, abnormal sleep patterns	[16]
Seizures	Chip teeth or bite the tongue or cheeks	[61,67]

(Table I). Interestingly, a number of autistic patients overreact to noise and tactile stimuli, while exposure to either pain or heat may not provoke any reaction at all.

Seizures can be associated with autism but are usually controlled by the use of anticonvulsant therapy [64]. The mouth is always at risk of being damaged during a seizure because autistic patients often chip their teeth or bite their tongue or cheeks. When seizure disorders are controlled, no problems arise with these patients in the dental office. However, there are autistic patients who are extremely sensitive to changes in their environment and, therefore, need more specialized attention by healthcare professionals, who should be prepared for this particularity.

In general, knowledge among dentists and oral healthcare professionals about the characteristics of autism and the appropriate therapy will tremendously improve the clinical attention needed by these patients. Drugs commonly used for autism-associated features display diverse systemic side effects, such as depression, diarrhea, nausea, somnolence, orofacial side effects, and adverse orofacial interactions with drugs frequently used in dentistry [14,65]. For example, in the case of autistic patients with symptoms of attention-deficit hyperactivity disorder, for which the therapy often includes stimulants, such as amphetamine and dextroamphetamine, co-administration of the analgesic meperidine for the treatment of pain could result in hypotension, fever, and even respiratory collapse in the worst-case scenario. These stimulants may also interact with relatively large doses of the narcotic pain-reliever propoxyphene, producing excessive CNS stimulation and seizure activity [66]. Therefore, dental therapeutic agents should be cautiously used in these cases, taking into account possible adverse drug interactions.

Conclusions

Orofacial pain can easily elude medical diagnosis in autistic patients and remain a 'silent disease', masked by the lack of ability of affected patients to clearly express their symptoms due to deficits involving communication and reciprocal social interaction. It is also possible that symptoms remain unobserved by either the family or their physician. Better comprehension of this syndrome could alert clinicians to the need to consider orofacial pain and its relatively high prevalence within the general population as one of the possible reasons for idiopathic aggravation of autism-associated behavioral core symptoms among autistic patients.

Acknowledgements

This work was supported by the National Council for Scientific and Technological Development (CNPq) of the Federal Republic of Brazil. F. Z.-C. is grateful to the Marie Curie Early Stage Research Training (EST) program for his previous funding.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Gadia CA, Tuchman R, Rotta NT. Autism and pervasive developmental disorders. J Pediatr (Rio J) 2004;80:S83–94 (in Portugeuse).
[2] Casanova MF. The neuropathology of autism. Brain Pathol 2007;17:422–33.
[3] Rapin I, Tuchman RF. Autism: definition, neurobiology, screening, diagnosis. Pediatr Clin North Am 2008;55: 1129–46, viii.
[4] Zimmermann M. Pathobiology of neuropathic pain. Eur J Pharmacol 2001;429:23–37.
[5] Scully C, Shotts R. ABC of oral health. Mouth ulcers and other causes of orofacial soreness and pain. BMJ 2000;321: 162–5.
[6] Siqueira JT, Lin HC, Nasri C, Siqueira SR, Teixeira MJ, Heir G, et al. Clinical study of patients with persistent orofacial pain. Arq Neuropsiquiatr 2004;62:988–96.
[7] Sarlani E, Balciunas BA, Grace EG. Orofacial pain–Part I: Assessment and management of musculoskeletal and neuropathic causes. AACN Clin Issues 2005;16:333–46.
[8] Sarlani E, Balciunas BA, Grace EG. Orofacial Pain–Part II: Assessment and management of vascular, neurovascular, idiopathic, secondary, and psychogenic causes. AACN Clin Issues 2005;16:347–58.
[9] Spencer CJ, Gremillion HA. Neuropathic orofacial pain: proposed mechanisms, diagnosis, and treatment considerations. Dent Clin North Am 2007;51:209–24.
[10] Graff-Radford SB. Facial pain. Curr Opin Neurol 2000;13: 291–6.
[11] Haraldstad K, Sorum R, Eide H, Natvig GK, Helseth S. Pain in children and adolescents: prevalence, impact on daily life, and parents' perception, a school survey. Scand J Caring Sci 2010 Apr 13 [Epub ahead of print].
[12] Sessle BJ. Why are the diagnosis and management of orofacial pain so challenging? J Can Dent Assoc 2009;75:275–7.
[13] Friedlander AH, Yagiela JA, Paterno VI, Mahler ME. The pathophysiology, medical management, and dental implications of autism. J Calif Dent Assoc 2003;31:681–2, 684, 684–91.

