Case Report

Cohen syndrome with neutropenia-induced periodontitis managed with granulocyte colony-stimulating factor (G-CSF): case reports

W. Kim Seow MDSc, DDSc, PhD, FRACDS P. M. Bartold BDS, PhD, FRACDS Y.H. Thong MD, DSc, FRCPath, FRACP
K .Taylor MBBS, FRCPA, FRACP W.

Cohen syndrome was first reported in 1973 in two siblings and one sporadic case.[1] Features mentioned in the original report included obesity/hypotonia, mental retardation, narrow hands and feet, ocular abnormalities, and characteristic facies consisting of maxillary hypoplasia, mild micrognathia, short philtrum, open mouth, prominent central incisors, and downslanting palpebral fissures. Although more than 100 cases have now been reported in the medical literature,[3–21] only two previous reports have appeared in the dental literature. The first described a young girl with Cohen syndrome showing typical craniofacial features such as short philtrum and prominent incisors but no periodontal involvement.[14] The second was a controlled study which demonstrated significant periodontal disease in a group of 15 Cohen syndrome patients with neutropenia, but craniofacial features were not described.[3]

Previous medical reports suggest Cohen syndrome to be a heterogenous disorder with variable expression of the classical features, and additional abnormalities such as microcephaly, seizures, cardiac valvular defects, and leukopenia.[3–21] Most studies have mentioned an autosomal recessive mode of inheritance in Cohen syndrome, although autosomal dominant patterns of inheritance may also be possible.[5, 12, 22] Although earlier mapping studies[19] have suggested the gene to be at 5q33.1 or 7p15.1, more recent studies[23] have mapped it to chromosome 8. The gene appears to be different from that of the Prader-Willi syndrome which shows some overlapping phenotypic features.[18]

Chronic neutropenia, which is characterized by a decrease in circulating neutrophils,[24] had been previously described in a few cases of Cohen syndrome,[25] but may not be a consistent feature. As neutrophils provide the first line of host defense against microbial invasion, chronic neutropenia is generally associated with increased prevalence and severity of infections,[24] including oral infections and periodontal disease.[26–29] The association of periodontal bone loss in Cohen syndrome and neutropenia was demonstrated in a recent paper which compared Cohen syndrome patients with controls matched for age, gender, and degree of mental deficiency.[3]

Management of neutropenia includes use of recombinant G-CSF, a glycoprotein which stimulates the survival, proliferation, differentiation, and function of neutrophil granulocyte progenitor cells and mature neutrophils.[30–32] Clinical trials have demonstrated efficacy of this agent in preventing infectious complications of severe chronic neutropenia, although the successful use of G-CSF in the case of Cohen syndrome has only been recently reported in three patients.[33]

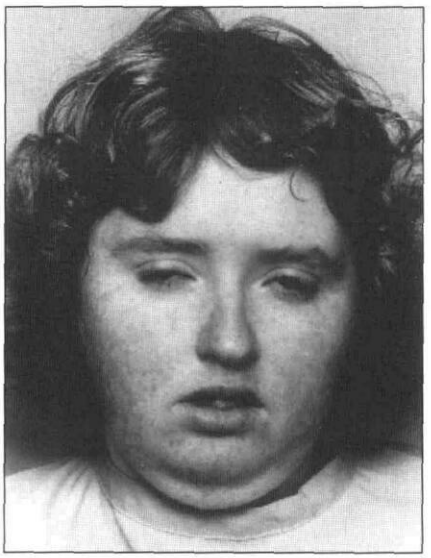
To date, the dental features of Cohen syndrome are still not well known. The present report of a brother and sister with Cohen syndrome and severe neutropenia treated with granulocyte colony-stimulating factor (G-CSF) aims to shed further light on the oral abnormalities and dental management in this syndrome, as well as the effects of medical therapy on the periodontal condition.

