

Sialadenosis in Patients with Advanced Liver Disease

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Abstract Sialadenosis (sialosis) has been associated most often with alcoholic liver disease and alcoholic cirrhosis, but a number of nutritional deficiencies, diabetes, and bulimia have also been reported to result in sialadenosis. The aim of this study was to determine the prevalence of sialadenosis in patients with advanced liver disease. Patients in the study group consisted of 300 candidates for liver transplantation. Types of liver disease in subjects with clinical evidence of sialadenosis were compared with diagnoses in cases who had no manifestations of sialadenosis. The data were analyzed for significant association. Sialadenosis was found in 28 of the 300 subjects (9.3%). Among these 28 cases, 11 (39.3%) had alcoholic cirrhosis. The remaining 17 (60.7%) had eight other types of liver disease. There was no significant association between sialadenosis and alcoholic cirrhosis ($P = 0.389$). These findings suggest that both alcoholic and non-alcoholic cirrhosis may lead to the development of sialadenosis. Advanced liver disease is accompanied by multiple nutritional deficiencies which may be exacerbated by alcohol. Similar metabolic abnormalities may occur in patients with diabetes or bulimia. Malnutrition has been associated with autonomic neuropathy, the pathogenic mechanism that has been proposed for sialadenosis.

Keywords Sialadenosis · Sialosis · Cirrhosis · Alcoholic cirrhosis · Parotid glands · Malnutrition

Introduction

Sialadenosis (sialosis) is characterized by bilateral enlargement of the parotid glands that is asymptomatic, does not affect salivary gland function, and is not related to any inflammatory or neoplastic process [1, 2]. This condition was initially associated with a number of vitamin and other nutritional deficiencies [3, 4]. Subsequently, alcoholism and alcoholic cirrhosis became the most frequently cited predisposing factors for sialadenosis [5–7] with incidence estimates of 30–86% [2, 6, 7]. Nevertheless, there have been conflicting findings as to whether alcoholism with or without cirrhosis, or other causes of cirrhosis can result in sialadenosis [2, 6, 8, 9]. Sialadenosis has also been observed with anorexia or bulimia nervosa, diabetes mellitus, obesity, pregnancy, medications, and exposure to chemicals. [2].

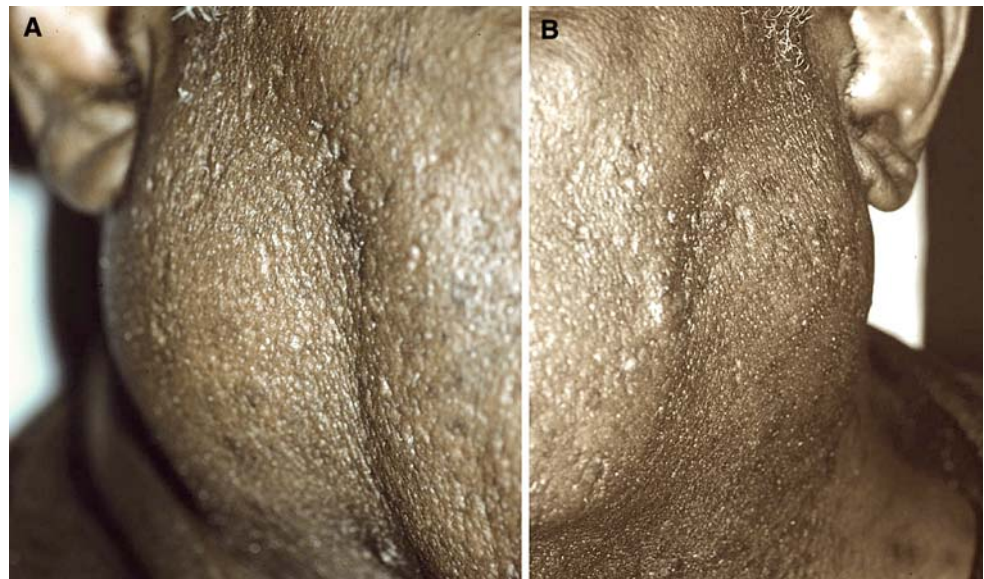
A possible confounding factor contributing to the etio-pathic overlap between sialadenosis and cirrhosis, alcoholism, or malnutrition may be related to the fact that cirrhosis is commonly associated with significant nutritional abnormalities in alcoholic as well as non-alcoholic patients [10–20]. It has been shown that calorie and protein deficiencies may affect nearly all patients who have developed advanced liver disease [19]. A comparative study of alcoholics with or without liver disease and patients with non-alcohol-related liver disease showed that members of each group manifested similar degrees of protein-calorie malnutrition [21]. Cirrhosis that results from alcohol abuse, however, may have more profound consequences because alcohol is also hepatotoxic [22]. The

