REVIEWS

Adv Clin Exp Med 2011, **20**, 4, 521–525
ISSN 1230-025X
© Copyright by Wroclaw Medical University

Mieszko Więckiewicz[1], Anna Paradowska[2], Beata Kawala[3], Włodzimierz Więckiewicz[4]

SAPHO Syndrome as a Possible Cause of Masticatory System Anomalies – a Review of the Literature

Zespół SAPHO jako możliwa przyczyna zaburzeń układu ruchowego narządu żucia – przegląd piśmiennictwa

[1] Division of Dental Materials, Faculty of Dentistry, Wroclaw Medical University, Poland
[2] Division of Dentofacial Anomalies, Department of Maxillofacial Orthopedics and Orthodontics, Faculty of Dentistry, Wroclaw Medical University, Poland
[3] Department of Maxillofacial Orthopedics and Orthodontics, Faculty of Dentistry, Wroclaw Medical University, Poland
[4] Division of Implantoprosthetics and Functional Disturbances of the Stomatognathic System, Faculty of Dentistry, Wroclaw Medical University, Poland

Abstract

SAPHO is a rare syndrome of unknown – probably mutlifactorial – etiology, affecting the joints, bones and skin. The name is an acronym from synovitis, acne, pustulosis, hyperostosis and osteitis. SAPHO occurs predominantly in young females. Bone defects are the most prevalent feature of the syndrome. The mandible is affected in about 10% of the cases and there are typical osteitic and sclerotic lesions. Limitation of motion in the temporomandibular joint, swelling and pain are the most common symptoms of TMJ involvement. Complete ankylosis is a rare condition. Anti-inflammatory non-steroid drugs, antibiotics and (in severe cases) tumor necrosis factor inhibitors are the most commonly used medications. In patients with ankylosis of the temporomandibular joint, follow-up observations indicate that surgical reconstruction of the joint seems to be the best solution (**Adv Clin Exp Med 2011, 20, 4, 521–525**).

Key words: SAPHO, TMJ disorders, ankylosis.

Streszczenie

SAPHO jest rzadką chorobą stawów, kości i skóry o nieznanej, prawdopodobnie wieloczynnikowej etiologii. Nazwa zespołu to akronim wzięty od słów *synovitis*, *acne*, *pustulosis*, *hyperostosis* i *osteitis* (zapalenie błony maziowej, trądzik, łuszczyca, hiperostoza, osteoza). SAPHO pojawia się częściej u młodych kobiet. Najczęściej występującą cechą zespołu są ubytki kości. Żuchwa jest objęta procesem chorobowym u ok. 10% chorych i występują w niej typowe zmiany sklerotyczne i zapalne kości. Ograniczenie ruchów w stawie skroniowo-żuchwowym (s.s.ż.), obrzęk i ból są najczęściej występującymi objawami zajęcia s.s.ż. Całkowita ankyloza jest rzadkim zjawiskiem. Niesteroidowe leki przeciwzapalne, antybiotyki i antagoniści czynnika martwicy nowotworów TNF są najczęściej stosowanymi lekami. U pacjentów z ankylozą w obrębie s.s.ż., chirurgiczna rekonstrukcja stawu wydaje się najlepszym postępowaniem terapeutycznym. Badania kontrolne wskazują, że jest to dobra metoda leczenia (**Adv Clin Exp Med 2011, 20, 4, 521–525**).

Słowa kluczowe: SAPHO, zaburzenia stawu skroniowo-żuchwowego, ankyloza.

SAPHO syndrome is a disease affecting the joints, bones and skin; it occurs in 1/10,000 people. The name of the syndrome was first used by Chamot et al. in 1987, and is an acronym for synovitis, acne, pustulosis, hyperostosis and osteitis [1, 2]. The real etiology remains unknown, but it may involve genetic, inflammatory and immunologic factors [1]. Usually, the syndrome is associated with sterile osseitis, but several bacteria may be connected with the disease. Pathogens that may

be involved are: *Staphylococcus aureus, Staphylococcus epidermidis* and *Proprionibacterium acnes* isolated from skin and joints, *Veillonella, Eikenella* and *Actinomyces spp*. isolated from mandibular lesions. It has been shown that *P.acnes* triggers the patients' immune systems and increases levels of IL-1, IL-8 and TNF-α [1–5]. The bacterial cells mimic host cells (molecular mimicry) and therefore are not recognized by host body as "aliens" and they are not fully eliminated by the host. Although a multifactorial background is hypothesized, genetic susceptibility is a crucial factor. The most probable gene is CARD15 (also associated with Crohn's disease), leading to overactivation of nuclear factor kappa-B [1–5]. Stress is another factor suspected of contributing to the pathogenesis of SAPHO syndrome [6].

