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Macroglossia in Beckwith-Wiedemann Syndrome: A Narrative Review

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A B S T R A K

Beckwith-Wiedemann syndrome has a wide spectrum of clinical features, namely macroglossia, defects in the abdominal wall and an increased risk of developing embryonal tumors during childhood. Macroglossia can cause several disorders such as airway obstruction, dysphagia, drooling, speech difficulties and other disorders. To determine the etiology and clinical picture and to differentiate macroglossia in BWS from macroglossia in other diseases so as to be able to make a diagnosis and plan the right treatment. Collecting and analyzing relevant references in the form of journals and textbooks accessed through the Google Scholar, Google Books, PubMed and Science Direct databases. Macroglossia in BWS and macroglossia in other diseases can be distinguished if an appropriate diagnosis is made by means of a complete clinical and physical examination so that clinical symptoms and possible etiological factors can be identified.

INTRODUCTION

Macroglossia is a condition in which the tongue enlarges and protrudes beyond the lingual alveolar ridge when the mouth is in a resting position. Macroglossia is classified into two categories, namely true macroglossia which is an enlargement of the tongue due to congenital abnormalities such as in patients with Beckwith-Wiedemann syndrome, and pseudo macroglossia which refers to the tongue being of normal size but looks large. According to Simmonds et al., based on data from 2003, 2006, 2009 and 2012 there were 726 new-borns with macroglossia and most of them occurred in female infants with a percentage of 59.1%. Macroglossia is reported to occur in 80–99% of patients with Beckwith-Wiedemann Syndrome (BWS).

Beckwith-Wiedemann syndrome is a congenital overgrowth disorder with an estimated incidence of 1 in 13,700 births. In 75-80% of cases, this syndrome occurs due to a genotypic abnormality of chromosome 11p (11p15.5). Beckwith-Wiedemann syndrome has a wide spectrum of clinical features including macroglossia, abdominal wall defects and an increased risk of developing embryonal tumors during childhood. Macroglossia can cause airway obstruction and respiratory insufficiency, dysphagia, drooling, difficulty speaking, musculoskeletal and dentoalveolar changes such as anterior open-bite, malocclusion, prognathism, diastema and incisor proclination so it is important for dentists to know the clinical picture of macroglossia to determine a plan. appropriate treatment and provide education to patients who do not know what macroglossia they are suffering from, with the help of an introduction to clinical features. In addition, in an effort to make a diagnosis and plan the right treatment, it is important for dentists to know the etiology and be able to differentiate macroglossia in BWS from macroglossia in other diseases.

LITERATURE REVIEW

A. Macroglossia

1. Macroglossia Definition

Macroglossia comes from the Greek word "macros + glossa" which is defined as an abnormal enlargement of the tongue. Macroglossia has existed since 1550 BC in the ancient Egyptian Eber's Papyrus. The term "Macroglossia" is also defined as prolonged, painless enlargement of the tongue, which can be recognized by observing the extension of the tongue beyond the teeth or the alveolar ridges in a resting position. Myer (1986) classified macroglossia into localized and generalized macroglossia, based on the extent of lingual involvement. While Vogel (1986), divides True Macroglossia as an enlarged tongue with underlying histological changes, and Pseudo macroglossia refers to a normal sized tongue but appears large against adjacent anatomical structures. In addition, macroglossia can also occur due to inflammation and trauma.Macroglossia is most common in infants and children. The reported prevalence of congenital macroglossia is less than 5 per 100,000 births, is twice as common in women as in men, and is twice as common in African-Americans compared with European descent.