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Fig. 1 a, b. Typical appearance of bilateral sialadenosis of the parotid glands in the study population



metabolism of alcohol leads to the formation of acetaldehyde and other products that can cause fatty liver, cirrhosis with fibrosis, or acute inflammation (alcoholic hepatitis) [23]. Thus, the impact of alcoholic cirrhosis on the development and progression of nutritional deficits may be even greater in patients with alcohol-related liver disease [16]. A study that compared multiple markers of nutritional status in cirrhotic patients found a significantly greater rate of malnutrition in the alcoholic patients than in those with hepatitis C [24].

Another factor that may have contributed to the more frequent observations of sialadenosis in conjunction with alcohol use may be reflective of the high prevalence of alcoholic liver disease among patients with cirrhosis. This has been estimated to be between 60 and 70% in Western Europe and the United States [23].

During a study that evaluated the oral health status and oral soft tissue pathologies in a population of candidates for liver transplantation, [25] the presence of sialadenosis was recorded. This was assessed for possible associations with the type of liver disease.

Methods

Between 2004 and 2005, 300 consecutive patients who were being evaluated for possible liver transplantation at the University of Pittsburgh's Starzl Transplant Institute underwent an oral examination in order to identify their dental treatment needs and the presence of other oral abnormalities [25]. Consent to participate in this study had been approved by the University's institutional review board which included patient permission to allow all

medical record information to be placed in a Transplant Research Registry. The presence of sialadenosis was based on visible evidence of bilateral parotid gland enlargement as determined by an experienced dental practitioner (JG) (Fig. 1). This information, along with patient demographics and liver disease diagnoses was coded in order to de-identify the subjects and entered in a spreadsheet program (Microsoft Excel V. II. 3, Redmond, WA).

Data Analysis

The data were imported from the MS-Excel spreadsheet into SPSS (SPSS for Windows, Version 14, SPSS, Inc., Chicago, IL, 2005) and analyzed for statistically significant differences in proportions or means depending on the measurement level of each dependent variable. Chi-square and *t*-tests for independent samples were used for these analyses.

Results

Sialadenosis was found in 28 subjects (9.3%). Their demographic characteristics and primary and secondary liver disease diagnoses are shown in Table 1. Determination of the primary and secondary disease was based on patient history, findings from the physical examination, laboratory data, and liver biopsy, when necessary.

Alcoholic cirrhosis was the most frequent underlying primary or secondary liver disease in 11 of the subjects (39.3%). Hepatitis C was the next most prevalent disease (six subjects). Both hepatitis C and alcoholic cirrhosis were