The syndrome occurs more often in females. It is commonly observed in childhood and early adulthood, and rarely after the sixth decade of life [1].

The most common changes present in SAPHO syndrome are presented in Table 1. Bone defects are the most prevalent feature of the syndrome. Changes in bone structure are mostly observed in the sternum, ribs and clavicles. Rarely, other bones (e.g. the spine, sacrum, ilium, peripheral long bones) are involved. The mandible is affected in about 10% of the afflicted, and there are typical osteitic and sclerotic lesions. The most commonly affected sites are the ascending ramus and posterior body of the mandible. Bones may ache, which can lead to sleep disturbances (especially since bone pain increases during the night) as well as affecting daily life. Hyperosteosis and periosteal thickening are also typical symptoms in mandible involvement [1, 7–9]. Other joints are more commonly involved. The symptoms of chronic arthritis usually affect larger joints (the sternocostal and sternoclavicular joints in about 73% of the cases, the manubiosternal joint in about 34%, the sacroiliac joint in about 20%). The involvement of the joints is usually unilateral [1, 10]. Acute pseudoarthritis that may mimic bacterial inflammation is also observed [1]. Limitation of motion in the temporomandibular joint (TMJ), leading to ankylosis, is often present. Pain when swallowing is also observed [1, 8]. Skin manifestations occur in about 75% of all cases, and may precede, occur simultaneously or follow the osteoarticular manifestations. The exacerbation of skin lesions usually accompanies an improvement in bone lesions [1]. Osteitis may be present in the synovitic tissues, eg. the upper thoracic wall [10]. Smith et al. reported an ocular manifestation of this syndrome, with swelling and bone lesions in the clinoid process and sphenoidal wings [11].

SAPHO syndrome is occasionally associated with inflammatory bowel diseases (mainly Crohn's disease), which occur in fewer than 4% of the cases; while 7 to 25% of Crohn's disease patients present joint involvement [1, 10, 12].

Kahn et al. described the diagnostic criteria for SAPHO syndrome in 1994 [13, after 1]. According to those authors, the presence of one of the criteria is enough to diagnose SAPHO. The diagnostic criteria are presented in Table 2, and the exclusion criteria for SAPHO syndrome are shown in Table 3 [1, 2].

Diagnosing SAPHO syndrome is very difficult. Not all of the symptoms are present, and some of them may manifest subtly. The symptoms do not always occur simultaneously (e.g. skin lesions may precede bone manifestations). Laboratory tests are usually normal, but a slight elevation of ESR (erythrocyte sedimentation rate) or C-creative protein (CRP) might be observed [1]. Elevated lev-

Table 1. Symptoms observed in SAPHO syndrome [1, 6–10]

Tabela 1. Obserwowane zmiany w zespole SAPHO [1, 6–10]

Region of the body/laboratory results (Obszar ciała/badania laboratoryjne)	Observed changes (Obserwowane zmiany)
Bones (Kości)	hyperostosis, osteitis, chronic recurrent multifocal osteomyelitis, sacroilitis
Joints (Stawy)	acute pseudoinfectious arthritis mimicking a bacterial disease, chronic lesions, psoriatic arthritis, enthesitis
Skin (Skóra)	psoriasis vulgaris, sores, palmoplantar pustulosis (PPP), forms of PPP, acne (acne conglobata, acne fulminans), hydra denitis suppurativa
Other (Inne)	chronic bowel disease, osteitis of upper thoracic wall
Cytokines (Cytokiny)	elevated levels of IL-1, IL-8, IL-18, TNF-α; increase in ESR and C-reactive protein levels

Table 2. The criteria for SAPHO syndrome [Kahn et al. after McPhilips et al.]