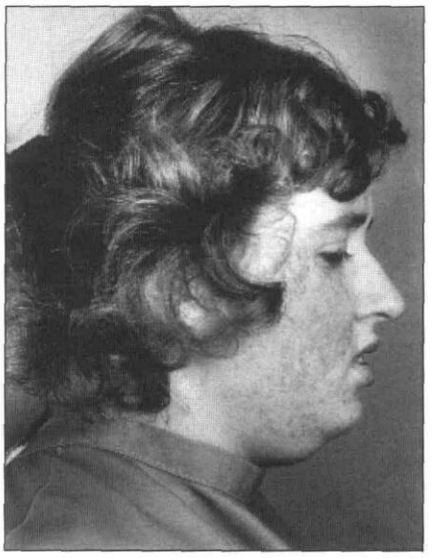
Case report

Medical history

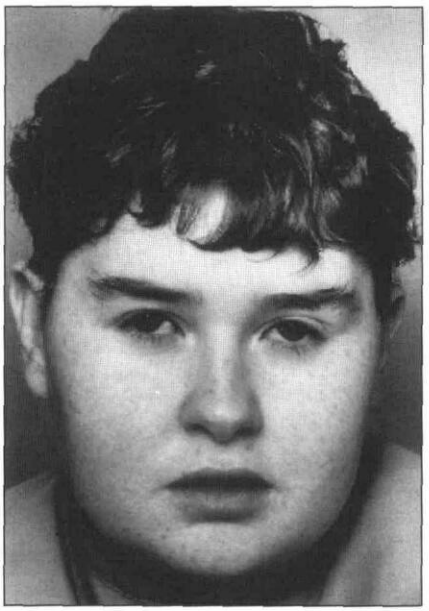
A male sibling, aged 15 years, and his sister aged 16 years, were referred to the University of Queensland Dental School by their general practitioner for management of severe periodontal destruction and recurrent oral ulceration. The children were products of full-term pregnancies of a nonconsanguineous marriage. There was an older male sibling who was normal. The birthweights of the female and male siblings were 6 lb and 4 lb, 11oz respectively. In early childhood, both children were found to have developmental delay with IQ assessed as 60–75, and they attended special schools. Myopia and retinitis pigmentosa were also diagnosed. In addition, they suffered recurrent oral, pharyngeal, ear, respiratory, and urinary tract infections. These infections were associated with persistent chronic neutropenia which had been noted since birth.

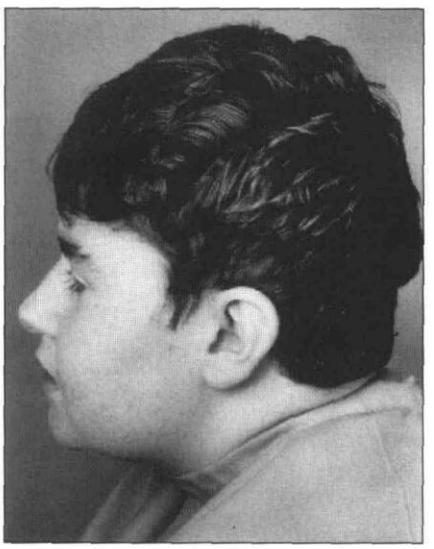
The family had moved frequently and although the children had been investigated extensively at major



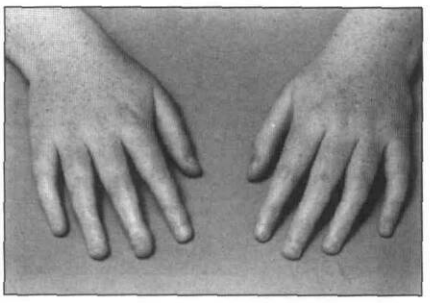


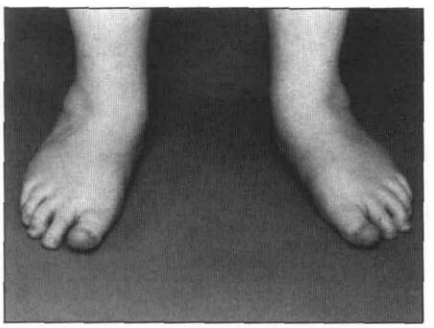
Figs 1a, 1b. Front and side views of 16-year-old female sibling with Cohen syndrome, showing typical features of downsloping palpebral fissues, maxillary hypoplasia, mild micrognathia, mildly reduced philtrum, and prominent incisors.





