An Algorithm Approach to Diagnosing Bilateral Parotid Enlargement

Si Chen, MD1, Benjamin C. Paul, MD1, and David Myssiorek, MD1

Abstract

Objective. This contemporary review aims to categorize the disease entities that cause bilateral parotid enlargement and to develop a question-based algorithm to improve diagnosis of bilateral parotid masses.

Data Sources. A PubMed search for bilateral and parotid showed 818 results. Of these, 68 relevant studies were reviewed to compile a list of disease processes that can cause bilateral parotid enlargement.

Review Methods. A total of 22 diseases entities were reviewed. The disease processes were initially grouped into 6 categories based on etiology: sialadenosis, infection, neoplasm, autoimmune, iatrogenic, and miscellaneous. For each lesion, the incidence, history, and physical examination were compiled in a matrix.

Conclusion. After reviewing the matrix, it was clear that grouping diseases based on specific history and physical findings limits the differential diagnosis. The most important factors included disease incidence, timing of onset, nodular or diffuse, pain, and overlying skin changes. With this algorithm, the differential diagnosis can be limited from 28 to 7 or fewer likely diagnoses for a given presentation.

Implications for Practice. Bilateral parotid disease has a wide differential diagnosis with an expanding number of available tests. An algorithm, based solely on data obtained from the history and physical examination in the first patient encounter, may reduce the differential and aid the clinician in deciding on further workup and treatment. Following the algorithm presented here should allow the clinician to arrive at a diagnosis rapidly without ordering unnecessary tests and wasting resources.

Keywords

bilateral parotid enlargement, algorithm

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each of these diseases were collected. A matrix was built based on consistently reported disease characteristics, including disease incidence, bilaterality, timing of onset, nodularity, pain, and presenting skin changes (Table 1). It should be noted that additional signs and symptoms, including facial nerve status, associated otalgia, and systemic symptoms, were considered although not included as the reported data are incomplete.

Next, an algorithm was constructed to narrow the diagnosis via permutation and factoring analysis. To make the algorithm most clinically relevant, history-based signs and symptoms served as initial branch points followed by signs identified on physical examination as this parallels the clinical workup. When reviewing the options with which to build the algorithm matrix (Table 1), various grouping strategies were tested with a goal of using the fewest branches to limit final subgroups. After testing the permutations with a goal of keeping history before physical exam in the final algorithm, the most efficient way to approach bilateral parotid enlargement was to first narrow the differential diagnosis by timing of disease onset, followed by pain, both key pieces of information obtained from the history of a patient’s disease. Last, the clinician may further hone the diagnosis based on nodularity of the lesions palpated during physical exam. Our algorithm is presented in Figure 1. Ultimately, the goal of this algorithm is to help the clinician limit the differential diagnosis on the first clinic visit of a patient presenting with bilateral parotid enlargement, before further laboratory or radiographic data are obtained.

It is important to keep in mind whether the suspected disease entity is more likely to present with bilateral or unilateral parotid enlargement. The approximate percentage of bilateral involvement in parotid enlargement is demonstrated in Figure 2.

It is important to recognize that this algorithm is based on the most common diseases and presentations of bilateral parotid enlargement. There may be situations of combined disease processes, abnormal presentations of common

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Rapid Onset</th>
<th>Pain</th>
<th>Nodular</th>
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Abbreviations: BLEC, benign lymphoepithelial cyst; DILS, diffuse infiltrative lymphocytosis syndrome; HIV, human immunodeficiency virus; MALT, mucosa-associated lymphoid tissue.
diseases, and rare diseases, which are not well captured by this algorithm. Regardless, reviewing this algorithm as well as an updated review of the common disease entities that underlie bilateral parotid enlargement is of value to the clinician.

Sialadenosis

Sialadenosis (sialosis) is associated with nutritional and hormonal disturbances, particularly chronic malnutrition, obesity, diabetes mellitus, alcoholism, liver disease, and eating disorders. Many drugs have been implicated in sialadenosis, most prominently antihypertensives. Some cases of sialadenosis have no known underlying systemic disease.

Sialadenosis is common among patients with eating disorders and chronic malnutrition. It affects 10% to 50% of patients with bulimia nervosa. Given that 19% of college-aged females may have bulimia nervosa, it is a common differential diagnosis of bilateral parotid involvement.

