MANIFESTATIONS OF LYOSOMAL STORAGE DISEASES IN THE STOMATOGNATHIC SYSTEM – A LITERATURE REVIEW

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ABSTRACT

The stomatognathic system comprises the mouth, teeth, jaws, pharynx, and related structures associated with mastication, swallowing, and speech. Lysosomal storage diseases (LSDs) are metabolic disorders, which cause an increase of systemic complications and are even life-threatening. They may also lead to a change in the socio-economic conditions of people suffering from these diseases, and their families. LSDs are inherited in an autosomal recessive pattern.

Many syndromes of lysosomal diseases represent anomalies of the craniofacial region and in the oral cavity. For the vast majority, treatment is not required, but for some of them it is necessary to reconstruct the morphology or the proper function. The appearance of the face can have a negative impact on the quality of the patient’s life. Breathing, chewing, speaking, smiling, and mimic movements are the consequences of facial deformities. Irregularities of the sensory organs can sometimes be observed – especially of hearing, smell, and sight. The most frequent manifestations of lysosomal diseases in the oral cavity are malocclusion, macroglossia, tooth eruption, and development disorders as well as periodontal disorders, for instance hypertrophy of the gingiva.

The population of people suffering from lysosomal diseases often have specific oral health needs compared to the population of generally healthy people. Many syndromes of lysosomal diseases represent anomalies of the craniofacial region and in the oral cavity. For the vast majority, treatment is not required, but for some of them it is necessary to reconstruct the morphology or the proper function. The appearance of the face can have a negative impact on the quality of the patient’s life. Breathing, chewing, speaking, smiling, and mimic movements are the consequences of facial deformities. Irregularities of the sensory organs can sometimes be observed – especially of hearing, smell, and sight.

INTRODUCTION

Lysosomal storage diseases (LSDs) are a group of 50 rare, inherited, metabolic disorders characterised by deficiencies in normal lysosomal function and by intralysosomal accumulation of undegraded substrates [26]. The underlying continuous accumulation in lysosomes leads to abnormalities in cells, tissues, and organs functioning. They can cause an increase of systemic disorders and can even be life-threatening. In addition, they may involve a change in the socio-economic conditions people suffering from these diseases and their families.

Most LSDs are inherited in an autosomal recessive manner. The only exceptions are three diseases: Fabry disease and Hunter’s disease (mucopolysaccharidosis type II), which exhibit X-linked recessive inheritance, and Danon’s disease, which is inherited via an X-linked dominant manner [44].

The clinical heterogeneity found in all LSDs leads to misdiagnoses and diagnostic confusion, which results in significant difficulties when gathering epidemiological data. The population of people suffering from lysosomal diseases often have specific oral health needs compared to the population of generally healthy people.

KEY WORDS: rare diseases, metabolic disorders, oral, head and neck.

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data and an underestimation of the impact of LSDs in the community.

The population of people suffering from rare diseases such as LSDs often have special oral health needs compared to the overall population of generally healthy people. The most common manifestations of those diseases within the stomatognathic system include: abnormalities of tooth development and eruption, disorders in hard tissue mineralisation and the number of teeth, malocclusion, dysfunctions and anomalies of the temporomandibular joint, cleft of the primary or secondary palate, and irregularities of the sensory organs – hearing, smell, and sight.

LPS can be classified, by the nature of the primary stored material involved, into the following groups (available International Statistical Classification of Diseases and Related Health Problems – ICD-10 codes are provided in brackets) [45]:

- (E75) Lipid storage disorders, e.g. Gaucher’s disease (E75.2),
- (E76.0) Mucopolysaccharidosis, e.g. Hunter syndrome (E76.1),
- (E77) Glycoprotein storage disorders, e.g. alpha-mannosidosidosis (E77.1),
- (E77) Mucolipidosis, e.g. mucolipidosis type II (E77.0),
- (E74) Glycogen storage diseases, e.g. Pompe disease (E74.0).