Figs 2a, 2b. Front and side views of 15-year-old male sibling with Cohen syndrome, showing milder facial changes compared to his sister (Fig 1).





Figs 3a, 3b. Slender hands and feet and tapering digits of female sibling. These limb abnormalities are typical of Cohen syndrome.

medical and genetic centers around the country, diagnosis of their medical condition had not been made previously. Previous medical investigations, which included chromosomal studies, biochemical screens, and skeletal survey had all shown normal results.

General examination

At initial presentation, both children appeared fairly cooperative for dental examination. Both showed moderate central obesity and short stature.

The siblings resembled each other (Figs 1a, 1b, 2a, 2b) They had round faces and wore spectacles with thick corrective lenses. The palpebral fissures were down-
sloping, and there was maxillary hypoplasia and mild micrognathia. Prominent incisor teeth with mildly reduced philtrum were observed.

Physical measurements for the female sibling were height 147 cm (< 3rd percentile), weight 70 kg (> 75th < 90th percentile) and head circumference 51cm (< 3rd percentile), and the male sibling height 145 cm (< 3rd percentile), weight 58 kg (> 3 <10th percentile), and head circumference 50 cm (3rd percentile). In both children, the hands and feet were long and slender, and the fingers and toes were tapered (Figs 3a, 3b).

Dental examination and treatment

Oral examination of the female showed that all the permanent teeth except the mandibular and maxillary right third molars were present. The enamel of all her teeth appeared hypomineralized, the most severe defects being seen in the maxillary incisors and first molars which showed yellow-brown opaque discoloration, and mild enamel hypoplasia (Fig 4).

In the male sibling, all the permanent teeth except the third molars and second mandibular premolars were present on clinical examination (Fig 5) As in his sis-

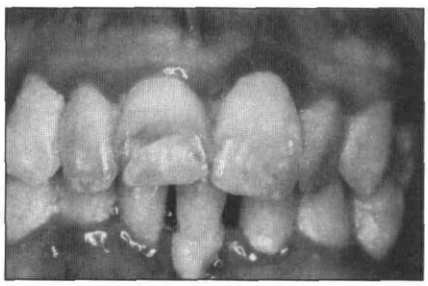


Fig 4. Dentition of female sibling. Note severe gingival inflammation associated with gross deposits of plaque and calculus. Also note generalized enamel hypomineralization defects.

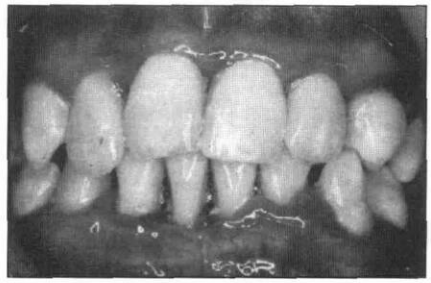


Fig 5. Dentition of male sibling. Note severe gingival inflammation and loss of attachment in the mandibular anterior teeth. Hypomineralization defects (diffuse enamel opacities) were present on most teeth, although these were less severe compared to his sister's.

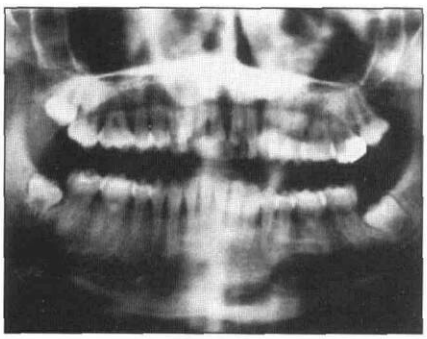


Fig 6. Panoramic radiograph of female sibling. The third molars were unerupted and impacted.

