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ORIGINAL ARTICLE

Diagnosis and initial management of children presenting with premature loss of primary teeth associated with a systemic condition: A scoping review and development of clinical aid

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Abstract

Background: Premature loss of primary teeth (PLPT) can be a rare presentation of systemic medical conditions. Premature loss of primary teeth may present a diagnostic dilemma to paediatric dentists.

Aims: To identify systemic conditions associated with PLPT and develop a clinical aid.

Design: OVID Medline, Embase and Web of Science were searched up to March 2023. Citation searching of review publications occurred. Exclusion occurred for conference abstracts, absence of PLPT and absence of English-language full text.

Results: Seven hundred and ninety-one publications were identified via databases and 476 by citation searching of review articles. Removal of 390 duplicates occurred. Following the exclusion of 466 records on abstract review, 411 publications were sought for retrieval, of which 142 met inclusion criteria. Thirty-one systemic conditions were identified. For 19 conditions, only one publication was identified. The majority of publications, 91% ($n = 129$), were case reports or series. Most publications, 44% ($n = 62$), were related to hypophosphatasia, and 25% ($n = 35$) were related to Papillon–Lefèvre. Diagnostic features were synthesised, and a clinical aid was produced by an iterative consensus approach.

Conclusions: A diverse range of systemic diseases are associated with PLPT. Evidence quality, however, is low, with most diseases having a low number of supporting cases. This clinical aid supports paediatric dentists in differential diagnosis and onward referral.

KEYWORDS

dental development, medical compromise, premature exfoliation, primary teeth, systemic disease, tooth loss

1 | INTRODUCTION

Exfoliation of primary teeth as part of dental development usually begins with the primary incisors from the age of 5.5 to 6 years.[1,2] Physiological exfoliation tends to be bilaterally symmetrical, with loss of mandibular primary teeth occurring before their maxillary counterparts, with the exception of second primary molars.[1,3] Girls tend to exfoliate their teeth at an earlier age than boys, but the sequence of tooth loss remains consistent in both groups.[2,3]

Premature loss of primary teeth (PLPT) most commonly occurs due to dental caries or traumatic dental injury. Loss of the primary incisor teeth prior to the age of 5 years, in the absence of caries or trauma, can be considered premature loss. The loss of primary incisors prior to the age of 3 years is less likely to be a variation in normal physiological exfoliation and presents a particular diagnostic concern. Such incidences of premature loss of primary teeth can be a rare presentation of a systemic medical condition, which may be of metabolic, inflammatory, neoplastic or immunological origin. These children will often be referred for specialist paediatric dentistry input for management in secondary or tertiary settings, in which they present a diagnostic dilemma to paediatric dentists and may require further clinical advice and support from our paediatric medical colleagues.[2]

The literature surrounding this topic has not been previously systematically explored; narrative reviews and book chapters have been previously published,[2,4] and these secondary texts may be referred to, but primary cases are often not cited. Additionally, there is conflation of generalised or molar-incisal pattern periodontitis with premature loss of primary teeth in many texts.[2] As a result, paediatric dentists may face uncertainty on how to manage and refer these children for subsequent medical investigation for potentially serious underlying medical conditions. This scoping review was therefore conducted to synthesise the primary cases in this area, and to support the development of a clinical aid to serve as a practical, diagnostic tool for paediatric dentists.

2 | AIM

To evaluate and synthesise the primary literature relating to PLPT as a manifestation of systemic disease.

3 | OBJECTIVES

1. To identify systemic conditions associated with PLPT through a scoping review of the literature.
2. To develop a clinical aid to support the diagnosis and immediate management of children presenting with PLPT.

Why this paper is important to paediatric dentists

- Children with premature loss of primary teeth are often referred for specialist paediatric dentistry input, in which they present a diagnostic dilemma.
- This article provides the first scoping review of systemic conditions associated with premature loss of primary teeth in primary case reports.
- It also provides an accessible clinical decision aid to support differential diagnosis and onward referral of these rare cases.

4 | MATERIALS AND METHODS

4.1 | Objective 1: Scoping review

OVID Medline, Embase and Web of Science were searched up to March 2023 with the search strategy ("early exfoliation" OR "premature exfoliation" OR "attachment loss" OR "early loss" OR "premature loss" OR "advanced dental development" OR "early shedding") AND ("primary teeth" OR "baby teeth" OR "milk teeth" OR "primary dentition" OR "deciduous dentition" OR "deciduous teeth"). Search term was developed iteratively, omitting terms relating to systemic disease to avoid producing too narrow of a search. Initial search occurred in August 2021, with repeat search completed in March 2023 to the review literature published in the interim analysis period. No restrictions were placed on publication date. Secondary and tertiary texts identified in the database searches underwent citation searching.

Duplicate records were removed and abstracts were screened by two researchers (CH and HA), with disagreement resolved by the third researcher (RB). Data were extracted directly to Microsoft Excel® (Microsoft®, Washington). Exclusion occurred for conference abstracts, where excessive mobility or premature loss was not reported first-hand, and where no English-language full text was available. Cases with reported excessive mobility were included with acknowledgement that this may progress to unobserved premature loss.

Included publications underwent full-text review in which the following data were extracted: type of publication, systemic condition, dental features, age at presentation (to determine whether exfoliation was truly premature),

initial medical investigations and results, onward medical referral, secondary investigations and results and oral management. A descriptive statistical analysis was carried out.

