Retained primary teeth in STAT3 hyper-IgE syndrome: Early intervention in childhood is essential

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Abstract

Objectives: To optimize dental management we evaluated development of the dentition and long-term outcome of dental treatment in STAT3 hyper-IgE syndrome (STAT3-HIES), a rare primary immunodeficiency clinically overlapping with atopic dermatitis. Next to eczema, elevated serum-IgE, and recurrent infections, STAT3-HIES patients present with characteristic facies, midline defects, and retained primary teeth. Materials and Methods: We assessed dental histories of 13 molecularly defined STAT3-HIES patients by questionnaires, radiographs, and dental investigations. Results: Primary tooth eruption was unremarkable in all STAT3-HIES patients. Primary tooth exfoliation and permanent tooth eruption was delayed in 83% of patients due to unresorbed tooth roots. Permanent teeth erupted spontaneously in all patients receiving primary tooth extraction of retained primary teeth during average physiologic exfoliation time. A complex orthodontic treatment was needed in one patient receiving delayed extraction of primary molars and canines. Conclusion: To enable spontaneous eruption of permanent teeth in children with STAT3-HIES, we recommend extracting retained primary incisors not later than 9 years of age and retained primary canines and molars not later than 13 years of age after having confirmed the presence of the successor permanent teeth by radiograph. Clinical Relevance: The association of STAT3-HIES with retained primary teeth is important knowledge for dentists in any field as timely extraction of retained primary teeth avoids dental complications.

Introduction

Abnormal shedding of primary teeth may occur in otherwise healthy individuals. The most common reason of persistence of primary teeth, however, is congenital absence of the permanent successor tooth. [1, 2] Ankylosis of primary teeth and impaction, abnormal position, and late eruption of successor teeth may likewise cause retention of permanent teeth.[2] In addition, there are several syndromes such as Gardner syndrome, cleidocranial dysplasia, tricho-dento-osseous syndrome, osteopetrosis, and Apert syndrome that are associated with persistence of primary teeth.[3-8]

Another rare cause of persistence of primary teeth is the primary immunodeficiency STAT3-hyper-IgE syndrome (STAT3-HIES).[9-11] STAT3-HIES belongs to the so-called orphan diseases defined by less than one affected in 2000 individuals. Despite STAT3-HIES being such a rare disease, it is often a differential diagnosis since it significantly overlaps with atopic dermatitis. Next to the atopic dermatitis findings such as eczema and elevated serum IgE, STAT3-HIES patients present with recurrent skin and lung infections followed by irreversible complication due to their immunodeficiency. Muco-cutaneous Candida infections may also be recurrently present. Non-immunologic findings such as characteristic facies, a high arched palate, midline defects, and retained primary teeth are variably associated.[9-11] Since all these findings accumulate over time and may not be present early in life, diagnosis is often delayed until skeletal findings or infectious complications occur.

STAT3-HIES is a monogenic disease caused by heterozygous mutations in the signal transducer and activator of transcription 3 (STAT3) gene.[12-14] STAT3 mutations result in a dominant-negative effect on
STAT3 function causing the characteristic findings of STAT3-HIES.[9-11] Treatment includes long-term antibiotic treatment with cotrimoxacol or a *Staphylococcus aureus* sensitive cephalosporin, immunglobulin replacement therapy, and if needed antifungal treatment to prevent infections and associated complications such as chronic lung disease after pneumonia.[15] Not only infection associated complications impact patients’ quality of life also retention of primary teeth can cause significant impairments. Therefore, we assessed the dental history of 13 patients with STAT3-HIES from childhood into adulthood focusing on exfoliation of primary teeth with the aim to raise awareness of STAT3-HIES and dental treatment in STAT3-HIES patients preventing dental complications.

**Methods**

Sixteen STAT3-HIES patients followed at the University Children's Hospital of the Ludwig Maximilian University (LMU) Munich were asked to complete a dental history questionnaire (Supp. Data S1). Thirteen STAT3-HIES patients (6 females and 7 males, median 20 years of age, range: 5 to 58 years of age) from 11 unrelated families agreed to take part in the study (Supp. Table S1). The patients’ families and dental care physicians were asked to assist completing the questionnaire. Inclusion criteria for participation were characteristic clinical findings of STAT3-HIES and a confirmed disease-causing heterozygous *STAT3* mutation. Exclusion criteria were dental abnormalities without any additional findings of STAT3-HIES and a missing genetic STAT3 defect.