With the rising incidence of metabolic syndromes, diabetes mellitus is an increasingly important cause of sialadenosis. Scully et al reported that 49% of sialadenosis patients were diabetic, although diabetes and liver disease often coexist in patients. One study showed that 48 of 200 diabetic patients (24%) had asymptomatic bilateral parotid enlargement. In some cases, parotid enlargement preceded the diagnosis of diabetes. Some authors have proposed that asymptomatic parotid gland enlargement warrants a search for diabetes and that salivary composition and function have potential to contribute to the clinical diagnosis and staging of diabetes. Although still controversial, abundant research has focused on the specific changes in secretory protein expression and salivary flow in salivary glands of diabetic patients, which may contribute to the oral complications of diabetes.

Sialadenosis is also frequently found in patients with alcoholism and alcoholic cirrhosis, with an estimated incidence of 30% to 86%. Whether alcoholism without cirrhosis and other causes of cirrhosis can result in sialadenosis has been debated. A recent study found sialadenosis in 28 of 300 liver transplant candidates (9.3%). Among these 28 patients with sialadenosis, 39.3% had alcoholic cirrhosis, and 60.7% had non–alcohol-related liver diseases. The study suggested that cirrhosis, irrespective of its etiology, may lead to the development of sialadenosis.

The pathogenesis of sialosis is not well established but may involve a neuropathic process of the autonomic innervations of the salivary glands in the setting of systemic
demyelinating polyneuropathy. Autonomic neuropathies are noted in patients with alcoholism, nonalcoholic liver diseases, and diabetes. Dysfunction of autonomic regulation leads to imbalance of acinar protein synthesis and protein secretion. Mandel and Surattanont proposed that the histologic findings of enlarged acini and glandular hypertrophy are a result of retained zymogen granules in the acinar cells. Ultrastructural studies of the sialosis tissue also showed evidence of axonal and myoepithelial cell degeneration with swelling of axon fibers and vacuolization.

More recently, different authors have described different histopathology pictures in diabetic and alcoholic sialosis. Diabetic sialosis has smaller acini, greater fatty infiltration in the glandular stroma, and normal-appearing epithelium. On the other hand, alcoholic sialosis exhibits a reduction in the proportion of fatty tissue of stroma and a significant growth of ductal epithelium that contributes to increase the caliber of the striated ducts. Also noted in alcoholic sialosis are accumulation of secretory granules in the acinar cells’ cytoplasm and enlarged excretory ducts.

**Infection**

The infectious causes of bilateral parotid enlargement include viral mumps, HIV, acute suppurative parotitis, tuberculosis, and bilateral parotid abscess. Of these, viral mumps and HIV are bilateral more than half of the time, whereas the rest are less likely to be bilateral (Figure 2).

Acute suppurative parotitis is bacterial infection of the parotid gland associated with dehydration, immune deficiency, and premature babies. Fattahi et al reported that acute suppurative parotitis affects up to 0.02% of all hospitalized patients and 0.04% of postoperative patients.

Tuberculosis is a rare cause of parotid enlargement. It is often mistaken for parotid tumors. In a series of 215 parotid tumor histology examinations, 6 were found to have tuberculosis instead. In 49 cases of tuberculosis parotitis, only 1 presented with bilateral parotid involvement.

Viral mumps, acute suppurative parotitis, and abscess can present acutely with pain. Nodular parotid lesions are present with HIV and abscess, and sometimes in tuberculosis (Figure 1).

**Viral Mumps**

Recently, large viral mumps outbreaks have been reported in developed countries. The resurgence of this disease comes with new challenges as its epidemiology has changed. Adolescents and young adults were affected in these outbreaks, compared with older reports in which young children were the most likely victims. Parotid symptoms may be absent in 10% to 30% of symptomatic cases. The report that some of the mumps patients had received vaccination brings to light the moderate efficacy of the mumps vaccine. New research is focused on improving the mumps vaccine and studying the immunological markers of mumps immunity.

When the diagnosis of mumps is considered, the clinician may obtain the diagnosis through laboratory testing. Often, a complete blood count will depict a normal white blood cell count with a possible viral-induced lymphocytosis. Amylase can elevate during mumps, and it is helpful to examine subtypes to distinguish mumps parotitis (amylose-S) and pancreatitis (amylose-P). Serum lipase is elevated in pancreatitis. Ultimately, definitive diagnosis can be made through serologic testing based on virus-specific IgM antibody as measured by direct or indirect enzyme-linked immunosorbent assay. A rise in IgG titers seen between the acute and convalescent phases of disease can be difficult to interpret due to cross-reactivity of paramyxovirus. Virus isolation from urine, saliva, semen, or cerebrospinal fluid is limited to the period of viral replication, which occurs 7 days before and until the first week after the onset of clinical symptoms. The window to isolate the virus is often passed by the time of consideration. Rapid polymerase chain reaction evaluation of cerebrospinal fluid for viral mumps RNA may be performed if there is concern for neurologic involvement.