Tabela 2. Kryteria diagnostyczne zespołu SAPHO [13 za 1]

1. Multifocal osteitis with or without skin manifestations (Wieloogniskowe zapalenie kości z lub bez objawów skórnych)
2. Sterile acute or chronic joint inflammation associated with either pustules or psoriasis of palms and soles, or acne, or hidradenitis (Jałowe ostre lub przewlekłe zapalenie stawów związane z krostami, łuszczycą dłoni i stóp, trądzikiem lub *hidradenitis*)
3. Sterile osteitis in the presence of one of the skin manifestations mentioned below (Jałowe zapalenie kości w obecności jednego z wymienionych powyżej objawów skórnych)

Table 3. Exclusion criteria for SAPHO syndrome [1]

Tabela 3. Kryteria wykluczające zespół SAPHO [1]

Infectious osteitis (Infekcyjne zapalenie kości)
Bone tumors (Guzy kości)
Non-inflammatory condensing lesions of the bone (Niezapalne ubytki kostne)

els of pro-inflammatory cytokines IL-8 and IL-18 and tumor necrosis factor α (TNF-α) are observed [1, 8]. HLA (human leukocyte antigen) B-27 has been reported as positive in up to 30% of the cases; more recent studies show the level as 4–14% [2, 9, 10, 14].

The use of medications is usually enough to treat the condition. Non-steroidal anti-inflammatory drugs are often used; they may relieve the skin and joint problems, but remission after such treatment is possible. If this therapy fails, other drugs (such as colchicine, corticosteroids, bisphosphonates, metotrexate, sulfasalazine, infliximab or zoledronic acid) are used [1, 2, 9, 15]. The use of tumor necrosis factor (TNF) inhibitors and infliximab has been reserved for more severe cases and is the third line of treatment [16]. Therapy with TNF inhibitors should be very cautious, as it can exacerbate cutaneous symptoms [17]. Antimicrobal therapy is used only when bacterial diseases of skin are observed. If the syndrome is recognized too late, surgical treatment is often necessary [9]. Unfortunately, the syndrome has a strong tendency to relapse [18]. In addition to pharmacological therapy, psychological therapy can be useful, as facial pain may cause depression and reccurent fear [19].

Differential diagnosis should consider malignancy, infections or metabolic conditions (e.g. Paget's disease), as SAPHO syndrome symptoms may resemble those conditions [9]. Crohn's disease and ulcerative colitis should also be considered due to cutaneous manifestations (e.g. *Pyoderma gangrenosum*) in both diseases and the possibility of bowel disorders. Differential diagnosis should also consider Sweet's syndrome and other neutrophilic dermatoses. The similarities of SAPHO symptoms to Majeed syndrome and PAPA syndrome mean that genetic testing is necessary to exclude those syndromes [20].

Temporomandibular Joint Involvement

TMJ involvement in SAPHO syndrome has rarely been described [1, 18]. The mandible is affected in about 10% of SAPHO cases. The most commonly affected sites are the ascending ramus and posterior body of the mandible. Hyperosteosis and periosteal thickening are typical in mandible involvement. A "bull's head" pattern may be observed in images of the sternocostoclavicular region, although this is not common [1, 7, 8, 20]. Limitation of motion in the TMJ, swelling and pain are also often present; the swelling can be associated with erythema and edema. Crepitation can also be the symptom. TMJ involvement in SAPHO is associated with mandibular asymmetry [1, 8, 15, 21, 22]. TMJ symptoms may also include bruxism [1]. Even though there are symptoms that may indicate dental problems, no dental foci are found in the oral cavity [22]. For patients with SAPHO syndrome with TMJ involvement, TMJ and facial pain are the most severe problems. TMJ tomography shows areas of osteitis and sclerosis of the alveolar bone, reactive cortical thickening, ankylosis and degenerative changes of the condyle [1, 7]. Masseteric hypertrophy is characterized by calcifications and fibrosis. MRI images reveal arthritic changes within the condyle, articular disc degeneration and bony ankylosis. Complete ankylosis of the TMJ is rare and to the authors' knowledge has been reported only a few times [1, 7].

Usually there are no signs of infection within the TMJ, so the use of antibiotics is not required, although azithromycin seems to be helpful [1, 7]. TMJ involvement can also be associated with progressive loss of hearing, leading to deafness and tinnitus [23, 24].