All patients except for patient #12 have been described previously.[16-19] Their STAT3-HIES diagnosis has been molecularly defined by diagnostic testing such as reduced Th17 cell counts and Sanger sequencing of the *STAT3* gene as previously described.[17] Primer sequences are available upon request. Mutations were reported using the nomenclature of den Dunnen and Antonarakis.[20]

Thirty-one radiographs of 11 patients were available for reviewing including radiographs provided by the local dental care physicians. Radiographs were not uniform since performed on regular dental care appointments by different dental care physicians. Twenty-two panoramic radiographs (PANs) of 9 patients (3 analogue / 19 digital) and 9 periapical radiographs of 3 patients (4 analogue/ 5 digital) were included. PANs were assessed focusing on: number of primary teeth, number of retained permanent teeth, agenesis, conservative dentistry, orthodontic treatment, and status of root resorption of primary teeth (no resorption, resorption) (Suppl. Table S2). Periapical radiographs were assessed concerning periapical status of the teeth and conservative dentistry (Supp. Table S3). The Universal Numbering System was used. Physiological age ranges of primary tooth exfoliation and permanent tooth eruption were defined according to the standards of the American Academy of Pediatric Dentistry defined according to Logan and Kronfeld.[21]

Written informed consent was obtained and the study was approved by the LMU review board (#381-13). Figures were generated with GraphPadPrism 5.0 (GraphPad Software Inc., San Diego, CA, USA) and Adobe Illustrator CS6 (Adobe Systems Inc., San José, CA, USA).
Results

Dental history of two STAT3-HIES patients

Dental histories of two patients exemplary show the outcome of different treatment strategies: In patient #4 primary teeth were all extracted at the average exfoliation time, while patient #3 received tooth extractions partly later in life.

All primary teeth erupted without problems in the average eruption time in patient #4. Up to the age of 9 years all primary mandible and maxillary central and lateral incisors were extracted. The successor permanent teeth erupted shortly afterwards (Fig. 1a, b). Radiograph at 12 years of age showed unresorbed and only slightly resorbed roots of the remaining primary teeth. Her remaining primary teeth were all subsequently extracted up to the age of 13 years with the permanent successor teeth erupting shortly afterwards.

In patient #3 primary teeth eruption was unremarkable and within the average eruption time. Primary incisors of patient #3 were extracted between 7 and 9 years of age with the exception of 2 incisors which exfoliated spontaneously. Permanent incisors erupted shortly afterwards. Primary canines and molars did not exfoliate spontaneously and persisted during the physiologic eruption period of the corresponding successor teeth. At 15 years of age all 4 retained canines were extracted. The successor teeth remained impacted in the jaw. In order to obtain additional space for the permanent canines, the still persistent primary first molars were removed at 16 years of age. The successor teeth still failed to erupt (Figure 2a, b). Therefore, bone ablation superior of the impacted permanent teeth was performed under anaesthesia and a complex orthodontic treatment to pull the permanent canines and first premolars into the oral cavity was started. After this operation, the canines and first premolars began to erupt. At 17 years of age the last 4 primary teeth were removed and the second premolars were included in the orthodontic treatment (Figure 2c, d). Finally, the top of the second premolars erupted 3 weeks after the last operation and all permanent teeth, which had been included in the orthodontic treatment, had erupted at 17 years of age. The extracted primary molars showed almost completely unresorbed roots (Figure 2e, f). To align the dental arch and to reach optimum teeth positioning, over 2 years of complex orthodontic treatment followed.

Primary teeth: eruption, spontaneous exfoliation, retention, and root resorption in STAT3-HIES

Eruption time, tooth size, tooth appearance, and number of primary teeth were unremarkable in all 13 STAT3-HIES patients. Due to age, patient #2 (5 years of age) had not yet lost any primary teeth. In 2 patients (#1, #5) all primary teeth exfoliated naturally within the normal age range, while 10 patients (83%) presented with retained primary teeth (2 to 20 teeth per patient) and delayed eruption of permanent teeth up to 35 years of age (Figure 3, Table 1). In 3 patients (#4, #6, #9) no primary tooth exfoliated spontaneously within the normal age range. Two patients (#10, #12) presented with retained incisors
while the presence of their primary canines and molars was adequate to age. In 5 patients (#3, #7, #8, #11, #13) both, spontaneous exfoliation and retention of 2 to 8 incisors, up to 2 canines and up to 6 molars was observed.