**HIV**

Since the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, there has been a decline in the prevalence of oral manifestations of HIV infection. However, the incidence of HIV-associated salivary gland diseases, mostly involving parotid glands, has remained the same in developing countries and even has increased in developed countries. Parotid gland enlargement reportedly occurs in approximately 1% to 10% of HIV-infected patients. Etiologies of parotid enlargement specific to HIV-seropositive patients include hyperplastic lymphadenopathy, benign lymphoepithelial cysts (BLEC), and diffuse infiltrative lymphocytosis syndrome (DILS).

Benign lymphoepithelial cysts occur in 3% to 6% of HIV-positive adults and in 1% to 10% of HIV-positive children. HIV-associated BLEC often presents early in the course of HIV infection with slowly progressive but asymptomatic parotid gland enlargement. In the era before the widespread use of HAART, the prevalence of DILS was at 3% to 4% of HIV-positive patients. Despite the success of HAART, Ceballos-Salobreña et al reported increased incidence of parotid gland enlargement in HIV-positive patients (4.5%) on HAART. A known adverse effect of protease inhibitors is fat accumulation in various parts of the body such as the back of the neck (buffalo hump) and intra-abdominal region. Protease inhibitors have been suggested to cause fatty infiltration of the parotid gland or parotid lipomatosis, resulting in glandular swelling.

**Neoplasm**

Warthin tumor, mucosa-associated lymphoid tissue (MALT) lymphoma, and oncocytomas are the neoplasms that may present with bilateral parotid enlargement. Warthin tumor accounts for 6% to 13.5% of all parotid tumors; only 5.7% to 14% are bilateral. There is increased risk of bilateral Warthin tumor in smokers.
Mucosa-associated lymphoid tissue lymphoma involving the parotid gland is less common but can be seen in patients with Sjögren’s syndrome, HIV, or chronic sialadenitis.\textsuperscript{37,38} The parotid glands may be the primary site of the MALT lymphoma.\textsuperscript{39,40} Berger et al\textsuperscript{41} reported 3 cases of parotid involvement in 42 cases of MALT lymphoma, whereas Takahashi and colleagues\textsuperscript{42} found 7 cases of parotid enlargement in 10 patients with MALT lymphoma. Bilateral parotid enlargement due to MALT lymphoma is very rare, noted by asymmetric enlargement.\textsuperscript{40}

Oncocytomas account for less than 1% of salivary gland tumors.\textsuperscript{1} In a review by Hyde et al\textsuperscript{43} only 20 cases of bilateral oncocytoma have been reported in the literature between 1927 and 2008. Brandwein and Huvos\textsuperscript{44} reported that 7% were bilateral among 68 cases.

Of the 3 neoplastic etiologies, only MALT lymphoma is reportedly rapid onset when causing parotid enlargement. None of them are likely to cause pain, but they are all nodular.\textsuperscript{1} Both Warthin tumor and MALT lymphoma can have a mix of solid and cystic components.\textsuperscript{1,40,45}

**Autoimmune**

Multiple autoimmune diseases may involve the salivary glands. Parotid enlargement is most often seen in Sjögren’s syndrome (SS), present in up to 55% of SS patients\textsuperscript{26} and bilateral 75% of the time.\textsuperscript{46} Parotid enlargement in SS can be multicystic.\textsuperscript{47,48} Both SS and recurrent parotitis may present with parotid enlargement that fluctuates in size. Chronic sclerosing sialadenitis, also referred to as a Kuttner’s tumor, displays an elevated IgG4/IgG ratio, is SS-A and SS-B negative, and is a steroid-responsive sclerosis of the salivary glands that is a pertinent negative in the differential diagnosis of SS. Chronic sclerosing sialadenitis often affects the lacrimal and submandibular glands, whereas bilateral parotid disease has yet to be reported to date.\textsuperscript{49}

Only 4% to 6% of sarcoidosis patients may have parotid involvement\textsuperscript{50}; however, it is bilateral in 30% to 70% of these patients.\textsuperscript{26} Orofacial manifestations such as salivary gland swelling should prompt workup for systemic sarcoidosis.\textsuperscript{51}

Salivary gland involvement is less common in Wegener’s granulomatosis (WG), reported in 3 of 70 cases of WG.\textsuperscript{52} Specks et al\textsuperscript{53} reported that 1 in 5 cases of salivary enlargement due to WG were bilateral, whereas Jones et al\textsuperscript{54} found 2 bilateral cases among 32 cases. Of note, salivary gland enlargement may be the early feature of a limited form of WG in which only 67% of patients are antineutrophil cytoplasmic antibody (ANCA) positive.\textsuperscript{1} This may alert the clinician to consider an autoimmune workup.