The treatment of SAPHO syndrome within the TMJ is not very different from treatment of

the systemic disease. Anti-inflammatory non-steroid drugs are most commonly used, but they are not very effective in treating SAPHO symptoms in the TMJ, as usually there are no significant signs of inflammation. As noted above, azithromycin seems to be helpful [1, 7], as well as hyperbaric oxygen therapy [7]. Zolodronic acid can be used to treat mandibular swelling and to relieve jaw pain [15]. Pamidronate infusions also lead to remission of the disease [22, 25]. Decortication of the mandible is helpful in some cases, but patient satisfaction is either partial or limited. In patients with ankylosis of the TMJ, surgical reconstruction of the joint seems to be the best solution, and relieves pain. Often, a partial or total condylectomy, coronoidectomy and arthroplasty is necessary to reconstruct the articular eminence and fossa; new methods of treatment include TMJ prostheses [1, 7, 22, 26, 27]. Unfortunately, surgical treatment is not always fully successful – there is a possibility of reankylosis of the TMJ. Alloplastic reconstruction (with a titanium condylar) is therefore preferred over a reconstruction using bone (e.g. a rib). To prevent reankylosis, a pedicled myofascial temporal muscle flap can be placed in the joint socket [7]; and an investigation of that type of treatment in a sheep model showed very good results with a significant decrease in the possibility of ankylosis [28]. Histologic examinations of ankylotic joints show nonsuppurative chronic osteomyelitis [22].

Follow-up observations show that surgical treatment of ankylotic joints is a good and stable method of treatment for SAPHO in the TMJ. It relieves all of the TMJ symptoms, including limitation of mandible motion; the patient regains full mandible functionality after about two years [7].

SAPHO syndrome may involve the temporomandibular joint and lead to its ankylosis. Therefore, clinicians should always consider it during diagnostic procedures for masticatory system problems. Surgical intervention is often necessary to treat TMJ problems; it relieves pain and improves jaw motion. However, early diagnosis may prevent the need for surgical treatment.

References

[1] **McPhillips A, Wolford LM, Rodrigues DB:** SAPHO syndrome with TMJ involvement: review of the literature and case presentation. Int J Oral Maxillofac Surg 2010, 39, 1160–1167.

[2] **Chamot AM, Benhamou CL, Kahn MF, Bernaneck L, Kapelan G, Prost A:** Le syndrome acne-pustulose-hyperostose-osteite (SAPHO) results d'une enuete nationale. 85 observations. Rev Rhum Osteoartic 1987, 54, 187–196.

[3] **Rozin AP:** SAPHO syndrome: is a range of pathogen associated rheumatic diseases extended. Arthritis Res Ther 2009, 11, 131–133.

[4] **Dobrowolska-Zachwieja A, Linke K, Jakubowska-Burek L, Kucharski M:** Genetic background of inflammatory bowel disease. Gastroenterol Pol 2009, 16, 6, 421–426.

[5] **Neubauer K, Kempiński R, Poniewierka E:** Anti-tumor necrosis factor alpha antibodies for remission maintenance therapy in inflammatory bowel disease. Adv Clin Exp Med 2010, 19, 2, 143–150.

[6] **Zhao Z, Li Y, Li Y, Zhao H, Li H:** Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome with review of the relevant Publisher work. J Dermatol 2011, 38, 155–159.

[7] **Muller-Richter UDA, Roldan JC, Mortl M, Behr M, Reichert TE, Driemel O:** SAPHO syndrome with ankylosis of the temporomandibular joint. Int J Oral Maxillofac Surg 2009, 38, 1335–1341.

[8] **Suei Y, Taguchi A, Tanimoto K:** Diffuse sclerosing osteomyelitis of the mandible: its characteristics and possibile relationship to Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO) syndrome. J Oral Maxillofac Surg 1996, 54, 1194–1196.

[9] **Mann B, Shaerf DA, Sheeraz A, Skinner J, Saifuddin A:** SAPHO syndrome presenting as widespread bony metastatic disease of unknown origin. Rheumatol Int 2011, 1742–1745.

[10] **Salles M, Olive A, Perez-Andres R, Holgado S, Mateo L, Riera E, Tena X:** The SAPHO syndrome: a clinical and imaging study. Clin Rheumatol 2011, 30, 245–249.

[11] **Smith M, Buller A, Radford R, Laitt R, Leatherbarrow B:** Ocular presentation of the SAPHO syndrome. Br J Opthalmol 2005, 89, 1069–1070.

[12] **Kosiara M, Łapińska J, Semianów-Wejchert J, Paradowski L:** Extraintestinal symptoms of inflammatory bowel disease. Gastroenterol Pol 2009, 16, 6, 475–480.