2. Macroglossia etiology

The exact etiology of macroglossia is difficult to define because of the many possible etiologies and contributing factors. According to Balaji (2016) explains Macroglossia according to its etiology is divided into four categories, namely:

a. Excessive tissue growth, such as in BWS, congenital hypothyroidism, chromosomal abnormalities, hemi hyperplasia, mucopolysaccharidosis and others.
b. Tissue infiltration, such as lymphatic malformations, haemangiomas, neoplasms, amyloidosis, and neurofibromatosis.
c. Pseudo Macroglossia in Down syndrome, Micrognathia, Muscle Hypotonia, and Angioedema.
d. Inflammation or infection

3. Differential Diagnosis of Macroglossia

The main differential diagnosis in macroglossia includes the conditions that cause pseudo macroglossia. pseudo macroglossia occurs due to conditions that cause displacement of the tongue so that the tongue is in an abnormal position and causes the tongue to appear enlarged, such as a shallow palate, enlarged tonsils, tumors of the oral cavity, abnormalities in the mandibular and maxillary arches, and hypotonia. Hypotonic in the orofacial muscles and tongue muscles with a small mouth cavity causes a large tongue in children with Down syndrome or relative macroglossia (pseudo macroglossia), namely the condition of the tongue being normal in size but due to delayed growth of the jaw causing a small mouth cavity showing a tongue like macroglossia. Other differential diagnoses include acute conditions that can cause temporary swelling of the tongue such as those caused by trauma, allergies, and infections, for example in acute swelling of the tongue and enlarged adenoids and/or tonsils.

4. Clinical Features of Macroglossia

Macroglossia is characterized by an enlarged and thick tongue accompanied by scalloping (fissures) and ulcers. It may be asymptomatic or present with symptoms such as sialorrhea, difficulty speaking, eating, and swallowing, and recurrent upper respiratory tract infections. Macroglossia can affect the mouth and pharynx during the swallowing phase, resulting in eating disorders and in small children the possibility of broncho aspiration. Macroglossia can also cause airway obstruction and obstructive sleep apnoea syndrome. If not treated properly in time, macroglossia can cause temporomandibular joint pain and dentoskeletal deformities such as open bite, prognathism, malocclusion, crossbite, buccal tipping of the posterior teeth, and other changes in the mandible or maxillary arch.

5. How to Diagnose Macroglossia

The diagnosis of macroglossia is based on the clinical history and physical examination. A history of pregnancy, birth, and family illness should be obtained at the time the history is taken. The prenatal diagnosis of congenital macroglossia was confirmed on ultrasound examination, which showed protrusion of the tongue over the lips. Keep in mind that newborns tend to have relatively large tongues. However, congenital macroglossia is often present at birth, especially if there are symptoms of difficulty breathing and swallowing. Clinical examination should evaluate the size and mobility of the tongue, as well as transnasal pharyngo-laryngoscopy to assess the base of the tongue and upper airway. This can be combined with functional endoscopic evaluation of swallowing (FEES) in children with swallowing disorders. Regarding the genetic causes of macroglossia in newborns, it is recommended to undergo evaluation with ultrasound and genetic examination for BWS. Children with macroglossia, without a clear diagnosis, should undergo a complete physical examination to determine the underlying cause.

6. Management of Macroglossia

a. Non-surgical Management

Non-surgical treatment in the form of conservative therapy is indicated in treatable causes of macroglossia such as hypothyroidism or amyloidosis and is also used before and after surgical treatment as a supportive therapy. One recommended conservative treatment is with the help of an oral stimulation plate (Fig. 1) for speech and swallowing therapy. In addition, lymphatic malformations in macroglossia can be treated with radiotherapy, sclerotherapy, cryotherapy, or steroid injections.

Figure 1. Oral stimulation device. a. Small wheel plate for the maxilla, b. Small ball plate for the maxilla, c. Historical method with wires on the maxillary incisors

b. Surgical management

Surgical treatment of macroglossia is indicated in cases of macroglossia causing airway obstruction, respiratory insufficiency, aesthetic disturbances, difficulty swallowing, speech, and articulation disorders. Surgical treatment of macroglossia can be done by tongue reduction in the form of a partial glossectomy, which is a surgical procedure on an enlarged tongue. Glossectomy technique according to Morgan is indicated in bilateral macroglossia by resecting the middle and tip of the tongue (Fig. 2 A-C). This technique begins with making a keyhole-shaped incision line (Fig. 2A) on the tongue with a marker, followed by general anesthesia and nasotracheal intubation. The incision is made using a scalpel and then equipped with electrocautery for better hemostasis. The resected

tongue was then sutured with vicryl suture. For unilateral macroglossia, you can use the Austerman and Machtens technique (Figure 3 D-F).