**MATERIAL AND METHODS**

The aim of this paper was to perform a review of the medical literature to present the manifestation of LSDs in the stomatognathic system. The literature was searched by using hand and electronic methods (PubMed, ResearchGate, ScienceDirect) for original papers, case studies, review papers, epidemiological databases, and books chapters, which concerned the manifestation of LSDs in the stomatognathic system. Publications were dated from 2001 to 2018 with the exception of some articles from before 2000 (1976, 1984, or 1999), which are still reliable with regard to current knowledge. The majority of articles were in English language, but there were also a few Polish articles taken into consideration during the preparation of this paper. The publications discussing the aforementioned issue of manifestation of LSDs in the stomatognathic system among the areas of dentistry, otolaryngology, paediatrics, biology, biochemistry, and genetics were analysed. Key terms used in the searches were: “lysosomal storage diseases”, “oral manifestations”, “dental findings”, “rare diseases”, “mucopolysaccharidosis”, “mannosidosis”, “mucolipidosis”, “Gaucher’s disease”, “Pompe disease”. Total number of using references was 49.

**GAUCHER’S DISEASE**

Gaucher’s disease (GD) is a panethnic lysosomal storage disorder, which is especially common among Ashkenazi Jews (it can reach up to 1 per 850 persons in this population) [41]. The prevalence varies from 1 : 50,000 to 1 : 200,000 in the general population [33]. The disease is inherited as an autosomal recessive deficiency of the lysosomal enzyme acid β-glucocerebrosidase [21]. The defect causes an accumulation of glycolipid material in macrophages. Infiltration of Gaucher cells – lipid-laden macrophages – in tissues can be associated with systemic pathology such as hepatosplenomegaly, pancytopenia, skin pigmentation, neurological symptoms, involvement of the bones, and severe bone pain [41, 48].

There are three recognised types of Gaucher disease: type 1 (chronic non-neuronopathic form) is the most common type, especially among the population of Ashkenazi Jews. It can be asymptomatic, usually discovered incidentally during examination of an unrelated haematological problem. Acute neuronopathic form – type 2 – a lethal disease expressed during infancy. Typical symptoms are strabismus, trismus, retroflexion of the head, laryngospasm, and aspiration pneumonia – the latter symptom being the main reason for untimely death, which usually occurs by two years of age. Type 3 is a subacute neuronopathic form, having an unstable course of illness, in which death occurs in the second or third decade of life [18, 41].

Oral and dental abnormalities are less common, but jaw involvement might be observed, as well as delayed eruption of permanent teeth, yellow pigmentation of the oral mucosa, petechiae, hyposalivation, dental pain, sinusitis, and osteomyelitis [20, 41, 46, 48].

More than 90% of affected patients are diagnosed with bone involvement [16, 41, 46]. Jaw lesions are often asymptomatic and can be detected as an incidental finding on routine dental radiographs [7]. The mandible is more commonly affected than the maxilla [16]. Various radiographic features in the jaw have been reported, but the most frequent presentations are pseudo-cystic or honeycombed radiolucent lesions, mostly in premolars regions [1, 41]. Osteopaenia and loss of trabecularity are commonly observed. Other radiographic findings include loss of lamina dura around affected teeth, generalised osteoporosis, widening of bone marrows spaces, displacement of the mandibular canal, and apical root resorption of teeth adjacent to the bone lesions [1, 20]. The root resorption is usually mild and can reverse by itself. Presumably, the apical region of teeth and all bone lesions are caused by the changing density of the accumulated Gaucher cells [16, 41]. Other craniofacial bones may also be affected, although that is reported rarely. In the maxilla, the alveolar bone generally has a normal appearance. Involvement of the maxillary sinus was reported only in a few cases as an obliteration [16, 41].

Manifestations within soft tissues in the oral cavity are rare and can be marked as increased pigmentation on oral mucosa. However, some authors have reported facial discoloration around the mouth [41].
An important issue regarding Gaucher diseases in oral care is increased bleeding tendency. It is caused by unsettled coagulation cascade, hypersplenism, or inappropriate platelet function [41, 48]. Hence, prophylaxis against an excessive bleeding is recommended for patients in cases of extraction, dental surgery, or periodontal therapy [18]. Patients with this disorder have a high risk of postoperative oral infection, so antibiotic prophylaxis is necessary. In certain cases of Gaucher disease, patients undergo monotherapy with bisphosphonates. Before all dental surgery procedures, the clinician should be aware of a possible complication: the risk of jaw osteonecrosis [41].