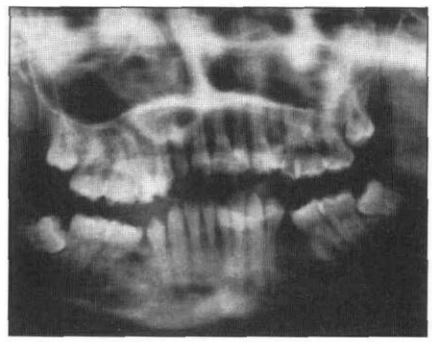
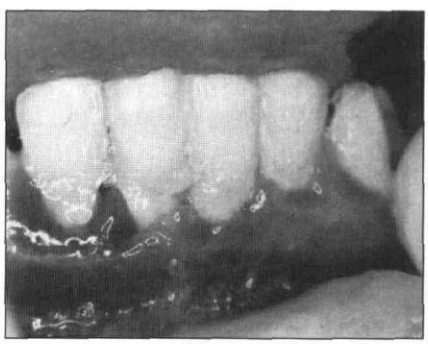
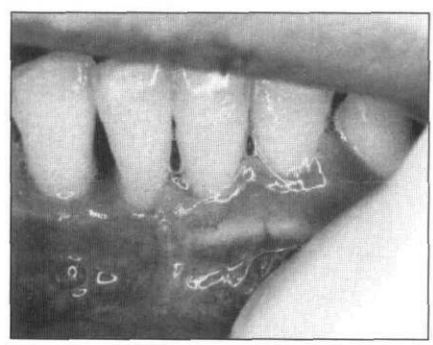


Fig 7. Panoramic radiograph of male sibling. There was agenesis of all second premolars, and the third molars were unerupted and impacted.





Figs 8a, 8b. Mandibular anterior teeth of male sibling before and after periodontal cleaning and medical treatment with G-CSF treatment which resulted in normalization of neutrophil levels. Note marked improvement in gingival health after treatment.

ter, the teeth also showed hypomineralization defects although these were considerably less severe.

Both children had Class II malocclusions with anterior overjet of 6 mm and mild anterior open bite. Panoramic radiographs (Figs 6 and 7) revealed impaction of third molars in both children, and confirmed agenesis of second premolars in the boy.

Periodontal examination

At the initial oral examination, large deposits of supra- and subgingival plaque and calculus deposits were noted around all teeth in both patients. The gingival tissues bled profusely upon gentle probing and generalized periodontal pocketing of between 4 and 6 mm was recorded . The male sibling was most severely affected with the periodontal tissues showing a fiery red, edematous appearance, particularly in the anterior regions (Fig 8a) The female sibling had generally less severe inflammation, although there were isolated areas of severely inflamed tissues, including gingival recession localized to the right mandibular central incisor (Fig 5).

Radiographs indicated early signs of bone loss around many teeth although the condition was not yet severely compromising the dentition. Subgingival plaque samples were taken from the maxillary central incisors and mandibular left first molar for each child. The male sibling had moderately high levels ($12–42 \times 10^4$) of *Porphyromonas gingivalis* at two of the three sites tested compared to his sister who showed less than 9×10^4 of this bacteria at the sites sampled.

Medical diagnosis and treatment

Based on the characteristic facies, central obesity, and tapering hands and feet, a provisional diagnosis of Cohen syndrome was suggested.[1] Other syndromes[22] presenting with obesity, mental retardation, and limb abnormalities such as the Prader-Willi and Moon-Biedel syndromes were excluded based on differences in craniofacial appearances, limb findings, and the timing and character of obesity.

The diagnosis of Cohen syndrome was confirmed by medical specialists. Further hematological investigations revealed the neutrophil counts to be 0.68×10^9/L for the sister and 0.13×10^9/L for the brother (normal range 2.0 to 7.5×10^9 /L). Serial neutrophil counts showed consistently low numbers, and excluded cyclic neutropenia.

Marrow examination of both siblings showed normal cellularity and adequate myeloid precursors, but reduction in mature myelopoeisis. Tests for antineutrophil antibodies were negative, and cytogenetic studies excluded Fanconi syndrome.[22]

A family history revealed that no other members of the family were affected. The mother and normal sibling did not show features of Cohen syndrome.

Treatment of the neutropenia was commenced with daily subcutaneous recombinant granulocyte stimulating factor[30–33] (G-CSF, filgastrim) at an initial dose of 12 μg/kg. Neutrophil counts normalized to around 3 x 10^9/L within a week, and the dosage was reduced to maintenance schedule of 3–5 μg/kg/day. Regular follow-up confirmed persistence of normal neutrophil counts with these dosages, associated with marked reduction in infections requiring antibiotic use.