Results were synthesised by grouping systemic diseases by prevalence and quality of evidence. Further literature review of medical features, investigations and treatment of systemic conditions was completed to support data synthesis and clinical aid development.

5 | RESULTS

Identification of 791 records occurred through database searches. Seven review papers were identified:[2,4–9] two relating to premature loss of primary teeth in general, four relating to hypophosphatasia and one relating to Papillon–Lefèvre syndrome. Citation searching was completed, resulting in the identification of 476 further unique records.

After removal of duplicates ($n=390$), the screening of abstracts resulted in a further 466 exclusions. The remaining 411 publications were sought for retrieval; records could not be retrieved for 78 publications due to lack of availability of full text ($n=46$) or lack of an English-language full text ($n=22$). Following full-text screening, exclusion occurred for: 46 conference abstracts and 145 publications in which PLPT was not reported first-hand. This included the following: literature reviews without primary cases (where citation search was subsequently completed), cases in which exfoliation was reported after age 5 years, or clinical attachment loss without mobility or loss of teeth was reported. A total of 142 primary texts therefore underwent full data extraction (Figure 1).

Thirty-one distinct systemic conditions were identified, but for 19 of these conditions, only one case report was identified in the scoping review (Table 1). Publications consisted predominantly of case reports and case series (91%; $n=129$), followed by laboratory studies, for example of exfoliated teeth or genetic analysis (6%; $n=8$). One publication related to a clinical trial of hypophosphatasia treatment asfotase alfa, and two cross-sectional studies and two cohort studies were included.

Most publications, 44% ($n=62$), were related to hypophosphatasia. A further 25% ($n=35$) were related to Papillon–Lefèvre syndrome and 2% ($n=3$) were related to odontohypophosphatasia, and Coffin–Lowry and Wiedemann–Steiner syndromes. Seven publications (5%) were related to neutropenias or immune deficiencies. No diagnosis of systemic disease was found in four cases (3%). No publications were related to glycogen storage disease, scurvy or Haim–Munk syndrome, which are referred to in previous summaries.[2]

5.1 | Objective 2: clinical aid development

Scoping review findings were synthesised with a further literature review of medical features, investigations and

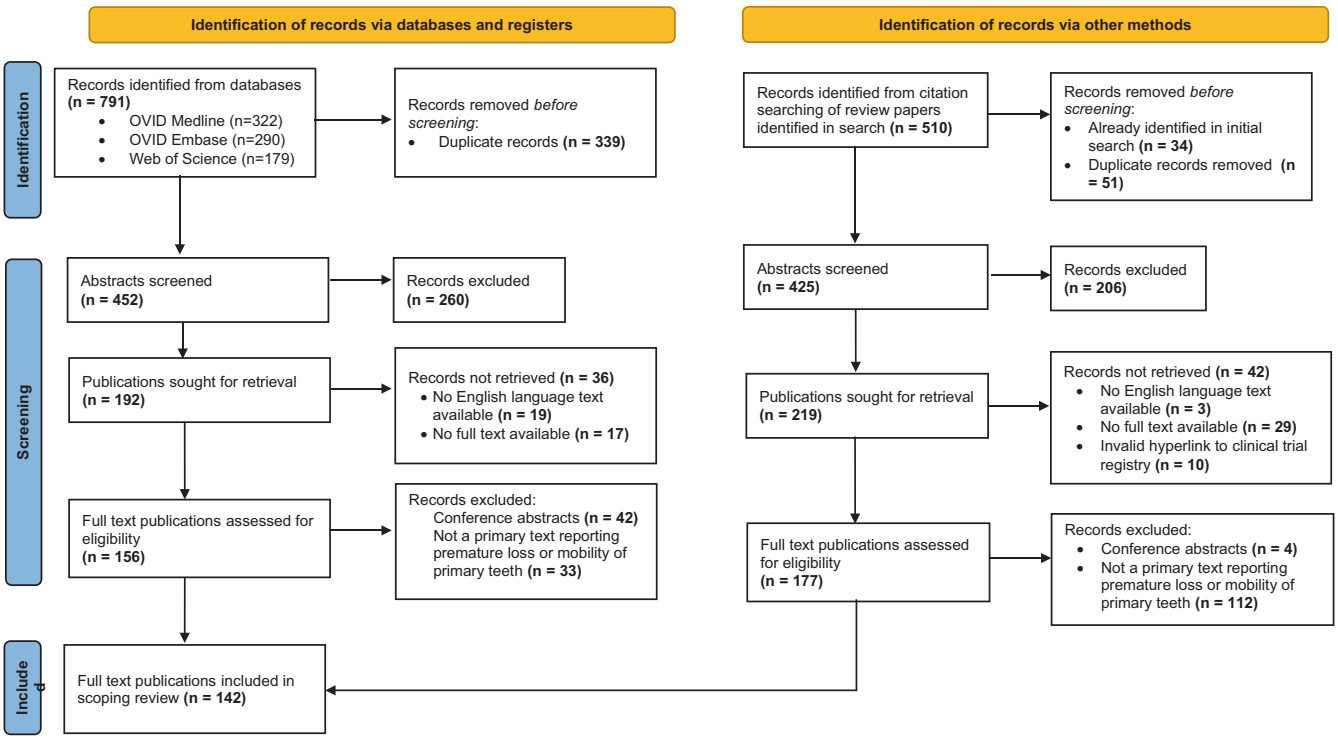

FIGURE 1 PRISMA SR flow.