Figure 2. Partial Glossectomy with the Morgan Technique

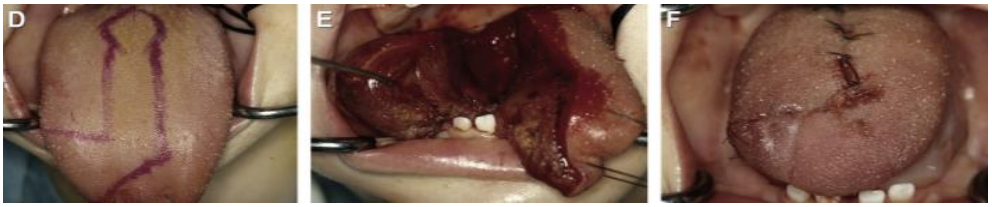

Figure 3. Partial Glossectomy with the Austerman and Machtens Technique

7. Beckwith-Wiedemann Syndrome (BWS)

1. Definition of Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS) was first reported by Beckwith JB and Wiedemann HR in the 1960s. BWS is a rare congenital disorder characterized by physical overgrowth with variable clinical symptoms and a predisposition to cancer. The incidence of BWS is estimated at 1 in 10,000 live births.

2. The etiology of Beckwith-Wiedemann Syndrome

BWS is an overgrowth disorder in children caused by an epigenetic change in chromosome 11p15. Imprinted genes present at this locus include insulin-like growth factor 2 (IGF2/H19) and cyclin-dependent kinase 1C (CDKN1C/p57KIP2). Hypermethylation of IGF2/H19, hypomethylation of CDKN1C/p57KIP2, or paternal uniparental disomic (pUPD) is commonly associated with BWS.

3. Clinical Features of Beckwith-Wiedemann Syndrome

Macroglossia is common in BWS patients (Figure 4). In addition, BWS is also characterized by the presence of macrosomia, abdominal wall defects (omphalocele), folds on the ears, facial nevus, nevus flames, renal abnormalities, visceromegaly, neonatal hypoglycemia, hemi hyperplasia, and an increased risk of embryonal tumors (e.g. Wilms tumor and hepatoblastoma).

Figure 4. Various manifestations of macroglossia in BWS: mild (A), moderate (B), strong (C).

4. Histological Features of Macroglossia in BWS

In the study of Oyama et al., the histological picture of macroglossia in BWS patients showed dense subepithelial eosinophilic areas consisting of many skeletal muscle fibers tightly arranged in a storiform and fascicular pattern, and rarely found minor salivary glands on the patient's tongue. The results of this study showed that the average diameter of muscle fibers did not show any difference between BWS sufferers and the control group, but there were significant differences in the number of muscle fibers. Thus, "Muscular Hyperplasia" is used as a more appropriate term to describe true-macroglossia in BWS patients than "Hypertrophy", because the amount of skeletal muscle in the tongue increases relative to its size. In addition, IGF2 was detected with more intense staining spread over the hyperplastic areas, indicating an increased number of skeletal muscle fibers. IGF2 is a growth factor that is important in skeletal muscle growth.

5. Beckwith-Wiedemann Syndrome Treatment

The following are some of the treatments that can be performed on BWS sufferers:

a. Prenatal care
   BWS is associated with increased gestational hypertension, preeclampsia, and preterm birth, so proper management of delivery and neonatal care is necessary.
b. Macroglossia
   As many as 40% of BWS patients with macroglossia undergo tongue reduction surgery. Non-surgical treatments such as speech and swallowing therapy are also needed as supportive therapy.
c. Hypoglycemia
   BWS-associated neonatal hypoglycemia is caused by excess insulin. Hypoglycemia can resolve within a few days, but in some cases persistent hyperinsulinism (HI) may occur, therefore newborns with suspected BWS should be screened for hypoglycemia.
d. Abdominal wall defect
   Treatment of this disorder should follow standard protocols and local practices and surgery is usually recommended.

e. Hemi hyperplasia
   Hemi hyperplasia is a condition in which one side of the body is larger than the other. The condition of Leg Length Discrepancy may require a shoe lift or surgical correction in some cases.
f. Tumor
   Tumor screening protocols are recommended for early detection of tumors, reducing morbidity, and improving patient survival.