Thus, only 36% of incisors, 29% of canines, and 27% of molars exfoliated spontaneously within the physiological exfoliation time [21] in the investigated STAT3-HIES patients with retained primary teeth.

In all these patients except for patient #3 and #12 the permanent first and second molars erupted on time (first molar: 5.5-7 years of age, second molar: 12-14 years of age). The first permanent molars of patient #12 appeared with a delay of approximately 2 years at 9 years of age and the maxillary second permanent molars of patient #3 had not yet reached the occlusal level at 17 years of age.

Delayed primary tooth root resorption was observed in 8 of the 10 (80%) STAT3-HIES patients older than 8 years of age, of whom radiographs were available. Detailed root resorption was assessed in 22 panoramic radiographs (Suppl. Table S2) in 3 age groups: (i) up to 9 years of age when physiologically all incisors should have exfoliated, (ii) 10 to 13 years of age when also canines and molars exfoliate and (iii) older than 13 years of age when no primary teeth should remain.

Between 8 and 9 years of age 4 patients (#4, #9, #11, #12) showed delayed root resorption of primary teeth with unresorbed roots in incisors, canines, and molars (Figure 4). Between 10 and 13 years of age 4 patients (#4, #6, #7, #9) still had up to 4 primary canines and 4 to 8 primary molars of which some had unresorbed roots. The assessment of panoramic radiographs in 3 patients (#3, #7, #8) above 13 years of age revealed in patient #3 3 primary canines and one primary molar in patient #7 with unresorbed primary tooth roots.

**Extraction therapy of retained primary teeth, orthodontic and conservative treatment**

Nine patients (#3, #4, #6 to #12) had one up to 20 primary teeth per patient extracted between 7 and 17 years of age to enable eruption of permanent teeth. In 7 of the 9 patients sequential tooth extraction was required including series of 2 to 8 extractions per patient. In 8 of 9 STAT3-HIES patients permanent teeth erupted shortly after the primary teeth had been extracted around the physiological exfoliation age.

Nine patients received an orthodontic treatment including removable or fixed dental braces. In patient #9 one permanent premolar in each quadrant had to be removed for orthodontic reasons to obtain more space for the remaining teeth. To correct the nasal and upper jaw configuration, patient #1 received an osteotomy of the maxilla including orthodontic correction. Five patients (#1, #5, #7, #8, #13) needed conservative dentistry while the other 8 patients did not have any fillings, endodontic treatments or inlays.

**No complication after extraction or orthodontic treatment**
Despite repeated oral candidiasis in 7 (54%), recurrent aphthous ulcers (1-12 times per year) in 2 (15%), and gingivitis in 4 (31%) patients, there were no infections after tooth extraction or orthodontic treatment in any of the patients (Table 1). Wound healing was unremarkable in all patients after extractions. As a measure of precaution, amoxicillin was given prior to complex dental treatment in patient #3 in addition to patient’s continued standard antibiotic treatment and immunoglobulin substitution therapy.

Abnormal dental and oral anatomy

There were 3 patients (#4, #7, #12) with abnormal dental anatomy of permanent teeth: agenesis of both maxillary second premolars in patient #4, an agenesis of the right-sided maxillary second premolar in patient #12, and a twice the normal size right-sided mandibular second premolar in patient #7. In 4 patients (#3, #8, #10, #11) permanent incisors were temporarily present lingual together with the primary incisors until the primary teeth were extracted. Patient #2 had an abnormal fissuring of the tongue (Supp. Figure S1).

Discussion

Here, we focused on dental and oral findings in STAT3-HIES patients with the aim to raise awareness for an optimized dental treatment in this rare devastating disease to prevent dental complications in adolescence.