TABLE 1 Summary of included records and medical conditions identified in scoping review displayed by relative prevalence and evidence quality.

Condition and number of publications identified in scoping review (n=)	Medical features	Intra-oral features	Medical investigations	Referral	Medical management
Relatively more common systemic conditions associated with premature loss of primary teeth					
Hypophosphatasia ($n=62$)[10,12–15,28–84]	Mutation in the ALPL gene causing non-function of tissue nonspecific alkaline phosphatase, a key regulator of hard tissue metabolism. Varied phenotype from fatal perinatal to mild adult onset.[85] • Delayed walking • Short stature • Skeletal deformities • Bone pain • Pathological fractures • Bowed limbs.[85,86]	Multiple included cases with patient-reported history of premature loss,[39,40,61,68] or mobility of primary teeth (not reported premature loss).[60,62] • Most commonly premature loss primary incisors.[86] • Hypoplasia • Bulbous crowns • Enlarged pulp chambers on radiographs • No evidence inflammatory periodontal disease • Sometimes craniosynostosis[85,86]	• Histology of exfoliated teeth shows the absence of cementum • Skeletal radiographs.[85] • Serum alkaline phosphatase—reduced.[86] • Urinary phosphoethanolamine—elevated.[86] • Vit B6 levels (pyridoxal 5′ phosphate)—elevated • ALPL gene changes[85,86]	Metabolic bone	Asfotase alfa for childhood-onset hypophosphatasia.[86]
Odontohypophosphatasia ($n=3$)[87–89]	Included on the spectrum of hypophosphatasia; premature loss of primary teeth without characteristic bone problems in other forms of hypophosphatasia. Children may develop bone symptoms with age and be re-diagnosed with a more severe form.[57]	One included a case of mobility of primary teeth (not reported premature loss)[88] • Most commonly premature loss of primary incisors.	• Histology of exfoliated tooth shows the absence of cementum.[88] • Serum alkaline phosphatase—may be reduced.[89] • Urinary phosphoethanolamine—may be elevated[59,89]	Metabolic bone	Monitor for the development of hypophosphatasia
Papillon–Lefèvre ($n=35$)[19–22,90–119]	Autosomal recessive mutation to CTSC gene (Capthesin C).[120] Variable severity of palmoplantar keratosis.[121] Capthesin C has immune system activating role—susceptibility to cutaneous and systemic infections due to T cell, B cell and neutrophil dysfunction.[121]	Multiple included cases with patient-reported history of premature loss,[95–97,105–107,109,113,115,116] or mobility of primary teeth (not reported premature loss)[93,112] • Gingivitis. • Periodontitis.[120] • Suppuration.[122] • Usually no change in tooth structure.[120,121] • Same premature tooth loss in permanent dentition.[121]	• Neutrophil function test • Skin biopsy • Biochemical analysis loss of CTSC activity • Genomic testing	Dermatology	• Oral retinoids, for example, etretinate, acetretin.[122] • Antibiotics Oral hygiene instruction and non-surgical periodontal therapy.[121]
Ehlers Danlos ($n=1$)[123]	Collective group of disorders of different genetic defects in collagen. Internationally classified into subgroups based on genetic cause and phenotype, including periodontal type (pEDS).[124] • Loose skin. • Excessively flexible joints and hypermobility • Fragile blood vessels, easy bruising, tendency to serious bleeding episodes.[125]	Periodontal type includes disease of periodontal tissues and premature tooth loss.[125] • Mean age of onset periodontal attachment loss 12 years in pEDS, and therefore predominantly affects permanent teeth.[125]	• Genomic testing	Paediatrician or Rheumatology	• Symptom management • Prevention of joint dislocation • Non-surgical management of periodontal disease in pEDS • Extraction of poor prognosis mobile teeth

TABLE 1 (Continued)

Condition and number of publications identified in scoping review (*n*=)	Medical features	Intra-oral features	Medical investigations	Referral	Medical management

Childhood haematological cancers (*n*=1)[126]	• Thrombocytopenia
	  • Bruising
	  • Petechiae
	  • Epistaxis
	• Neutrophil dysfunction and/or neutropenia makes prone to infection
	• Pallor
	• Hepatomegaly and splenomegaly[127]
		Uncertain association with premature loss of primary teeth, one case series identified from 1983 with premature loss in children with acute lymphoblastic leukaemia and non-Hodgkin's lymphoma.[126]
		• Spontaneous gingival bleeding
		• Gingival hyperplasia (gingival infiltration with leukaemia cells)
		• Mucositis.[127,128]
		• Enamel hypoplasia.[129]
				Oncology	• Cancer treatment
					• May have haematopoietic stem cell transplant in cases of refractory or relapse