[13] **Kahn MF, Hayem F, Hayem G, Grossin M:** Is diffuse sclerosing osteomyelitis of the mandible part of the synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome? Analysis of 7 cases. Oral Surg Oral Med Oral Pathol 1994, 78, 594–598.

[14] **Hayem G, Bouchaud-Chabot A, Benali K, Roux S, Palazzo E, Silbermann-Hoffman O, Kahn MF, Meyer O:** SAPHO syndrome: a long-term follow-up study of 120 cases. Semin Arthritis Rheum 1999, 29, 159–171.

[15] **Kopterides P, Pikazis D, Koufos C:** Successful treatment of SAPHO syndrome with zoledronic acid. Arthritis Rheum 2004, 50, 9, 2970–2973.

[16] **Castellvi I, Bonet M, Narvaez JA, Molina-Hinojosa JC:** Successful treatment of SAPHO syndrome with adalimumab: a case report. Clin Rheumatol 2010, 29, 1205–1207.

[17] **Massara A, Cavazzini PL, Trotta F:** In SAPHO syndrome anti-TNF-a therapy may induce persistent amelioration of osteoarticular complaints, but may exacerbate cutaneous manifestations. Rheumatology 2006, 45, 730–733.

[18] **Kahn MF, Hayem F, Hayem G, Grossin M:** Is diffuse sclerosing osteomyelitis of the mandible part of the synovitis, acne, pusyulosis, hyperostosis, osteitis (SAPHO) syndrome? Analysis of 7 cases. Oral Surg Oral Med Oral Pathol 1994, 78, 594–598.
[19] **Drobek W:** Analysis of psychological profiles in patients with chronic orofacial pain. Dent Med Probl 2009, 46, 324–327.
[20] **Govoni M, Colina M, Massara A, Trotta F:** SAPHO syndrome and infections. Autoimmunity Rev 2009, 8, 256–259.
[21] **Hurtado-Nedelec M, Chollet-Martin S, Nicaise-Roland P, Grootenboer-Mignot S, Ruimy R, Meyer O, Hayem G:** Characterization of the immune response in the synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome. J Reumatol 2008, 47, 1160–1167.
[22] **Zemann W, Pau M, Feichtinger M, Ferra-Matschy B, Kaercher H:** SAPHO syndrome with affection of the mandible: diagnosis, treatment, and review of literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011, 111, 190–195.
[23] **Amital H, Applbaum YH, Aamar S, Daniel N, Rubinow A:** SAPHO syndrome treated with pamidronate: an open-label study of 10 patients. Rheumatology 2004, 43, 658–661.
[24] **Utumi ER, Sales MAO, Shinohara EH, Takahashi A, Coracin FL, Rocha RG, Cavalcanti MGP:** SAPHO syndrome with temporomandibular joint ankylosis: clinical, radiological, histopathological, and therapeutical correlations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008, 105, e67–e72.
[25] **Marsot-Dupuch K, Doyen JE, Grauer WO, deGivry SC:** SAPHO syndrome of the temporomandibular joint associated with sudden deafness. AJNR Am J Neuroradiol 1999, 20, 902–905.
[26] **Garcia-Marin F, Iriarte-Ortabe JI, Reychler H:** Chronic diffuse sclerosing osteomyelitis of the mandible or mandibular location of S.A.P.H.O. syndrome. Acta Stomatol Beld 1996, 93, 65–71.
[27] **Baltenperger M, Graetz K, Bruder E, Lebeda R, Makek M, Eyrich G:** Is primary chronic oseomyelitis a uniform disease? Proposal of a classification based on a retrospective analysis of patients treateding the past 30 years. J Craniomaxillofac Surg 2004, 32, 43–50.
[28] **Shimizu M, Kurita K, Matsuura H, Ishimaru JI, Goss AN:** The role of muscle grafts in temporomandibular joint ankylosis: short term experimental study in sheep. In J Oral Maxillofac Surg 2006, 35, 842–849.

Address for correspondence:

Mieszko Więckiewicz
Division of Dental Materials, Faculty of Dentistry
Wroclaw Medical University
Krakowska 26
50-425 Wrocław
Poland
Tel.: +48 660 47 87 59
E-mail: m.wieckiewicz@onet.pl

Conflict of interest: None declared

Received: 27.04.2011
Revised: 17.06.2011
Accepted: 1.08.2011