Horwitz et al. reported a greater risk of early development of periodontitis. Correct oral hygiene, and regular procedures such as scaling and root-planning, may lead to delayed progression of periodontal diseases [1, 20].

**MUCOPOLYSACCHARIDOSIS**

Mucopolysaccharidosis (MPS) is a congenital, genetically determined, metabolic disease that belongs to a heterogeneous group of LSDs. Glycosaminoglycans – GAGs (formerly known as mucopolysaccharides) undergo accumulation in lysosomes due to complete lack or deficiency of specific enzymes from the group of hydrolases, which are responsible for the catabolism of these substances [29]. Thus far, 11 different enzyme deficiencies have been identified, which are a cause of seven types of MPS [36]. GAGs accumulate in many cells of the body, resulting in dysfunction of these cells, which may cause progressive damage to organs of the body such as heart, bones, joints, and respiratory and nervous systems [29, 36]. All mucopolysaccharidosis, except MPS II (Hunter disease), are transmitted in an autosomal recessive pattern. In the case of MPS II, inheritance is sex-linked recessive. The mutated gene is located on the X chromosome (more precisely Xq28) [29]. All males possessing the above-mentioned mutation are affected. The overall incidence of MPS is difficult to estimate due to the numerous types of disease and no standardised statistics. Jureckova et al. reported that the prevalence of all types of mucopolysaccharidosis in the Polish population between 1970 and 2010 was 1.81 per 100,000 live births (the number of live births from 1970 to 2010 in Poland is estimated at 21,686,890) [23], in comparison to a higher prevalence in the Netherlands (4.5 per 100,000 live births) or the Czech Republic (3.72 per 100,000 live births) [23].

One of the most important features of MPS patients is that this disorder is associated with a variety of phenotypes. The disorder can be seen as early as in the neonatal period. It develops slowly as a result of the progressive accumulation of mucopolysaccharides in cells [29, 36]. A marker of progressive GAG accumulation in tissues is the GAG concentration excreted in urine [36]. Some researchers postulate a view on the correlation of the severity with urinary GAG excretion or linking the efficiency of GAG synthesis with poor enzymatic activity [39]. The concentration of GAG in urine decreases with age, in both healthy and MPS patients. Nevertheless, in the vast majority of patients with MPS, this concentration exceeds or has a limit value in relation to the accepted laboratory standards for healthy people [25].

Musculoskeletal abnormalities are present in every form of MPS, but the degree of advancement varies. They may be a sign of disease progression. Deformations of the bone cause significant disabilities and may even be a reason for shortening the lifespan. Patients with MPS III (Hurler disease), IH/S (Hurler-Scheie disease), II (Hunter disease), IV (Morquio disease), and VI (Maroteaux-Lamy disease) very often have lessened height and growth retardation [36, 37].

The common specifics for all MPS is dysostosis multiple, i.e. a bone disorder syndrome, which concerns the entire skeleton to varying degrees. These changes are visible in X-ray imaging. The pathogenesis of this abnormality is based on the deposition of GAG in osteocytes and chondrocytes, which results in the loss of normal bone and cartilage architecture, and thus disturbances of the growth of these tissues [30, 36]. Most patients with MPS present with the following: macrocephaly, deformation of pituitary and premature atresia of saggital suture, resulting in reshaping of the skull – known as boat-shaped skull [30]. In addition, skeletal abnormalities also affect the occipital bone together with the first two vertebrae of the spine – the atlas and the axis. Disturbed structure of these vertebrae causes destabilisation of the entire cervical spine and problems with head movements [30, 36].

The main problems associated with the sense of sight are corneal opacity, glaucoma, photoreceptor degenerative changes (retinopathy), atrophy of the optic nerve with swelling of the optic disc, squinting (usually divergent), and hyperopia [3].

Among patients with MPS there is a common issue of a narrowing of the upper respiratory tract, which may be a cause of OSAS (obstructive sleep apnoea syndrome). Researchers say that the causes might be: adenotonsillar hypertrophy (due to accumulation of GAG inside tonsils), short neck, and joint instability of cervical vertebrae [11, 36, 42]. Due to the extremely sticky secretion of mucous glands and the impaired mucociliary transport system of respiratory epithelium, patients with MPS are predisposed to recurrent infections of the upper respiratory tract, including paranasal sinuses [36, 42].