Severe congenital neutropenia (n=1)[16]	Group of disorders in which absolute neutrophil count is <500 with maturation arrest of myeloid precursors.[130] Most commonly due to mutation in ELANE gene most common (70–80% of cases).[131] • Recurring fevers and susceptibility to bacterial infections[132] • Increased risk of leukaemia[130,132]	• Recurrent ulceration[132] • Periodontitis	• Bone marrow aspirate. • Full blood count Severe neutropenia. • Genomic testing[133]	Haematology or Immunology	• Granulocyte colony-stimulating factors.[132] • Antibiotics as needed • Haematopoietic stem cell transplant for those at high risk of leukaemia.[130]
Cyclic neutropenia (*n*=2)[134,135]	Inherited autosomal dominant disorder. Most commonly due to mutations in ELA-2 or ELANE.[132] Severe neutropenia occurring in typically 21-day cycles, with recovery of neutrophil counts in intervening period.[136] • Recurring fevers and susceptibility to infection (bacterial) in neuropenic cycles.[133]	One included case was premature loss of primary molar at age 7.5 years[134] • Recurrent oral ulceration.[136] • Gingivitis • Alveolar bone loss[135]	• Full blood counts • Multiple over a number of cycles[137] • Differential leukocyte count.	Haematology or Immunology	• Granulocyte colony-stimulating factor[132] • Antibiotics as needed
Autoimmune neutropenia (*n*=1)[18]	Usually occurs within the first 2 years of life and may be associated with development of neutrophil specific auto-antibodies.[133] • Recurring fevers and susceptibility to infection (bacterial).[133]	Included case reports mobility of primary teeth (rather than premature loss)[18] • Recurrent oral ulceration • Gingivitis • Recession	• Full blood count • Differential leukocyte count.[133] • Granulocyte immunofluorescence test	Haematology or immunology	Up to 90% of cases will spontaneously resolve.[133] • Granulocyte colony-stimulating factor.[133] • Antibiotics as needed
Chronic idiopathic neutropenia (*n*=2)[17,138]	Chronic neutropenia in the absence of identification of neutrophil specific auto-antibodies.[133] • Recurring fevers and susceptibility susceptibility to infection (bacterial)[132,133]	• Hyperplastic gingivae • Recurrent oral ulceration[17] • Alveolar bone loss • Permanent tooth mobility[138]	• Full blood count • Differential leukocyte count.[133]	Haematology or Immunology	• Granulocyte colony-stimulating factor.[132] • Antibiotics as needed. • Haematopoietic stem cell transplant for those at high risk of leukaemia.[130]
Idiopathic immune deficiency (*n*=1)[139]	• Susceptibility to infection.[139]	• Gingivitis • Candidiasis • Recession[139]	• Full blood count • Neutrophil function tests.[139]	Haematology or Immunology	• Granulocyte colony-stimulating factor.[139] • Changing medications if medication related.[140]

(Continues)

TABLE 1 (Continued)

Condition and number of publications identified in scoping review (*n*=)	Medical features	Intra-oral features	Medical investigations	Referral	Medical management
Rare systemic conditions associated with premature loss of primary teeth					

Coffin–Lowry syndrome (*n* = 3)[141–143]	X linked dominant mutation in RPS6KA3 gene.[144,30]
	• Developmental delay and delayed psychomotor development.
	• Short stature
	• Facial anomalies
	  • Macrocephaly
	  • Hypertelorism,
	  • Downward slanting palpebral fissures
	  • High vaulted palate
	  • Maxillary hypoplasia
	• Digit deformity
	  • Puffy hands
	  • Short tapering fingers
	• Seizures and drop attacks
	• Sensorineural hearing defect
	• Kyphosis or scoliosis
	• Pectus excavatum
	• Mitral regurgitation.[144,145]
		• Thick prominent lips
		• High vaulted palate
		• Hypodontia.[144]
			• Predominantly clinical diagnosis
			• Histology of exfoliated teeth.[143]
			• Genomic testing
				Paediatricians
				Neurology
					• Symptom management of drop attacks
					• Surgical correction of spinal deformity.[144]

Langerhans cell histiocytosis (*n* = 3)[146–148]	Inflammatory myeloid neoplasia with mutations in MAPKinase (MAPK) pathway.[149] Single or multiple locations therefore varied presentations.[149] In children, the skull is most affected.[150] • Bone pain if bone involvement • Hearing loss if temporal or mastoids affected.[150] • Otitis media.[150] • Bone marrow involvement results in pancytopenia[151] • Liver or spleen enlargement and jaundice.[149] • May have diabetes insipidus[150] Skin involvement.[149]	Two included cases of mobility of primary teeth (rather than reported premature loss)[147,148] • Oral features if jaw involvement • Gingivitis • Premature eruption of teeth.[147,151] • Oral ulceration.[149]	• Radiographic examination • Biopsy of involved organs.[149] • Biopsy of mucosa may show Langerhans cell infiltrate[151]	Haematology and Oncology	• Single bone lesions may be treated with surgery or steroid injections. • Multifocal lesions may be treated with chemotherapy, radiotherapy and systemic steroids.[151]
Cherubism (*n* = 2)[152,153]	Childhood-onset inflammatory bone disease characterised by bilateral, symmetrical proliferative fibro-osseus lesions limited to the mandible and maxilla.[154] Mutation in SH3BP2 gene, usually inherited in autosomal dominant manner.[154,155] • Bone degeneration and replacement with fibrous tissue • Multiple bilateral cysts in mandible and maxilla.[154,155]	• Displaced and unerupted, delayed eruption or missing permanent teeth[153,154] • Cyst formation around unerupted teeth.[156] • Premature loss of primary teeth.[153]	• Genomic testing.[154155] • Radiographic imaging. • Biopsy of lesion	Oral and maxillofacial surgery	• Surgical curettage with or without bone grafting.[154156] • Likely craniofacial, orthodontic and ophthalmology input.[154]

TABLE 1 (Continued)