METHODOLOGY

The method used in writing this literature review is to collect and analyze relevant reference sources or references in the form of articles, research journals, case reports and descriptives from 2016-2021 and textbooks using the keywords "Macroglossia", "True Macroglossia" and " Beckwith-Wiedemann Syndrome" accessed through the Google scholar database, Google Books, PubMed and Science Direct.

RESEARCH RESULT AND DISCUSSION

Macroglossia is an enlargement of the tongue which can cause functional and aesthetic disturbances in the oral cavity. To avoid the possibility of macroglossia developing more severely, it is necessary to treat the macroglossia as early as possible, but the treatment measures taken depend on the etiology of the enlarged tongue. In the case report of Oyama Y et al. (2020), explained that a 5-year-old female patient came with complaints that her tongue was enlarged, causing difficulty breathing and swallowing. The patient was diagnosed with Beckwith-Wiedemann syndrome. Based on the etiology, macroglossia in BWS patients results from skeletal muscle hyperplasia so that it is called True macroglossia, where the main treatment is tongue reduction with the keyhole technique to reduce the size of the tongue. Meanwhile, macroglossia in Down syndrome patients is pseudo macroglossia, due to stunted jaw growth so that the oral cavity is smaller and the ability of weak muscle tone causes the tongue of patients with Down syndrome to appear larger than normal size. Therefore, surgery with mandibular distraction or widening of the oral cavity in Down syndrome patients is more effective than tongue reduction.

In the case report of Jun Hye Kim et al. (2019), described a 7-year-old boy patient who came to the hospital with the main complaint of an enlarged tongue. Enlargement of the tongue causes the oral cavity to become drier and can interfere with mastication. Apart from macroglossia, there is an enlarged mass in the right submandibular area which was present when the patient was born and caused the patient to have difficulty breathing. When she was 3 years old, she underwent a surgical procedure to remove the mass, which was a lymphangioma, through histopathological examination. Then at the age of 5 years, the patient underwent sclerotherapy with three injections of 95% alcohol, this treatment was performed as a treatment for lymphatic malformations in patients. For the treatment of macroglossia, reduction glossectomy can be performed with a combination of the U-shaped anchor technique and modified keyhole resection and the treatment results are quite good.

Then in the case report written by Gadiwala Y et al. (2016), described a 64-year-old female patient who came with complaints of an enlarged tongue that caused an anterior open bite, speech disorders, dysphagia, and apnoea. The patient has a history of hypertension and hypothyroidism. On MRI and laboratory examination, congo red staining and deposits of amyloid monospecific antibodies were shown. From the results of the examination the patient was diagnosed with Amyloidosis. The treatment measures taken are reduction of the tongue and possibly a tracheostomy to maintain the airway due to swelling of the tongue. In this case the size of the patient's tongue has decreased significantly but further action is needed due to the possibility of recurrence.

CONCLUSIONS AND RECOMMENDATIONS

Dentists have an important role in determining the diagnosis and treatment of macroglossia, so it is important to have in-depth knowledge about the etiology, clinical picture, how to diagnose and differential diagnosis of macroglossia. Macroglossia treatment will not be successful without proper diagnosis and elimination of the etiology. The diagnosis is determined by a complete clinical and physical examination so that clinical symptoms and possible etiological factors can be determined. In addition, supporting examinations can be carried out if needed to support a more precise diagnosis.

a. Public

This literature study can provide knowledge to the public regarding Macroglossia caused by Beckwith-Wiedemann Syndrome, so that if there are symptoms such as Beckwith-Weidemann Syndrome, the public can consult a dentist or Oral Disease Specialist so that proper treatment is available.

b. Dentistry Practitioner/Student/Resident Oral Medicine Specialist

This literature study can provide additional information for dentists/dental nurses/students/Oral Medicine Specialist Residents so that this reference can become a guideline in the management of Beckwith-Wiedemann Syndrome.

ADVANCED RESEARCH

This literature study can be used as a guideline for further research, namely descriptive and analytic research to describe the characteristics of macroglossia in sufferers of Beckwith-Weidemann Syndrome.

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