Chronically recurrent osteomyelitis of the jaws demands a lot of patience on the part of both the patient and the treating physician. In many cases, extensive bone resection and reconstruction are the final solution. But everything should be done to avoid this last measure, especially in young adolescent patients.

Generally, chronically recurrent osteomyelitis of the jaws is found in the mandible alone. The pertinent literature does not provide data on which age group of patients is affected most often. Primarily, data of adult patients are reported in the literature. Up to now, only very few publications have dealt with this disease in children and juveniles (ie, patients younger than 18 years). With 1 exception,1 the articles found in the literature were single case reports.2-5

At “Westdeutsche Kieferklinik,” University Hospital Düsseldorf, 4 cases of chronically recurrent mandibular osteomyelitis in juvenile patients were treated in the years 1988 to 2002. Reports in the literature suggest that hyperbaric oxygen therapy (HBO) may be helpful as an adjuvant therapy for chronically recurrent osteomyelitis.6-11 Since a pressure chamber at the University Hospital Düsseldorf allowing HBO was obtained, 3 patients were submitted to adjuvant HBO in addition to conventional treatment.

Mode of Action of HBO

Hyperbaric oxygenation means that, in a pressure chamber, 100% oxygen is inhaled under increased surrounding pressure and significantly increased oxygen uptake is achieved by physical solution of oxygen in blood plasma. Under hyperbaric condi-
tions, oxygen diffusion is optimized\textsuperscript{12,13} (ie, oxygen is reaching body cells whose supply is jeopardized by trauma, inflammation, or disturbed blood circulation). The mechanisms of HBO in the treatment of chronic osteomyelitis are manifold. The major aim of HBO is to increase the partial pressure of oxygen in the diseased bone. Niinikoski and Hunt\textsuperscript{14} and Mader et al\textsuperscript{15} showed that the characteristically low oxygen content in diseased bone was significantly raised by inhalation of 100\% oxygen under hyperbaric conditions. The additional supply of oxygen is of decisive importance for treatment of the hypoxic situation in osteomyelitic tissue:

- HBO induces new formation of capillaries (ie, neoangiogenesis).\textsuperscript{16-18}
- The performance of phagocytes (neutrophilic granulocytes) is determined by the amount of available oxygen (ie, if the amount of oxygen available is not sufficient the performance deteriorates considerably).\textsuperscript{19} Molecular oxygen is taken up by leukocytes and in the oxidative phase transformed into highly energetic oxygen radicals. Consequently, the production rate of free radicals and the capacity of oxidative elimination of bacteria is decisively determined by the local oxygen pressure.\textsuperscript{20}
- In addition, HBO has a direct suppressive effect on anaerobic organisms because many of the anaerobic germs cannot cope with the oxygen radicals by means of protective, intercellular enzymes.\textsuperscript{21}
- The active transport of antibiotics across bacterial walls is not possible under hypoxic conditions or only to a very limited extent.\textsuperscript{22} HBO can induce this transport and intensifies the effect of some antibiotics synergistically.\textsuperscript{15,22,23}
- Collagen synthesis comprises several metabolic steps, depending on oxygen, and is insufficient in the hypoxic environment produced by chronic osteomyelitis. Improved oxygen supply during HBO therapy, as a result of increased oxygen pressure, stimulates and normalizes fibroblast proliferation,\textsuperscript{24-26} as well as collagen synthesis,\textsuperscript{16} and supports the formation of a protective matrix.\textsuperscript{27}
- After their differentiation from fibroblast-like mesenchymal cells into osteoblasts, the osteoblasts produce a layer of immature fibrillary bone. The immature bone is replaced by mature lamellar bone and remodeled functionally by resorption and deposition of osteoclasts and osteoblasts.\textsuperscript{27} It has been demonstrated in several studies that HBO was able to support the process of osteogenesis, which is dependent on oxygen.\textsuperscript{28-32}

### Patients and Methods

Three patients presented the identical clinical picture as follows: variable swelling of soft tissues covering the affected mandibular section, intermittent pains in the affected region, no abscess formation, no discharge of pus or fistula formation, and no signs of sequestrum formation. The case histories and radiologic findings were analyzed retrospectively. All histologic examinations were performed at the Institute of Pathology of University Hospital Düsseldorf.

HBO was performed 5 days per week according to the nationally and internationally approved therapeutic regimen TS 240-90 (240 kPa, 90 minutes of inhalation of 100\% oxygen, total duration per treatment; 134 minutes).

### Report of Cases

**CASE 1**

An 11-year-old girl presented with varying pain and swelling of the left cheek. Tentative diagnosis by magnetic resonance imaging (MRI) was chronic osteomyelitis. The patient was admitted to the hospital. Therapy included high-dosage intravenous antibiotics (penicillin G, 5 million IU/3 times daily over 4 weeks). For safety reasons, the germ of the left third molar was removed. At the same time, a biopsy was taken from the mandible and soft tissue. Histologic findings were fibrosing chronic osteomyelitis. The clinical symptoms regressed and the patient was discharged 4 weeks later. She experienced recurrence 2 months later, with the same symptoms (Figs 1A-D). High-dose antibiotics were administered again, which included targocid 800 mg/day and adjuvant HBO according to the therapy regimen mentioned above. The combination therapy included a total of 40 sessions; the patient was discharged from the hospital without any remaining symptoms. Follow-up MRI was conducted 6 months later (Figs 1E,F). There has not been any recurrence or return of symptoms after 74 months of follow-up.