Condition and number of publications identified in scoping review (*n*=)	Medical features	Intra-oral features	Medical investigations	Referral	Medical management
Leukocyte adhesion deficiency (*n*=1)[157]	Autosomal recessive group of rare disorders (types I-III) affecting leukocyte transport. • Increased susceptibility to bacterial and fungal infections.[158,159] • Absence of pus formation at infection sites • Delayed detachment of umbilical cord in type 1.[158,159] • Hypotonia • Distinct facial features • Short stature • Developmental delay Impaired platelet function in type III: • Epistaxis • Purpura.[159]	Included case reports mobility of primary teeth (rather than reported premature loss).[157] Type I: • Periodontitis • Tooth loss • Ulceration.[159] Type II: • Periodontitis[159] Type III: • Gingival bleeding[159] In addition: • Bone loss primary and permanent dentitions • Oral ulceration • Candidiasis	• Full blood count • Genomic testing[159] • Flow cytometry with antibodies to detect CD18 (Type I).[159]	Immunology	• Symptom-based antibiotic therapy (prophylactic when severe)[158] • Monoclonal antibodies (e.g., ustekinumab)[158] • Recombinant FVIIa for type III.[160] • Haematopoietic stem cell transplant for severe type I.[158]

Wiedemann–Steiner syndrome (*n*=3)[161–163]	Autosomal dominant mutation in KMT2A gene.[164]
	• Distinctive facial features
	  • Thick eyebrows
	  • Wide set eyes
	  • Narrow palpebral fissures
	• Hypertrichosis
	• Developmental delay.[161,164,165]
		• Premature eruption of primary teeth and permanent teeth.[161]	• Genomic testing	Paediatrician	

Chediak–Higashi syndrome (*n*=1)[166]	Autosomal recessive CHS1 gene mutation a.k.a LYST gene[137,167,168] Rare Lysosomal storage disorder.[169] • Oculocutaneous hypomelanosis • Bleeding tendency • Haemophagocytic • Lympohistiocytosis • Late-onset progressive neurological impairment (sensory or sensorimotor)[170] • Susceptibility to infections	• Periodontitis	• Genomic testing • Blood film.[137]	Haematology or Immunology	• Haematopoietic stem cell transplant to correct haematological defects.[137]
No reported diagnosis (*n*=4)[11,23–25]			Possibly generalised periodontal disease without systemic cause or undiagnosed systemic conditions.		

(Continues)

TABLE 1 (Continued)

Condition and number of publications identified in scoping review (*n*=)	Medical features	Intra-oral features	Medical investigations	Referral	Medical management
Rare systemic conditions with limited and uncertain evidence of association with premature loss of primary teeth					
Chronic graft vs host disease (*n*=1)[171]	Haematopoietic stem cell transplant recipients. Donor T cells respond to histo-incompatible antigens on host tissues.[172] Skin, gastroinstestinal tract and liver most common target organs.[172]	• Oral ulceration • Mucositis • Lichenoid changes • Perioral fibrosis, • Periodontitis[171]	Predominantly a clinical diagnosis • Biopsy of target organs.[172]	Will already be under care of oncology and transplant teams.	Prevention: • Calcineurin-based inhibitor to block T-cell activation, for example, ciclosporin, tacrolimus • Low-dose methotrexate or mycophenolate. Treatment: • Prednisolone[173]
Congenital adrenal hyperplasia (*n*=1)[174]	Group of autosomal recessive disorders affecting cortisol biosynthesis. Results in low cortisol and/or aldosterone deficiency and/or excess androgens.[175] Excessive androgens: • Fast body growth and premature completion of growth resulting in short stature. • Ambiguous genitalia in females Aldosterone deficiency • Excess water loss and salt wasting • Hypovolaemia • Low blood pressure (in salt losing type) Low cortisol • Adrenal crisis risk[175]	Included case reports mobility of primary teeth (rather than reported premature loss)[174] • Alveolar bone loss • Tooth surface loss • Accelerated eruption of permanent teeth.[174]	• Neonatal screening.[175] • Non-classical congenital adrenal hyperplasia—corticotropin stimulation test.[175] • Genomic testing.[175]	Endocrinology	• Glucocorticoids
Congenital syphilis (*n*=1)[176]	Mother-to-child transmission of Treponema pallidum. Early syphilis (<2years old) • Hepatosplenomegaly • Lymphadenopathy • Rash • Haemolytic anaemia • Thrombocytopenia • Rhinitis.[177] Late syphilis (>2years old) • Interstitial keratitis • Sensorineural deafness.[177]	• Hutchinson's incisors • Moon's and Mulberry molars • High arch palate • Perioral scarring from early skin inflammation.[178] • Mucocutaneous lesions.[177]	• Blood test for antibodies to spirochete infection • Identification of Treponema pallidum[179]	GP or Paediatrician	• Penicillin[177]

TABLE 1 (Continued)

