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Case Report

Laryngeal Neurofibroma in a 15-Month-old Female with Neurofibromatosis Type 1 and its Association with Spoken Communication Disorders: Case Report and Review of the Literature

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Abstract

We present a case of a 15-month-old female patient with a laryngeal neurofibroma of the larynx associated with Neurofibromatosis Type 1 (NF 1) and how it affected her spoken communication ability. In this report, we review the literature describing the rarity of Neurofibromatosis type 1 and laryngeal neurofibromas, the locations of laryngeal neurofibromas, the differential diagnosis for laryngeal neurofibromas, spoken communication disorders associated with NF1, early intervention and the role of concomitant recurrent otitis media in our patient. Following a review of the literature, suggestions for early intervention and assessments of language and speech for children with NF1 is discussed.

Keywords: Neurofibroma; Neurofibromatosis; Laryngeal; Laryngomalacia; Otitis media

ABBREVIATION

NF1: Neurofibromatosis 1,

INTRODUCTION

Neurofibromatosis type 1, also referred to as Von Recklinghausen's disease, is an autosomal dominant neurocutaneous disorder that manifests in various tissues [1]. The diagnostic criteria are as follows, patients must have two or more of the following: 6 or more café-au-lait macules (>0.5 cm in children of >1.5 cm in adults), 2 or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma, axillary or groin freckling, optic glioma, 2 or more Lisch nodules (iris hamartomas visualized on slit lamp examination), sphenoid wing dysplasia or bowing of long bone (with or without pseudarthrosis) and first degree relative with an NF1 diagnosis [2]. Individuals with this diagnosis may present with varying degrees of these signs and symptoms owing to the principle of variable penetrance [3]. Neurofibromatosis type 1 has a prevalence of 1 in 4000 births and an incidence of 1 in 3300 births, thus displaying the rarity of the disease [4].

Neurofibromas are peripheral nerve sheath tumors composed of proliferation of schwann cells, fibroblasts and perineural cells [5]. Furthermore, neurofibromas have a propensity to proliferate in the larynx supraglottically, especially at the aryepiglottic fold due to the dense innervation and connection of the internal branch of the superior laryngeal and recurrent laryngeal nerves [4]. The neurofibroma is classified as either plexiform or non-plexiform; this is of importance due to plexiform lesions being poorly localized, infiltrative, and involving several nerves causing improbable complete resection with a likelihood of recurrence [6] [16]. Incomplete resection and recurrence put patients at further risk of complications such as tracheostomy, communication or learning disorders, and even death [2][4][5][7]. In addition, laryngeal neurofibromas are an uncommon manifestation of Neurofibromatosis type 1, as only 62 pediatric cases were recorded in the world-wide literature review in 2014 with the mean age of onset being 4.1 years [5]. Laryngeal neurofibromas account for only 0.03% to 0.1% of benign tumors of the larynx [8]. The most common symptoms are stridor, dysphagia and dysphonia [5]. Other symptoms include dyspnea, snoring, cough, or hoarseness [5].

We present a case of a 15-month-old female with a pre-established diagnosis of neurofibromatosis type 1 who presented with stridor, snoring, slow speech development and low tone of voice. We also demonstrate the importance of early diagnosis and excision of laryngeal neurofibromas and the age of onset of symptoms with regards to spoken communication development. In addition, we briefly describe the complexity of disease presentation with concomitant otitis media that can negatively impact communication development.

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CASE PRESENTATION

A 15-month-old female with pre-established diagnoses of Neurofibromatosis Type 1, presented with recurrent otitis media, chronic snoring and laryngomalacia. The patient was being followed by genetic counselling for her diagnosis of neurofibromatosis type 1.

The patient presented to her pediatrician for her 15-month-old check-up. Her mother complained that the patient had chronic snoring, coughing at bedtime, and growth concerns. The mother also complained of the child's slow development of speech and low tone.

On physical examination, the patient's weight was at the 10.38th percentile and height was at the 25.61th percentile for age. Her tympanic membranes were noted to be dull, erythematous and bulging bilaterally. She was also noted to have several brown macules of various sizes, mostly on her trunk. The remainder of the physical exam was within normal limits.

The patient was referred to an otolaryngologist for further evaluation of the child's snoring and low tone of voice. While at the otolaryngology clinic, a flexible fiberoptic nasopharyngoscopy was performed. A large mass emanating from the right arytenoid partially covering the right glottis was discovered. Biopsy of the mass was performed, and microscopic examination showed loosely arranged small groups and single spindle cells in background of fibrocollagenous stroma . The cells showed scant cytoplasm and oval elongated and regular nuclei , no Verocay bodies, no nuclear palisading and hyalinized thickening of vessel walls. Only mild atypia was noted and no necrosis or increased mitosis (**Figure 1A-B-C**). The cells were strongly positive for S-100 (**Figure 1D**). The histomorphologic features were consistent with a neurofibroma. Vocal cord function could not be assessed due to the space occupying lesion. An audiogram performed in the clinic showed a moderate conductive hearing loss.