Besides retention of primary teeth, STAT3-HIES patients have various oral manifestations such as high arched palate and midline defects.[9-11, 22, 23] Accordingly, one of our patients had a mild abnormal fissuring of the tongue which are also reported in other STAT3-HIES patients and may consist of larger tongue lesions with deep midline clefts anterior to the circumvallate papillae.[10] Gingivitis (31%) and aphthous ulcers (15%) were frequent findings in our STAT3-HIES cohort; however, comparable to frequencies observed in the general population.

While primary tooth eruption was unremarkable, 83% of our assessed patients showed persistent primary teeth with delayed primary tooth exfoliation and permanent tooth eruption; thus, persistent primary teeth were found slightly more frequent compared to 64% to 75% of STAT3-HIES patients in previous reports.[9, 11, 22] One patient had a premolar twice the normal size and agenesis as possible cause of primary tooth retention was only observed of one tooth each in two patients.

Tooth eruption is a physiologic process, which is still not completely understood. Various tissue changes, such as resorption and apposition of the alveolar bone, and resorption of the primary tooth root accompany tooth eruption, which is likely triggered by vascular pressure and the growth of the permanent tooth's root.[24, 25] Whereas bone undergoes constant physiological turnover, the resorption of primary tooth roots only occurs during the change from primary to second dentition.[26]
Osteoclasts and odontoclasts have been associated with tooth eruption, and dysregulated osteoclastogenesis leading to dental implications, such as abnormal shedding of primary teeth.[27] In cleidocranial dysplasia and osteopetrosis delayed tooth eruption has been associated with deregulated osteoclast number or function and skeletal alterations such as scoliosis and spontaneous fractures.[28-30] In STAT3-HIES a rather increased number of osteoclasts is reported and suggested to result in the associated skeletal symptoms such as scoliosis and pathologic fractures.[31] Osteoclasts are known to be essential to resorb the alveolar bone to form an eruption pathway.[32, 33] Thus, the increased number of osteoclasts in STAT3-HIES is an explanation for an unremarkable formation of the eruption pathway in the alveolar bone and consequently regular eruption of primary teeth and permanent teeth after primary tooth extraction in STAT3-HIES patients.

Delayed resorption of primary tooth roots has been hypothesized to cause persistence of primary teeth in STAT3-HIES by us and others.[11, 22, 23] This hypothesis is supported by our finding of a more frequent spontaneous exfoliation of the incisors which have only one smaller root. In contrast, canines, whose roots reach deeper, and molars, which are fixed with two or three roots, were more likely to persist.

Abnormal persistence of Hertwig's epithelial root sheath (HERS) on the surface of extracted primary teeth has been suggested to explain impaired tooth root resorption in STAT3-HIES.[11] However, tooth roots of mice with normal dentition are also reported to show persistence of some HERS cells, that are incorporated by the thickening cementum layer.[34] Thus, the persistence of HERS cells in STAT3-HIES may be a physiologic phenomenon, which does not disturb tooth root resorption and hence does not contribute to primary tooth retention. Impaired function of odontoclasts – a specialized form of osteoclasts – seems more likely to limit root resorption in STAT3-HIES. Osteoclasts are suggested to be regulated by the extracellular matrix proteins osteopontin (OPN) and bone sialoprotein (BSP)[27, 35] and have been associated with tooth root resorption.[36-39] Since reduced OPN expression has been reported in STAT3-HIES[40] we hypothesise that OPN concentrations in the proximity and within odontoclasts may not be reached in primary teeth of STAT3-HIES patients resulting in diminished activation of odontoclasts and consequently retention of primary teeth. Very slow primary tooth root resorption may explain why in a few STAT3-HIES patients, also in our cohort, primary teeth naturally exfoliated without intervention in adolescence or even adulthood.