Condition and number of publications identified in scoping review (*n*=)	Medical features	Intra-oral features	Medical investigations	Referral	Medical management
Erythromelalgia (*n* = 1)[180]	Mutations in SCN9A gene resulting in altered sodium channels and neuron excitability. Neuropathy resulting in triad of redness, burning pain and warmth in extremities relieved by cooling and elevation. Episodic but of continuous nature.[181] In episodes, triad of symptoms in extremities: • Pain • Redness • Warmth	• Bone loss • Mobility • Gingivitis.[180]	• Genomic testing	Paediatrician or Neurology	Symptomatic relief • Ice water • Elevating affecting limbs
Familial (Infantile) malignant osteopetrosis (*n* = 1)[182]	Dysregulated osteoclasts resulting in osteosclerosis. Excessive bone deposition around cranial foramina resulting in nerve compression. Excess bone interferes with medullary haematopoiesis resulting in bone marrow suppression.[183] • Progressive optic, facial, oculomotor and auditory dysfunction as well as hydrocephalus.[184] • Short stature • Macrocephaly • Frontal bossing.[183] • Pancytopenia[183] and severe immunocompromise.[182]	• Micrognathia • Delayed dental development.	• Full blood count • Radiographs[183]	Metabolic bone team or haematology	• Haematopoietic stem cell transplant to manage pancytopenia[184]
Fanconi syndrome (*n* = 1).[185]	Congenital or acquired inadequate reabsorption in the proximal renal tubules of small molecules, for example, glucose, amino acids, uric acid, phosphate, bicarbonate.[186] Loss of phosphate affects bone development. • Polyuria • Polydipsia • Delayed growth • Muscle weakness • Features of rickets and osteomalacia.[186]	• Delayed eruption permanent teeth • Lack of differentiation between enamel and dentine on radiographs.[185]	• Bone profile—low phosphate • Urine sample—contains amino acids and glucose	Renal team	• Management of renal failure • Correction of underlying cause of Fanconi syndrome
Hereditary sensory and autonomic neuropathy type VIII (*n* = 1).[187]	Autosomal recessive mutation in PRDM12 gene.[188] • Insensitivity to pain • Self-mutilation • Decreased sweating and tear production • Absence of corneal reflex resulting in corneal scarring • Repeat infections of skin and bone.[188]	Premature loss in included case believed to be due to auto-extraction.[189] • Traumatic ulceration to tongue and lips.[189]	• Genomic testing	Neurology	

(Continues)

TABLE 1 (Continued)

Condition and number of publications identified in scoping review (n=)	Medical features	Intra-oral features	Medical investigations	Referral	Medical management
Metaphyseal dysplasia—Braun–Tinschert type ($n=1$)[190]	Metaphyseal widening and under-modelling of bone of extremities (tubular bones). Unusually severe varus deformity of the radii and flat exostoses of the long bones. Skull is unaffected.[191]	Premature eruption permanent successors in reported case.[190]		Paediatrician	

Microcephalic osteodysplastic primordial dwarfism or Seckel syndrome Type II ($n=2$)[192,193]	Autosomal recessive mutation in PCNT gene.[194] May have chronic kidney disease, anaemia, thrombocytosis, hypertension, insulin resistance and Moyamoya[194]
	• Extremely short stature
	• Microcephaly
	• Facial features:
	  • Broad nose
	  • Low columella.
		• Microcephaly
		• Microdontia[194]
		• Oligodontia
		• Altered morphology
		• Gingivitis[192]
		• Root resorption
		• Gingival recession[193]
			• Genomic testing	Paediatrician	

Weary–Kindler syndrome ($n=1$)[195]	Associated with FERMT1 pathogenic variants.[196] • Vesicopustules • Eczema • Poikiloderma • Acral keratotic papules	Case report with patient-reported history of premature loss of primary teeth • Small mouth • Limited mouth opening[195]	• Genomic testing	Dermatology	• Skin care • Avoid sunlight
Acatalasemia ($n=1$)[197]	Genetic enzyme defect resulting in catalase deficiency.[198] Catalase deficiency results in an inability to break down hydrogen peroxide.[199] • Usually asymptomatic but may be associated with diabetes mellitus.[199]	Included case is of patient-reported history of mobility of primary teeth (not reported premature loss)[197] • Oral ulceration and oral gangrene (Takahara's disease).[199]	• Genomic testing	Paediatrician	• Symptom management
Familial renal hypophosphataemia with intracerebral calcifications ($n=1$)[200]	Reporting of a novel case series of siblings with: • Renal hypophosphataemia • Intracerebral calcifications • Abnormal facies • Hyperextendable joints • Non-rachitic bone changes • Short distal phalanges	• High arched palate • Gingival hyperplasia • Opalescent dentine and rapid tooth wear		Paediatrician	• Management of renal hypophosphataemia
Mucocutaneous dyskeratosis with premature tooth loss ($n=2$)[201,202]	Two cases with similar presentations of: • Dyskeratosis of skin and oral mucosia • Ocular involvement in one case[202]	One included case reports primary teeth mobility (rather than reported premature loss)[201] • Alveolar bone loss • Gingival swelling and hypertrophy • Angular cheilitis[202] • Mobility and loss of permanent teeth in one case[202]		Paediatrician	• May require onward referral to dermatology or ophthalmology for management of skin and eye lesions

TABLE 1 (Continued)