The mass was surgically removed with adequate safe margins and tympanostomy tubes were paced. In a one year follow up, the patient showed moderate improvement of her symptoms after which she was lost to follow up.

DISCUSSION

Neurofibromatosis type 1 is a neurocutaneous disorder characterized by cafe au lait macules, axillary freckling, neurofibromas, optic gliomas, lisch nodules, sphenoid wing dysplasia and long bone bowing. Individuals with neurofibromatosis type 1 display various signs and symptoms through variable penetrance. The histomorphologic features and immunohistochemistry profile of neurofibromas and differentiation from other neural tumors are well established. Rarely, a Hybrid peripheral nerve sheath/perineurioma can occur as reported by Nicole DiTommaso et al [17]. Laryngeal neurofibromas are rare manifestation of NF 1. These tumors have a high propensity to proliferate in the supraglottic region of the larynx due to the extensive innervation in this area. The most common symptoms of laryngeal neurofibromas are but not limited to, stridor, dysphagia and dysphonia. The most common diagnosis for a pediatric patient presenting with stridor is laryngomalacia [4][9]. Following laryngomalacia, the second most common diagnosis would be vocal cord paresis [4]. Several other diagnoses can be considered for patients presenting with stridor, including but not limited to; croup, subglottic stenosis, vascular anomalies, congenital cysts, obstructive sleep apnea, or tumors [4][9]. The tumors could include various types such as a hamartoma

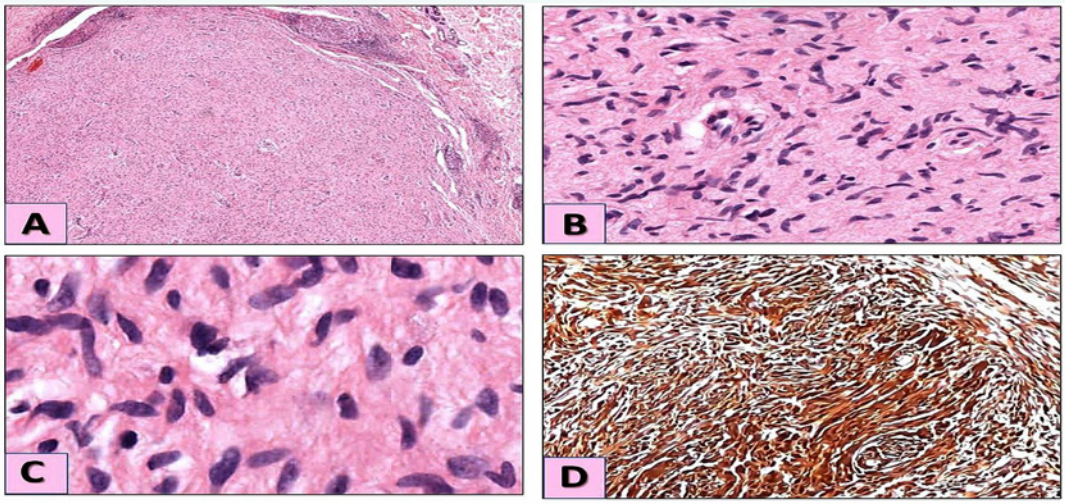

Figure 1 Pathologic examination of the excised Neurofibroma
Figure 1A: Low power view showing well defined nodular mass (H&E stain X20)
Figure 1B: Medium power view showing loosely arranged small groups and single spindle cells in background of fibrocollagenous stroma (H&E stain X40)
Figure 1C: High power view showing spindle-shaped cells with benign morphology and no malignant features or abnormal mitosis (H&E stain X60)
Figure 1D: Neurofibroma cells positive for S-100

or neurofibroma [4]. Of note, there is a vast differential diagnosis that is associated with stridor as the primary presenting symptom. In most recent studies, SARS-CoV-2 infection has been shown to present as upper respiratory symptoms, stridor and respiratory distress in the pediatric population [10]. Neurofibromas have a propensity to originate in the aryepiglottic fold due to the vast nerve supply in this region. The aryepiglottic fold is the most common location for a neurofibroma of the larynx, demonstrated by 34% of patients in the study conducted by Chinn et al [5]. Our patient's neurofibroma originated from the right arytenoid. Compared with 34% of patients with neurofibromas of the larynx originating from the aryepiglottic fold, only 18% of patients with neurofibromas have them occur in the arytenoid [5]. In addition to the uncommon nature of NF1 and the diagnosis of laryngeal neurofibromas, the location of our patient's neurofibroma adds to the rarity of this case.