[14] Friedlander AH, Yagiela JA, Paterno VI, Mahler ME. The neuropathology, medical management and dental implications of autism. J Am Dent Assoc 2006;137:1517–27.
[15] Clark GT, Ram S. Four oral motor disorders: bruxism, dystonia, dyskinesia and drug-induced dystonic extrapyramidal reactions. Dent Clin North Am 2007;51:225–43, viii–ix.
[16] Muthu MS, Prathibha KM. Management of a child with autism and severe bruxism: a case report. J Indian Soc Pedod Prev Dent 2008;26:82–4.
[17] Lavigne GJ, Khoury S, Abe S, Yamaguchi T, Raphael K. Bruxism physiology and pathology: an overview for clinicians. J Oral Rehabil 2008;35:476–94.
[18] Svensson P, Jadidi F, Arima T, Baad-Hansen L, Sessle BJ. Relationships between craniofacial pain and bruxism. J Oral Rehabil 2008;35:524–47.
[19] Tolosa E, Marti MJ. Blepharospasm-oromandibular dystonia syndrome (Meige's syndrome): clinical aspects. Adv Neurol 1988;49:73–84.
[20] Klawans HL, Tanner CM, Goetz CG. Epidemiology and pathophysiology of tardive dyskinesias. Adv Neurol 1988; 49:185–97.
[21] Blanchet PJ, Rompre PH, Lavigne GJ, Lamarche C. Oral dyskinesia: a clinical overview. Int J Prosthodont 2005; 18:10–9.
[22] Casey DE. Pathophysiology of antipsychotic drug-induced movement disorders. J Clin Psychiatry 2004;65(Suppl 9): 25–8.
[23] Blanchet PJ, Popovici R, Guitard F, Rompre PH, Lamarche C, Lavigne GJ. Pain and denture condition in edentulous orodyskinesia: comparisons with tardive dyskinesia and control subjects. Mov Disord 2008;23:1837–42.
[24] Lee KH. Oromandibular dystonia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:491–6.
[25] Carlson CD, Cavazzoni PA, Berg PH, Wei H, Beasley CM, Kane JM. An integrated analysis of acute treatment-emergent extrapyramidal syndrome in patients with schizophrenia during olanzapine clinical trials: comparisons with placebo, haloperidol, risperidone, or clozapine. J Clin Psychiatry 2003; 64:898–906.
[26] Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373:31–41.
[27] Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. Paediatr Drugs 2007;9:343–54.
[28] Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004;140:441–51.
[29] Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. Pain Suppl 1986;3:S1–226.
[30] Ren K, Dubner R. Neuron-glia crosstalk gets serious: role in pain hypersensitivity. Curr Opin Anaesthesiol 2008;21:570–9.
[31] Okada-Ogawa A, Suzuki I, Sessle BJ, Chiang CY, Salter MW, Dostrovsky JO, et al. Astroglia in medullary dorsal horn (trigeminal spinal subnucleus caudalis) are involved in trigeminal neuropathic pain mechanisms. J Neurosci 2009;29: 11161–71.
[32] Guo W, Wang H, Watanabe M, Shimizu K, Zou S, LaGraize SC, et al. Glial-cytokine-neuronal interactions underlying the mechanisms of persistent pain. J Neurosci 2007;27:6006–18.
[33] Avivi-Arber L, Lee JC, Sessle BJ. Effects of incisor extraction on jaw and tongue motor representations within face sensorimotor cortex of adult rats. J Comp Neurol 2010; 518:1030–45.
[34] Suter MR, Wen YR, Decosterd I, Ji RR. Do glial cells control pain? Neuron Glia Biol 2007;3:255–68.
[35] Nelson KB, Grether JK, Croen LA, Dambrosia JM, Dickens BF, Jelliffe LL, et al. Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation. Ann Neurol 2001;49:597–606.
[36] Miyazaki K, Narita N, Sakuta R, Miyahara T, Naruse H, Okado N, et al. Serum neurotrophin concentrations in autism and mental retardation: a pilot study. Brain Dev 2004;26:292–5.
[37] Pardo CA, Eberhart CG. The neurobiology of autism. Brain Pathol 2007;17:434–47.
[38] Zakrzewska JM. Facial pain: neurological and non-neurological. J Neurol Neurosurg Psychiatry 2002;72 (Suppl 2):ii27–ii32.
[39] Scully C, Porter S. Orofacial disease: update for the clinical team: 9. Orofacial pain. Dent Update 1999;26:410–17.
[40] Benoeliel R, Pertes RA, Eliav E. Orofacial pain: Current therapy in pain. In: Smith H, editor. Saunders Elsevier: Philadelphia, PA; 2009. p. 121.
[41] Ricketts DN, Pitts NB. Traditional operative treatment options. Monogr Oral Sci 2009;21:164–73.
[42] Palkovicova L, Ursinyova M, Masanova V, Yu Z, Hertz-Picciotto I. Maternal amalgam dental fillings as the source of mercury exposure in developing fetus and newborn. J Expo Sci Environ Epidemiol 2008;18:326–31.
[43] Guzzi G, Grandi M, Cattaneo C. Should amalgam fillings be removed? Lancet 2002;360:2081.
[44] Pizzichini M, Fonzi M, Giannerini F, Mencarelli M, Gasparoni A, Rocchi G, et al. Influence of amalgam fillings on Hg levels and total antioxidant activity in plasma of healthy donors. Sci Total Environ 2003;301:43–50.
[45] Weiner JA, Nylander M. The relationship between mercury concentration in human organs and different predictor variables. Sci Total Environ 1993;138:101–15.
[46] Mutter J, Naumann J, Guethlin C. Comments on the article "the toxicology of mercury and its chemical compounds" by Clarkson and Magos (2006). Crit Rev Toxicol 2007;37: 537–49.
[47] Ask K, Akesson A, Berglund M, Vahter M. Inorganic mercury and methylmercury in placentas of Swedish women. Environ Health Perspect 2002;110:523–6.
[48] Drasch G, Schupp I, Hofl H, Reinke R, Roider G. Mercury burden of human fetal and infant tissues. Eur J Pediatr 1994; 153:607–10.
[49] Luglie PF, Campus G, Chessa G, Spano G, Capobianco G, Fadda GM, et al. Effect of amalgam fillings on the mercury concentration in human amniotic fluid. Arch Gynecol Obstet 2005;271:138–42.
[50] Vimy MJ, Hooper DE, King WW, Lorscheider FL. Mercury from maternal "silver" tooth fillings in sheep and human breast milk. A source of neonatal exposure. Biol Trace Elem Res 1997;56:143–52.
[51] Nelson BK. Evidence for behavioral teratogenicity in humans. J Appl Toxicol 1991;11:33–7.
[52] National Research Council Committee on the toxicology of methymercury. Toxicological effects of methylmercury. Washington D.C.: Nacional Academy Press; 2000.
[53] Mutter J, Naumann J, Schneider R, Walach H, Haley B. Mercury and autism: accelerating evidence? Neuro Endocrinol Lett 2005;26:439–46.
[54] Bernard S, Enayati A, Roger H, Binstock T, Redwood L. The role of mercury in the pathogenesis of autism. Mol Psychiatry 2002;7(Suppl 2):S42–3.
[55] Geier DA, King PG, Sykes LK, Geier MR. A comprehensive review of mercury provoked autism. Indian J Med Res 2008; 128:383–411.
[56] Geier DA, Kern JK, Geier MR. A prospective study of prenatal mercury exposure from maternal dental amalgams and autism severity. Acta Neurobiol Exp (Wars) 2009;69: 189–97.