Dental treatment consisted of oral hygiene instruction, including suggestion for the use of an electric toothbrush. Full-mouth subgingival debridement was attempted using local anesthesia and nitrous oxide sedation. However, cooperation of the patients was limited under these management techniques, and full subgingival debridement and scaling, together with removal of the third molars, was subsequently performed under general anesthesia.

In both children, there was excellent response of the periodontal tissues to treatment. Inflammation and pocket depths were reduced considerably within a few weeks after treatment (Fig 8b). No post-treatment microbiological assays were performed.

Discussion

The pediatric dentist occasionally encounters children with undiagnosed dysmorphology, and may thus be the first to diagnose a patient's condition. In these case reports, the diagnosis of Cohen syndrome explained the craniofacial, limb, and ophthalmic abnormalities, as well as the obesity, mental retardation, and neutropenia. Also, definitive diagnosis of the condition enabled institution of correct medical management strategies, including genetic counselling.

Although a few previous studies have described the neutropenia in Cohen syndrome to be intermittent and relatively harmless,[11] the present cases showed significant systemic infections and periodontal disease. Our findings are thus similar to those of the study of Alaluusua and coworkers,[3] in which patients with Cohen syndrome showed significantly more periodontal destruction compared to matched controls. In addition, as in that study, higher levels of periodontal pathogens, particularly *Porphyromonas gingivalis*, were also found in our patients. The increased levels of these bacteria are likely to be the result of depressed numbers of neutrophils and lowered host defence mechanisms in the gingiva.

Our study has also shown that the children's neutropenia can be effectively controlled by regular G-CSF injections, which leads to a marked decrease in the number of general infections suffered by the children. Also, great improvement in gingival health was noted after G-CSF therapy which resulted in normal neutrophil numbers, together with periodontal scaling and cleaning (Figs 8a, 8b). Although the effects of treatment by G-CSF in Cohen syndrome have not been described previously, successful results on the periodontal tissues have been reported after G-CSF therapy in other neutropenic patients such as agranulocytosis.[34] Long term complications of G-CSF therapy include splenomegaly, hepatic dysfunction, renal dysfunction, fever, fluid retention, pericardial and pleural effusions, and cardiac arrythmias. However, apart from mild long bone pain at the beginning of therapy, these children suffered minimal side-effects.

The present study also demonstrates that hypomineralization enamel defects may be a feature of Cohen syndrome that have not been reported before. Similar enamel defects have been observed in many syndromes with ophthalmic lesions,[22,35,36] suggesting similar susceptibility of ophthalmic and dental enamel tissues to developmental insults, probably associated with their common origin from neural crest cells. Thus, as Cohen syndrome also demonstrates ophthalmic involvement, it is reasonable to propose that the enamel defects are likely to part of this syndrome.

On other hand, the coincidental presence of the enamel defects cannot be completely excluded. In this regard, the positive history of toothpaste ingestion and residence in water-fluoridated areas during infancy suggest that the enamel lesions may have resulted from fluorosis, which presents a similar clinical appearance.

In view of their high susceptibility to periodontal disease and enamel breakdown, preventive care consisting of regular professional prophylaxis, scaling, and topical fluoride application should be central to the dental management of Cohen syndrome. It is unclear if correction of Class II malocclusion with orthodontic appliances would be stable because of the abnormal muscle tone. In view of the mental retardation, behavior management may be challenging. In addition to psychological support, conscious sedation with nitrous oxide may be required for routine dental work. In the present report, although the children benefited from nitrous oxide sedation for minor procedures, general anesthesia was necessary for complete deep scaling and debridement.

Dr. Bartold is professor of Periodontology and Dr. Seow is associate professor in Pediatric Dentistry, University of Queensland Dental School, Brisbane, Australia. Dr. Thong is professor of Child Health, University of Queensland, Australia, and Dr. Taylor is director of Cancer Services, Mater Public Hospitals, South Brisbane, Australia.

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