**Iatrogenic**

Bilateral parotid enlargement can be a rare complication of medical and surgical therapies.

**General Anesthesia**

Parotid swelling is a rare complication of general anesthesia, termed anesthesia mumps. It occurs a few hours after general anesthesia with endotracheal intubation, bronchoscopy, and upper gastrointestinal endoscopy.\textsuperscript{55} Patients complain of mild facial pain usually without difficulty swallowing or breathing. Different combinations of unilateral or bilateral parotid and submandibular swelling have been described. The pathophysiology is not clear but may involve trauma, infection, and salivary stasis due to dehydration. Postoperative sialadenitis often spontaneously resolves within 5 to 7 days without sequelae.\textsuperscript{56}

**Iodide Mumps**

Iodide mumps is seen after injection of iodinated contrast media for radiographic studies. This disorder presents as acute or delayed painless swelling, predominantly in the submandibular and parotid glands, and almost always bilateral.\textsuperscript{57} There have been 30 reported cases of iodide mumps between 1956 and 2010.\textsuperscript{58} The incidence of iodide mumps is increasing with the escalating use of computed tomography and angiography.\textsuperscript{59,60} It occurs with both ionic and non-ionic contrast agents, but 90% occur with ionic agents.\textsuperscript{61}

In patients with immediate swelling of bilateral parotid glands within 1 hour of contrast administration, a hypersensitivity reaction is the likely mechanism.\textsuperscript{62} Delayed onset of parotid swelling 6 to 12 hours after contrast administration may be attributed to toxic accumulation of iodine in the salivary glands.\textsuperscript{63}

**Radiation Sialadenitis**

Radiation sialadenitis is salivary gland toxicity occurring in up to 18% to 26% of patients receiving radioactive iodine therapy for thyroid cancer.\textsuperscript{64,65} Alexander et al\textsuperscript{66} reported that among 203 patients with salivary gland toxicity, 40 patients had bilateral parotid swelling. Bilateral parotid gland and/or submandibular gland enlargement are more common than unilateral involvement.\textsuperscript{56}

With external beam radiation, symptoms are dependent on radiation dosage.\textsuperscript{63} Low-dose radiation (20-30 gy) may cause reversible damage, whereas high-dose radiation (50+ gy) often causes irreversible injury. The changes occur in 3 stages: stage I, mild inflammatory interstitial change with moderate individual gland acinar atrophy; stage II, increased inflammatory infiltrate with fibrosis of the interstitium with epithelial metaplasia in the ductal system; and stage III, cirrhotic parenchymal alteration with clear inflammatory activity with near-complete parenchymal atrophy. The time frame for stage I changes is on the order of days, and stage III changes are rarely seen before 3 months and may take years to fully develop. The average time to the development of late-stage disease is 4.8 months.\textsuperscript{65,67}

**Miscellaneous Causes**

**Kimura Disease**

Kimura disease is a rare, chronic inflammatory disease that presents with painless soft tissue swelling around the head and neck area.\textsuperscript{58} Kimura disease is more prevalent in Eastern Asian populations; however, rare cases have been reported in patients of European, African, Hispanic, and Arabic descent. Eighteen patients in 54 cases of Kimura...
disease had parotid enlargement. A unilateral parotid mass is more common; however, bilateral parotid involvement has been reported.

Solitary or multiple lesions are found in deep subcutaneous tissue, with pruritus in the overlying skin. It is frequently associated with regional lymphadenopathy involving parotid glands and periauricular, axillary, and inguinal lymph nodes. Peripheral blood eosinophilia and elevated serum IgE are almost always present.

**Polycystic Parotid Disease**

Polycystic parotid disease presents with intermittent painless swelling of the parotids. It is seen in female and young adult patients. There have been 13 reported cases of polycystic parotid disease since 1962, 10 of which were bilateral.

**Implications for Practice**

History and physical exam findings such as disease onset, pain, and nodularity are key elements in the algorithm to quickly narrow the differential diagnosis of bilateral parotid enlargement. Following the algorithm presented here should allow the clinician to rapidly narrow the differential diagnosis and arrive at a diagnosis rapidly without ordering unnecessary tests and wasting resources. New research and case reports will allow continued update and improvement of the diagnostic algorithm.

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**Author Contributions**

Si Chen, design, acquisition of data and analysis and interpretation of data, drafting of the article; Benjamin C. Paul, design, acquisition of data and analysis and interpretation of data, drafting of the article; David Myssiorek, concept and design, interpretation of data.

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**References**