Our assessment, and particularly the complex orthodontic treatment of patient #3, however, underlines the necessity to perform timely extractions of primary teeth in STAT3-HIES patients during the physiological exfoliation range of the primary tooth. If primary teeth are extracted later in life, we observed the risk of impaction of permanent successor teeth as shown in patient #3. Orthodontic extrusion of impacted teeth in STAT3-HIES patients was not recommended due to increased enamel fragility and carioreceptivity in a previous report.[23] Yet even in patient #3 with multiple extractions, bone ablation, and subsequent complex orthodontic extrusion of impacted permanent teeth none of the anticipated complications were observed. None of our patients had complications such as wound healing issues or infections of the extraction wounds. As a measure of precaution, however, we recommend to
give antibiotic prophylaxis such as amoxicillin prior to complex dental treatment in addition to the continuous medication STAT3-HIES patients receive.[23, 41, 42]

In conclusion, permanent teeth develop normal in STAT3-HIES patients if retained primary teeth are extracted around physiological exfoliation age. Complications such as wound healing were not observed, and infection risks can be limited by adequate antibiotic prophylaxis. We would like to advice, however, to confirm the presence of the successor by radiograph prior to tooth extraction.

**Declarations**

**Author contributions:**

IM, RH, EDR designed the study; IM, BH, CK, BDS, EP, GD, TM, RH, EDR provided and analyzed data; IM, BH, CK, EDR were the principal writers of the manuscript. All of the authors reviewed the manuscript and contributed in writing.

**Compliance with Ethical Standard:**

Conflict of Interest: Authors declare that they have no conflict of interest.

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Ethical approval: All procedures performed involving human participants were approved by the LMU review board (#381-13) and are in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Written informed consent was obtained from all individual participants or their legal guardian included in the study.

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Additional Files

Table 1: Dental and oral findings of STAT3-HIES patients

Supplementary Data S1: Dental questionnaire for patients with STAT3-HIES

Supplementary Figure S1: Midline defect in a STAT3-HIES patient

Abnormal fissuring of the tongue in patient #2 consisting of an asymptomatic 2 mm deep midline v-shaped, pyramidal cleft located anterior of the circumvallate papillae.

Supplementary Table S1: Clinical and molecular findings of the STAT3-HIES patients

Supplementary Table S2: Dental findings in panoramic radiographs

Supplementary Table S3: Dental findings in periapical radiographs

Figures
Figure 1

Permanent teeth eruption after timely extraction in a STAT3-HIES patient At 8 years of age patient #4 had 18 retained primary teeth, whose roots show only very little root resorption in a panoramic radiograph (a). Subsequently, mandible and maxillary central and lateral primary incisors were extracted and the panoramic radiograph at 12 years of age (b) shows that all successor teeth erupted spontaneously. Agenesis of maxillary second premolars is shown. The canines were extracted at 13 years of age and erupted shortly afterwards (not shown).

Figure 2

Complex orthodontic treatment to induce permanent teeth eruption in a STAT3-HIES patient after delayed primary teeth extraction At 15 years of age the panoramic radiograph of patient #3 shows 4 persistent primary canines and all 8 primary molars. Maxillary second permanent molars have not yet reached the occlusal level (a). One year after extraction of the primary predecessors the permanent canines and first and second premolars of patient #3 were still impacted (b). Intra-operative pictures of the extraction of
the primary first and second molars with fixation of the orthodontic treatment on the permanent teeth and subsequent bone ablation at the age of 17 years are shown (c, d). The extracted second primary molars of patient #3 at 17 years of age had barely any root resorbtions (e, f).

Figure 3

Course of spontaneously exfoliated and extracted primary teeth in STAT3-HIES patients The number of primary teeth remaining in the oral cavity is shown in all patients except for patient #1 who had not yet reached the age of teeth shedding and patient #2 and #5 with inconspicuous shedding of primary teeth. The grey area represents the average exfoliation period of primary teeth according to Logan and Kronfeld. [21] Due to timely extraction, the primary teeth exfoliation of patients #6 and #10 is within the average age range.
Figure 4

Exemplary panoramic radiographs of STAT3-HIES patients with delayed root resorption (a) The panoramic radiograph of patient #12 shows persistence of all primary teeth with delayed root resorption of most primary teeth at 8 years of age. The first permanent molars have not yet reached the occlusal level while the superior alveolar bone had already been resorbed. (b) At 9 years of age patient #11 had 3 retained primary incisors, primary canines and molars with barely resorbed and unresorbed primary tooth roots. (c) At 10 years of age patient #6 had multiple retained primary molars in the maxilla and mandible with unresorbed and barely resorbed tooth roots with completed bone resorption superior to the second permanent molars on the left side and almost complete resorption on the right side.

Supplementary Files

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