Condition and number of publications identified in scoping review (*n*=)	Medical features	Intra-oral features	Medical investigations	Referral	Medical management
Short-bowel syndrome (*n*=1)[203]	Short-bowel syndrome can be either congenital or acquired following the surgerical resection of the small intestine.[203] Case series of two children with other complex co-morbidities including recurrent infections • May receive parental nutrition	Two cases presented, with premature loss occurring in one patient.[203] • Alveolar bone loss • Gingival recession		Paediatrician	• Management of nutrition
Considered to be associated with premature loss of primary teeth in the seminal literature but no evidence identified in scoping review					
Haim–Munk syndrome (*n*=0)	Autosomal recessive mutation of CTSC as in Papillon–Lefèvre.[121] • Palmoplantar keratosis • Susceptibility to infections, particularly pyogenic skin infection Features to differentiate from Papillon–Lefèvre: • Flat feet • Arachnodactyly • Onychogryphosis • Acral osteolysis.[204]	• Periodontitis. • Loss of permanent teeth if untreated.[205]	• Neutrophil function test • Skin biopsy • Biochemical analysis loss of CTSC activity • Genomic testing	Dermatology	• Oral hygiene instruction • Non-surgical periodontal therapy • Oral retinoids, for example, etretinate, acetretin.[205]
Glycogen storage disease (*n*=0)	Enzyme deficiency affecting glucose storage and glycogen breakdown. Results in neutrophil dysfunction. 23 distinct diseases, classified by the enzyme deficiency involved. • Delayed growth and short stature.[206] • Hypoglycaemia • Seizures.[206] • Susceptibility to infections.[137]	Type Ib most associated with oral features.[137,206] • Recurrent bacterial infections • Recurrent oral ulceration.[137]	• Full blood count • Neutrophil function tests • Blood glucose • Lactate, liver function test and urea and electrolytes.[206]	Metabolic medicine, endocrinology, and immunology	• Granulocyte colony-stimulating factor.[137] • Multi-disciplinary management depending on disease extent.[206]
Scurvy (*n*=0)	Severe vitamin C deficiency resulting in reduced antioxidant immune defences to oxidative stress. Defective collagen synthesis resulting in weakened capillary vessels and bleeding tendency.[207] • Petechiae • Purpura • Joint swelling • Osteopenia • Susceptible to fractures • Arthralgia • Poor wound healing.[208]	• Gingival bleeding • Mobility of teeth.[208]	• Full blood count • Vitamin C plasma levels.[208]	Paediatrician	• Increase vitamin C intake through diet and supplementation

(Continues)

TABLE 1 (Continued)

Condition and number of publications identified in scoping review (n=)	Medical features	Intra-oral features	Medical investigations	Referral	Medical management
Wiskott–Aldrich syndrome (n=0)	Severe X linked mutation of WASp,[209] characterised by thrombocytopenia, immune deficiency and eczema.[137,210] Additionally, increased risk of lymphoma.[210] • Petichiae • Purpura • Eczema • Recurrent infections.[210]	• Gingival ulceration and bleeding tendency.[210]	• Genomic testing	Paediatrician or haematology	• Curative haematopoietic stem cell transplant.[209]

treatment of each systemic condition to support clinical aid development (Table 1). Through this process, four distinct categories were identified as distinguishing features: haematological features, skeletal features (including craniofacial), neurological features and skin features. An iterative consensus approach was applied to streamline findings into an accessible clinical aid (Figure 2); this summarises pertinent diagnostic features to support specialists in paediatric dentistry in assessing, diagnosing and referring children with PLPT.

6 | DISCUSSION

This evidence synthesis provides a broad overview of systemic features of conditions associated with PLPT. This paper is novel in its comprehension, and in condensing this information into a practical clinical diagnostic aid.

Clinicians should take a systematic approach to history and examination for these children. Although many conditions will already have been identified, PLPT can aid or confirm a systemic diagnosis. In conditions such as delayed development, recurrent infection or skeletal problems, although these may already be under investigation, PLPT may support definitive diagnosis.[10] In some cases, premature loss, however, may be the first sign of a systemic condition. This was evident in the scoping review in multiple published hypophosphatasia,[11–15] neutropenia[16–18] and Papillon–Lefèvre[19–22] cases in particular.

The aim of this study was to identify systemic conditions associated with PLPT. As such, the inclusion criteria of the scoping review were for cases in which loss of teeth or excessive mobility had occurred, although attachment loss was included in the search strategy for completeness. Search strategies with specific terms relating to systemic disease were trialled but were found to produce more narrow results, with publications utilising more specific disease terms and diagnoses omitted. This is noted in a recent narrative review of PLPT, which yielded roughly a third of the results when compared to this scoping review in a more specific search strategy.[4] A search strategy omitting reference to systemic disease and inclusion of citation searching of review papers was more time-consuming, with manual exclusion of cases of PLPT relating to caries and traumatic dental injury occurring. However, it supported the completion of a comprehensive scoping review. The number of included cases of hypophosphatasia and Papillon–Lefèvre identified in the scoping review was impacted by citation searching of five review articles specific to these individual diseases.[5–9] Two review papers more broadly relating