The face of patients with MPS has characteristic features. Face dysmorphia is caused by the deposition of GAG within the facial soft tissues and lips. The facial features are coarsening, lips are prominent, the bridge of the nose is shortened, and the base of the nose to the
quantitative disturbances in enamel structure, which appear as enamel hypoplasia, as well as abnormalities in the anatomical structure of the teeth (misshapen teeth), peg-shaped or hypoplastic [4, 40]. Patients who suffer from MPS type VI (Marretoux-Lamy syndrome) are predisposed to developing union cysts (DC, dentigerous cysts) [47].

**ALPHA-MANNOSIDOSIS**

Alpha-mannosidosis is a rare lysosomal storage disease of the glycoprotein family, which is inherited in an autosomal recessive pattern [43]. The fundamental cause of alpha-mannosidosis is mutation in the gene encoding for the lysosomal α-D-mannosidase. It results in defective mannosidase activity and leads to the accumulation of mannose-rich oligosaccharide chains in tissues [5, 43]. It is characterised by the gradual onset of signs and symptoms affecting the physical and mental development as well as visual changes, hearing loss, and skeletal abnormalities [43]. Patients seem to be healthy at birth, without any signs of the disease, and their condition worsens with age [43]. During first year of life, they may develop hydrocephalus [19]. Recurrent infections of the respiratory system or ears, and impairment of hearing, speech, and mental function are early symptoms [2, 5]. The most prominent clinical features are dysostosis multiplex, immune deficiency, mental retardation, hearing loss, and abnormal motor function, e.g. ataxia [2, 32]. Alpha-mannosidosis is estimated to occur about in 1 in 500,000 live births [32].

Alpha-mannosidosis is divided into two separate phenotypes. The first of them – severe form – is characterised by hepatosplenomegaly, serious skeletal abnormalities, and early death at < 3-8 years of age as a consequence of severe infections. Type II – a milder juvenile-adult form – has slow progression, manifesting as hearing loss and mental retardation [2, 5, 32].

Diagnosis is based on measuring acid α-mannosidase activity in leukocytes. Genetic diagnostics by mutation analysis is rarely available and rarely used [32].

The progression and clinical expression of the diseases can vary from patient to patient. The face appears somewhat coarse (gargoylism) [22], becoming more evident in the second decade of life. The facial appearance of children with alpha-mannosidosis includes macrocephaly with prominent forehead, rounded eyebrows, and broad nose with a flattened bridge [15, 22]. The ears are usually relatively large and low-set. Ophthalmological traits such as slight corneal opacities, cataract, amblyopia, or strabismus are also common to this disorder [9, 32].

The neck is often short, which may cause problems in breathing. The trachea becomes stenotic by storage material and is often softer than normal due to abnormal construction of cartilages in the trachea. The tonsils top is wide [4, 11]. The mentioned facial features in the en face position are shown in Figure 1.

Mucopolysaccharidosis also has a significant impact on the oral cavity. It usually manifests itself in the form of macroglossia, which along with putting a tongue to the front, between the dental arches, is a factor that causes malocclusion [4, 11]. In the studies of Ponciano et al. the research group consisted of 12 people with diagnosed MPS (without specifying its specific type) and a 12-person control group. The researchers observed in 92% of cases with people with MPS frontal bite and limitations in the opening of the mouth. In a half of the cases, there was a gap between the central incisors in the study group, known as diastema (Figure 2) [40]. Furthermore, we can observe the following: delayed eruption of teeth,
and adenoids often become enlarged and can contribute to block the airway. To avoid obstruction of the upper respiratory tract they should be removed [17, 32].

Oral features linked with alpha-mannosidosis include prognathism, macrognathia, and widely spaced teeth. In the literature other oral findings are described in a 26-year-old man, such as hypertrophy and hyperplastic nodules of the gingiva, associated with alpha-mannosidosis [22]. Kalsi et al. presented the case of siblings diagnosed with alpha mannosidosis, who were probably affected by the hereditary form of periodontal disease with severe progress [24]. It is most likely that the main reason of the development of periodontal disease among alpha-mannosidosis patients is a humoral and cellular level immunodeficiency, and especially reduction of the number of PMNLS and decreased number of antibodies [24, 32].