[57] Palmer RF, Blanchard S, Wood R. Proximity to point sources of environmental mercury release as a predictor of autism prevalence. Health Place 2009;15:18–24.
[58] Clarkson TW, Magos L. The toxicology of mercury and its chemical compounds. Crit Rev Toxicol 2006;36: 609–62.
[59] Echeverria D, Woods JS, Heyer NJ, Rohlman D, Farin FM, Li T, et al. The association between a genetic polymorphism of coproporphyrinogen oxidase, dental mercury exposure and neurobehavioral response in humans. Neurotoxicol Teratol 2006;28:39–48.
[60] Sugita M. The biological half-time of heavy metals. The existence of a third, "slowest" component. Int Arch Occup Environ Health 1978;41:25–40.
[61] Loo CY, Graham RM, Hughes CV. The caries experience and behavior of dental patients with autism spectrum disorder. J Am Dent Assoc 2008;139:1518–24.
[62] Rada RE. Controversial issues in treating the dental patient with autism. J Am Dent Assoc 2010;141:947–53.
[63] Rogers SJ, Ozonoff S. Annotation: what do we know about sensory dysfunction in autism? A critical review of the empirical evidence. J Child Psychol Psychiatry 2005;46:1255–68.
[64] Tuchman R. Treatment of seizure disorders and EEG abnormalities in children with autism spectrum disorders. J Autism Dev Disord 2000;30:485–9.
[65] Malone RP, Waheed A. The role of antipsychotics in the management of behavioural symptoms in children and adolescents with autism. Drugs 2009;69:535–48.
[66] Friedlander AH, Yagiela JA, Mahler ME, Rubin R. The pathophysiology, medical management and dental implications of adult attention-deficit/hyperactivity disorder. J Am Dent Assoc 2007;138:475–82.
[67] Robbins MR. Dental management of special needs patients who have epilepsy. Dent Clin North Am 2009;53:295–309, ix.