This particular case highlights the importance of high index of suspicion by clinicians for laryngeal neurofibromas especially in the setting of patient with NF1. Our patient came in with a pre-established diagnosis of NF1 at the time of presentation for stridor, excessive snoring and slowed speech development. In patients with NF1 presenting with these symptoms, a pathologic diagnosis of a laryngeal neurofibroma should be ruled out prior to simply giving the diagnosis of more common etiologies such as laryngomalacia. In this particular setting, a complete diagnostic workup should be initiated, which should include ; laryngoscopy, computed tomography, magnetic resonance imaging, and biopsy of space occupying lesions for definitive diagnosis [11]. Our case highlights the vital role of early diagnosis for early and optimal management.

In patients with Neurofibromatosis Type 1, the consequences on spoken communication development are substantial. The appearance of a laryngeal neurofibroma only compounds the negative impact on normal communication development. Children develop their communication skills from birth, with expressive communication around 6 months, such as babbling and cooing. Around the one-year mark, children are expected to have a small vocabulary and be comfortable saying simple words such as "mama" or "dada", and at 18 months the child should be saying several individual words [11]. At the time of presentation, our patient's speech should have been inclining and she should have been able to communicate several words effectively. The patient's mother reported that her speech was slow to appear and not easily understood, confirming the impact of the disease on her spoken communication development.

In another case report of neurofibroma in a patient at age 5, it was reported that communication developmental milestones were within normal range [8]. No speech impediments were noted. A 4-year old patient who underwent complete excision of laryngeal neurofibroma was also found to have communication milestones within the normal range [12]. This patient had had worsening stridor for two years prior to surgical intervention but was not reported to have any developmental abnormalities during that time. Of note, the age of these two cases (5-year-old and 4-year-old) do not consider errors in spoken communication development as the individuals would have been past this stage of development when the masses were significant. It is important to note the significance of age of onset and presentation of laryngeal neurofibromas in order for early intervention to preserve language and spoken communication development, especially in the younger pediatric population whose skills have not previously been established.

It is well established that NF1 is associated with receptive and expressive communication disorders, phonetic disorders, and articulation disorders [7]. However, it remains unknown as to the exact reason for this association. It also should be noted that there is a known association of NF1 with cognitive impairment in children [13]. The cause of the communication disorders could be linked with cognitive impairment or the anatomical pathology itself.

In addition, our patient was also noted to have recurrent otitis media with effusion, which is known to have detrimental effects on hearing and speech such as conductive hearing loss, sensorineural hearing loss if prolonged, expressive language delay and speech perception difficulties [14]. Obviously, in our patient the recurrent otitis media with effusion and laryngeal neurofibroma both had an impact on her language and spoken communication development. We are unsure of the degree of impact each disease process had on her language and communication development individually; this is an area that should be of further investigation. Even so, patients with recurrent otitis media with effusion, hearing loss, language or speech delay, or signs of laryngeal involvement, should be referred to an otolaryngologist for further investigation of the possible disease processes with appropriate intervention [14].

Excision of the laryngeal neurofibroma should occur promptly following diagnosis to ensure better outcomes. It is recommended that a minimally invasive approach with maximal excision of the tumor should be achieved [15]. Open surgical approaches may have better access to the tumor and lead to complete excision, but this approach is associated with risk of damaging adjacent structures, longer hospital stays, and a visible scar [12]. However, due to the complexity of the tumor and the involvement of the neurovasculature, complete excision may not be possible [15]. In such cases, patients may suffer from tumor recurrence with persistent symptoms, tracheostomy, gastrointestinal tube placement, language and spoken communication disorders, and compromised quality of life [15].

Our patient presented much younger than has been largely previously reported and as such created new challenges. The effect that NF1 has on language development is not well studied and it is our hope that our case will aid in continuous investigation of this association. The rarity of NF1, laryngeal neurofibromas in general, and the location of our patient's lesion should be noted and appreciated. There are limited studies on the direct association between laryngeal neurofibromas and communication or phonetic disorders. As such, children with NF1 should be evaluated with a complete diagnostic work-up as soon as appropriate to prevent irreversible impairment. We hope this case report will add to the repertoire of research on this topic

and provide clinicians with more insight about the effect that NF1 has on language development, allowing for early and appropriate diagnosis and informed management decisions.

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