**CASE 2**

A 13-year-old boy presented after the unerupted left second molar had been exposed surgically 2 years earlier and an eruption cyst, also located in the region of the left second molar, had been removed 15 months later. Subsequently, he experienced recurrent pain and swelling in the region of the angle of the mandible. Computed tomography 3 months later confirmed the clinical diagnosis of chronic osteomyelitis. He was treated with intravenous antibiotic therapy and decortication of the left angle of the mandible. Histologic finding was fibrosing chronic osteomyelitis. The boy was discharged from hospital free of
FIGURE 1. A, Orthopantomogram revealing an almost normal condition in the region of the left mandible. B, MRI following gadolinium administration with a T1-weighted axial tomogram: a rise in signal intensity in the left mandible is noted along with extensive enhancement of contrast medium in the masseter muscle and small enhancement in the pterygoidal muscle. C, T2-weighted axial MRI with a signal-rich tomogram and enlargement of the diameter of the left masseter muscle indicating an inflammatory process. D, T2-weighted coronary MRI suppressing fatty tissue [detail] showing extremely signal-rich tomogram of inflamed bone and soft tissues. E, MRI following gadolinium administration with a T1-weighted axial tomogram: no essential signs of inflammatory changes in bone or soft tissues are noted with almost symmetrical conditions when compared with the healthy right side. F, T2-weighted axial MRI showing no essential signs of inflammatory changes in bone or soft tissues with almost symmetrical conditions when compared with the healthy right side.

symptoms. Three months later he was readmitted to the hospital, given high-dosage antibiotic therapy, and discharged with only minor remaining symptoms, for which he continued antibiotic therapy orally with clindamycin 300 mg 3 times daily. Because of persistent swelling, the patient was admitted to University Hospital Düsseldorf for combination therapy with clindamycin 600 mg 3 times daily intravenously and HBO. Therapy was discontinued after 20 HBO sessions after full remission of inflammatory symptoms because of antibacterially induced nausea. The patient experienced another recurrence 3 months later. MRI demonstrated massive progression of osteomyelitis from the condyle to the mandibular midline. He again received combination therapy with 530 mg clindamycin 3 times daily and HBO. Pain and swelling continued to improve. Because of the frequent relapses experienced thus far, a maximum duration of treatment was applied continuously. Thus, despite complete freedom of any symptoms the combination therapy was continued after the forty-fifth HBO session until the sixtieth HBO session. The third recurrence occurred 10 weeks later, with serious pain and extensive swelling. MRI revealed that more than half of the mandible was affected. Before an extremely extensive surgical resection, it was decided to perform conservative combination therapy for a last time. After the eighth HBO session the patient was completely free of any pain and the swelling receded continually following the twelfth treatment. Nevertheless, intravenous antibiotics and HBO therapy were continued and after the fortieth HBO treatment the patient was discharged from hospital free of all symptoms. He has been symptom-free for the past 29 months.

CASE 3

According to her parents, a 10-year-old girl had suffered from swelling and pain in the right mandible recurring in 3-month intervals for the past 5 years. After antibiotic therapy, the patient’s condition always improved for a short time. Two years earlier, the first diagnosis of chronic osteomyelitis occurred without any consequences regarding therapy. On admission to the hospital, a painful swelling of the right angle of the mandible and sensitivity to pressure was found. MRI and scintigraphy confirmed the diagnosis of extensive chronic mandibular osteomyelitis. Combination therapy with 2 million IU/d penicillin G intravenously twice daily and HBO were prescribed. After the fifth session a gradual disappearance of symptoms was observed; freedom from pain occurred after the ninth session; swelling receded after the seventh session. Because of an intolerance to penicillin, there was a change of antibiotics to clindamycin 150 mg 3 times daily. After 40 HBO sessions the patient was completely free of all symptoms and was discharged from the hospital. Since then, 20 months have gone by and the patient is still completely free of symptoms.

Discussion

All 3 patients suffered from chronically recurrent mandibular osteomyelitis in childhood and were treated with a combination of high-dosage intravenous antibiotics and adjuvant HBO. They have been followed up from 20 to 74 months and have been free of symptoms or complaints for an average 41 months. Consequently, there is a very great chance for them to be healed completely.

The most important therapeutic success is believed to lie in the fact that, at least so far, treatment has been possible without any major surgical intervention. This would undoubtedly have led to disturbances of growth considering the young age of the patients. In addition, many studies have pointed out that surgical therapy for chronic mandibular osteomyelitis often leads to inconsistent results and short-term success only, so that it should be very important to weigh the pros and cons of surgery. Baltensperger et al. emphasized that, especially in young patients, excessive ablative surgery should be avoided. In their retrospective analysis covering patients with chronic osteomyelitis over a period of 30 years, they found that in patients with primary chronic mandibular osteomyelitis the results after 2 to 6 major surgical interventions were not any better than after only 1 single operation or an exclusively conservative treatment.