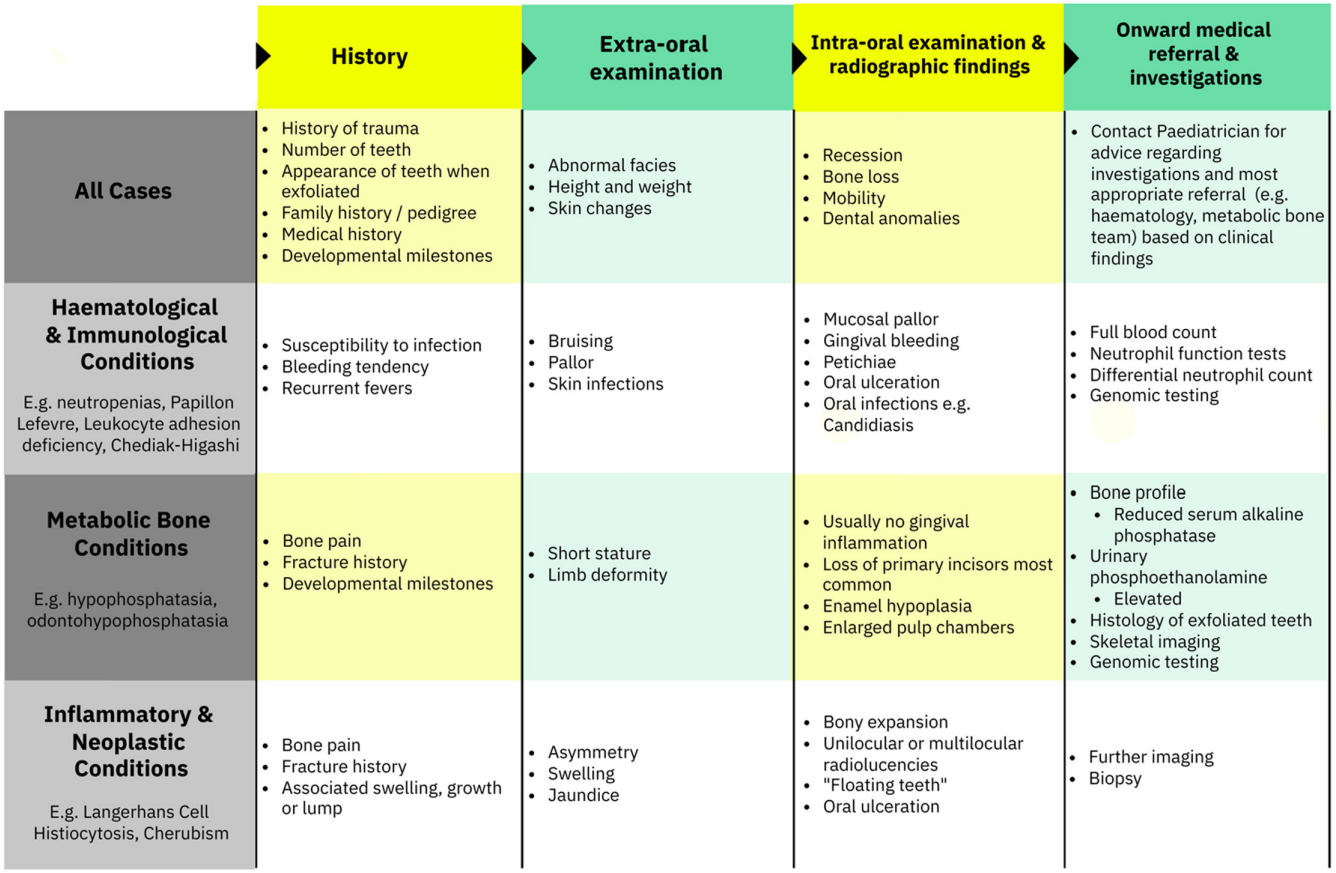

FIGURE 2 Clinical aid to support differential diagnosis and onward referral of premature loss of primary teeth.

to PLPT, however, also underwent citation searching for inclusion.[2,4]

There were a small number of cases included in the scoping review in which a definitive systemic diagnosis was not found at the time of publication, but premature tooth loss had occurred and a diagnosis of periodontitis was made.[11,23–25] Similarly, conditions previously associated with PLPT were not identified in the scoping review (e.g., Haim–Munk syndrome, glycogen storage disease and scurvy).

It is beyond the scope of this article to provide the detailed oral and general management of each condition, however, a few general principles apply. Clearly, by definition, management needs to be interdisciplinary with close liaison with the paediatric team. In some cases, it is likely that if the systemic condition can be addressed, then PLPT can be delayed or arrested.[26] The management of the early loss may therefore be intrinsically connected to the management of the systemic condition. Clinicians should be aware that in most cases, the premature loss will extend to the permanent dentition should intervention not be possible or undertaken.

The maintenance of optimal oral hygiene is a good principle to follow. Poor oral hygiene can exacerbate the periodontal health and accelerate premature loss.[27] Families should have access to regular, high-quality, preventative services. Although children may not be at high risk of dental caries, they should be managed as being high risk due to the implication of developing dental caries on their reduced dentition. Children should be considered high risk for periodontal disease and managed appropriately. Consideration should be made as to whether the systemic condition is likely to have implications for the treatment of any oral disease that does develop.

Children should remain under specialist paediatric dental care. Parents and carers should be kept fully informed of the consequences of the disease process, particularly its implications for the permanent dentition. The management decisions will be complex, and clinicians should engage in shared decision-making whenever possible.

As this literature review focused on primarily reported cases, it is acknowledged that there may be other oral features not identified in the evidence synthesis. Clinicians are encouraged to take a pragmatic approach so as not to exclude a differential diagnosis from this diagnostic aid due to a novel finding.

Premature loss of primary teeth secondary to systemic conditions is a rare but important presentation. This scoping review has demonstrated that it can be caused by a

diverse range of medical conditions, many of which may be unfamiliar to the clinician. Furthermore, there are a number of conditions reported to be associated with premature loss but for which no, or limited, primary evidence has been found. The clinical aid developed from the scoping review provides an evidenced-based tool to which clinicians can refer when presented with such cases. This clinical aid acts as an aide memoir to remind clinicians of relevant information to gather in the history and enables clinicians to link specific features to broad aetiological categories.

AUTHOR CONTRIBUTIONS

R.B. conceived the idea. C.H. and H.A. collected and collated data. C.H., H.A., and R.B. analysed data. C.H. led the writing. All authors provided input to clinical aid development and have approved the manuscript. The BSPD QIRC provided peer review and methodological support.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest were identified by any of the authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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