MUCOLIPIDOSIS – TYPE II

Deficiency of the enzyme N-acetylglucosaminyl-1-phosphotransferase is the fundamental cause of the mucolipidosis, and the differential diagnosis with other LSD’s is based on the age of occurrence, clinical symptoms and severity [6]. The frequency of the mucolipidosis types II and III is estimated at 1 : 422,000 [34]. Also known as pseudo-Hurler polydystrophy, mucolipidosis type III (ML III) appears to be milder than mucolipidosis type II (ML II), in which patients exhibit coarse facial features, early restricted joint movements, and more severe psychomotor delay [8].

The most important clinical features are the skeletal abnormalities. All patients have abnormally shaped bones (commonly known among patients with LSDs – dysostosis multiplex) and cartilage degradation caused by increased secretion of osteoclastic enzymes [13]. Coarse facial features, gingival hypertrophy, thickened skin around the ears, low nasal bridge, and widely-spaced teeth are fundamental symptoms of ML II in the stomatognathic system. Eruption of teeth could appear as incomplete, but this is an effect of impressive gingival hypertrophy. Additional findings include the epicanthi folds, mild corneal haziness, and prominent telangiectatic capillaries over the cheeks. Craniosynostosis is observed in some patients. The otitis media appears frequently amongst patients suffering from ML II [31, 35].

GLYCOGEN STORAGE DISEASES (GSD)

Pompe disease is also known as glycogen storage disease type II or acid alpha-glucosidase (GAA) deficiency. The disease is an autosomal recessive metabolic disorder, characterised by a defect in acid α-glucosidase, which is a lysosomal hydrolase, encoded by glucosidase acid alpha gene on the 17th chromosome. This enzyme normally degrades the α-1,4 and α-1,6 linkages in glycogen, maltose, and isomaltose. The deficiency of this enzyme results in the accumulation of structurally proper glycogen in lysosomes and cytoplasm, mainly are affected miocytes of transversal rhabdomyed muscles [27, 49]. The prevalence of this disorder is approximately 1 : 40 000 [49]. The diagnosis of Pompe disease is based on skin or muscle biopsy. It leads to check an activity of GAA enzyme [49].

Weakness of muscles is a main symptom of Pompe disease. Patients find difficulty in walking, breathing, or swallowing [49]. During an examination, we can observe bilateral ptosis (drooping or falling of the upper eyelid) and generalised loss of tenseness of mimetic and mastication muscles (the facial hypotonia). We can notice malocclusions, hypoplasia of the middle floor of the face, and prognathism. Inappropriate activity of chewing muscles, reduced lip seal, and tongue enlargement with reduced tension cause difficulties in adequate feeding. Patients have to abide by a special high-protein, low-carbohydrate diet [12, 28]. The signs for Pompe disease should include problems with tooth eruption and abnormal development of teeth [10].

The dentition is characterised by taurodontic roots, often in first molars in the maxilla. The oral manifestation is more likely to occur as double teeth, especially fusion of primary incisors. We can find delayed eruption of primary teeth or even some absence of secondary teeth germs, which leads to hypodontia [10]. Repeated gingival swelling could be associated with tooth eruption. Gingival overgrowth is thought to be caused by insignificant glycogen accumulation in the fibroblasts [38].

CONCLUSIONS

Manifestation of LSDs in a stomatognathic system may lead to early detection of LSDs, especially in the absence of systemic symptoms. Both general practitioners and dentists have to be knowledgeable about abnormalities in the stomatognathic system, which can occur in the population with the rarest genetic diseases. Knowledge about LSDs should be widespread because of their interdisciplinary nature. Dentists should be aware of possible oral and radiographic manifestations of those diseases and the role of dental treatment in improving the patient’s oral health and quality of life. Maintaining good oral health is a huge challenge. Nevertheless, prevention of dental decay, hypersensitivity, and periodontal disease are extremely important. Regular dental visits with advanced prevention treatment are recommended.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
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