In none of the 3 patients was it possible to undertake microbiological investigations for bacteria isolation because of the lack of abscesses, pus, or fistula or sequestrum formation. If no microbiologic results are possible, we usually prefer high doses of penicillin G administered intravenously 3 to 4 times per day at 5 to 10 million IU as a bactericidal antibiotic medication because penicillin is the only antibiotic substance that can be given in this high concentration without limitations. If there is a hypersensitivity or allergy against penicillin, in our opinion clindamycin is the second best antibiotic substance of choice. However, we are convinced that high-dose antibiotic therapy should always be administered intravenously, because osteomyelitis needs not only to reach the level of minimum inhibitory concentration, but especially peak levels of antibiotic concentration in the blood. In former times we used nonsteroidal agents as anti-inflammatory treatments, but did not see a clear benefit concerning late results. For this reason these substances have not been evaluated for the patients in this article.

It was decided that MRI would be used for the objective evaluation of the therapeutic success
achieved in these patients. MRI is equivalent to skeletal scintigraphy as far as sensitivity and evaluation of osseous structures affected by osteomyelitis are concerned, but is highly superior to scintigraphy regarding the diagnostic interpretation of soft tissues. In addition, MRI does not expose the patient to x-rays, which is highly advantageous for follow-ups, especially in young patients.

In the pertinent literature, various concepts of HBO therapy were introduced and the different concepts were discussed most controversially, starting with the number of HBO sessions, the various degrees of over-pressure, the duration of exposure to pure oxygen per session, up to the question whether HBO therapy should be combined with surgery or not. Considering the physiological processes taking place during HBO, we believe that at least 40 sessions combined with the administration of high doses of antibiotics are required even in those cases where an early positive response to the combination therapy is observed (ie, a reduction of swelling and pain). This number of HBO sessions is also recommended by the latest Hyperbaric Oxygen Therapy Committee Report of the North American Undersea and Hyperbaric Medical Society (UHMS). The second case report presented here clearly shows that because of the poor blood supply prevailing in bone affected by chronically recurrent osteomyelitis, a therapy longer than “normal” may sometimes be required before HBO-induced neoangiogenesis induces adequate blood supply in the hypoxic bone thus ensuring the oxygen indispensable for any remodeling processes. Early discontinuation of HBO therapy would not fully utilize the possibilities of HBO treatment. Even though the total number of 120 HBO sessions with this patient seems extraordinarily large, it was fully justified considering the young age of the patient, the extensive dimensions of the region affected by the disease, and the amount of bone to be resected otherwise. A recent article recorded 164 HBO sessions required for therapeutic measures in chronic osteomyelitis; unfortunately, without providing details on the modalities of the HBO therapy applied or any information on the results achieved.

In the 3 patients described herein, the therapy regimen used was “TS 240-90.” Remodeling processes are impaired if HBO does not follow the regimen of 90 to 120 minutes of inhalation of 100% hyperbaric oxygen at 200 to 300 kPa once a day. Oxygenation below this level slows down the healing of bone because of the reduced activity of fibroblasts, osteoblasts, and macrophages. If the partial pressure of oxygen is increased above the optimum level, remodeling is characterized by an increased deposition of collagen fibers poor in structure. The therapy regimen TS 240-90 should be used to support the healing of osteomyelitic bone in an optimum manner by adjuvant HBO therapy.

The small number of cases presented here does not allow any final statement regarding the extent to which HBO therapy contributed to the good results observed in these patients. Because chronic osteomyelitis is rare in children, it will not be possible to perform prospective randomized studies. In addition, the patients presented were very heterogeneous and the cases exclusively concerned serious recurrences after unsuccessful conventional treatment. For ethical reasons, it is not possible to exclude such patients from HBO therapy simply because they take part in a randomized study. Jamil et al correctly emphasized that it is therefore necessary to perform multicenter, randomized, standardized studies on HBO therapy as an initial treatment of chronic osteomyelitis.

According to our experience, HBO is a promising option of adjuvant treatment of chronically recurrent mandibular osteomyelitis in children and juveniles in combination with intravenous administration of high doses of antibiotics to fully heal this refractory disease without major surgery at such a young age. This considerably improves the quality of life of patients seriously suffering from this chronically recurrent disease. It should also be kept in mind that the successful application of HBO therapy in chronically recurrent mandibular osteomyelitis shortens the duration of the patients’ hospitalization, thus reducing overall medical costs.

We do not want to precipitate unwarranted enthusiasm for the role of HBO as an adjuvant therapy regimen for chronically recurrent mandibular osteomyelitis in children and juveniles, and are convinced that this subject needs further investigation. For the reasons mentioned above, it is not possible to perform statistically significant, prospective, randomized studies of chronic osteomyelitis. However, retrospective, multicenter studies are urgently recommended to obtain more reliable data.

References

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