Table 1 Characteristics of the 28 subjects with sialadenosis

Gender	Age	Primary liver disease	Secondary liver disease
F	43	Autoimmune hepatitis	None
F	66	Autoimmune hepatitis	None
F	47	Alcoholic cirrhosis	None
M	65	Alcoholic cirrhosis	None
M	54	Alcoholic cirrhosis	None
F	50	Alcoholic cirrhosis	None
F	64	Alcoholic cirrhosis	None
M	47	Alcoholic cirrhosis	None
M	59	Alcoholic cirrhosis	Hepatitis C
M	48	Alcoholic cirrhosis	Hepatitis C
M	42	Alcoholic cirrhosis	Hepatitis C
F	46	Alcoholic cirrhosis	Hemochromatosis
M	48	Hemangioma	None
M	62	Hemochromatosis	None
M	50	Hepatitis C	None
M	57	Hepatitis C	None
M	66	Hepatitis C	None
F	55	Hepatitis C	Alcoholic cirrhosis
M	44	Hepatitis C	HIV
M	49	Hepatitis C	HIV
M	25	Hepatitis, not specified	None
M	64	Non-alcoholic steatohepatitis	None
F	54	Non-alcoholic steatohepatitis	None
F	65	Non-alcoholic steatohepatitis	None
F	54	Postnecrotic cirrhosis, cryptogenic	None
M	58	Postnecrotic cirrhosis, cryptogenic	None
M	57	Postnecrotic cirrhosis, cryptogenic	Non-alcoholic steatohepatitis
F	45	Primary biliary cirrhosis	None

present in four patients. The 12 remaining cases of sialadenosis were distributed among the seven other liver diseases shown in Table 1. Statistical analyses found no significant association between sialadenosis and alcoholic cirrhosis ($P = 0.389$). Of the 300 liver transplant candidates in this study, 92 (30.7%) had alcoholic cirrhosis as their primary or secondary liver disease. The rate of sialadenosis among these 92 cases was 11.9%.

Laboratory data regarding the nutritional status of these subjects may have been available but were not retrieved. It was determined that the identification of specific nutritional abnormalities and deficiencies as well as their etiology would not be possible due to the complexity and interdependency among all of the metabolic complications associated with liver failure [11]. A summary of the features of nutritional deficits that may be encountered with cirrhosis are listed in Table 2. It should be noted that manifestations of malnutrition have been reported to approach 100% among patients with end-stage liver disease [19].

Discussion

In this study of 300 candidates for liver transplantation, sialadenosis was not significantly related to alcoholic cirrhosis or other underlying liver disease. Nevertheless, initial observations suspected that sialadenosis developed only in patients with cirrhosis resulting from alcoholism [2, 26]. This finding has been supported by other reports which stated that sialadenosis occurred very rarely in conjunction with non-alcoholic cirrhosis or in only 10% of alcoholics who did not have cirrhosis [7, 9]. These concepts were supported by a postmortem study of 28 alcoholics which determined that an increase in parotid volume due to accumulation of adipose tissue was limited to the subjects who had developed cirrhosis [8]. Other clinical findings have shown, however, that sialadenosis could occur in alcoholics without cirrhosis or whose liver disease had not progressed to cirrhosis [2]. The disparities among these reports are reflected in an estimated 26–86% prevalence range for sialadenosis among alcoholics [2, 7]. Similarly,

Table 2 Features associated with nutritional deficits in end-stage liver disease [10–20]

Generalized malnutrition
Reduced nutritional intake
Nausea and anorexia
Taste disturbances
Dietary restrictions
Cachexia
Muscle wasting
Loss of muscle strength
Reduced protein synthesis and break down of protein leading to protein loss
Loss of protein through drainage of ascitic fluid
Increased nitrogen excretion
Hypoalbuminemia
Zinc deficiency
Increased metabolism and energy expenditure
Weight loss
Reduced body mass index
Decline in body cell mass
Loss of body fat
Generalized malabsorption
Impaired absorption of fat soluble vitamins
Reduced vitamin storage
Increased insulin resistance
Increased resistance to growth hormone
Decreased hepatic glycogen storage

a wide range (45–80%) has been estimated for the rate of alcoholic cirrhosis among patients with sialadenosis [9].

In the present study, sialadenosis was found in only 11 of the 92 patients (12%) who had alcoholic cirrhosis as their primary or secondary liver disease. By comparison, alcoholic cirrhosis was the underlying liver disease in 11 of the 28 subjects with sialadenosis (39.3%). This rate could be reflective of the fact that alcoholic cirrhosis was the predominant cause of the liver disease in these liver transplant candidates (92 of the 300 or 30.7%).

The present study determined that 17 of the 28 subjects with sialadenosis (60.7%) had seven different non-alcohol-related liver diseases (Table 1). A possible explanation for this can be based on the premise that these diseases (with the exception of the liver hemangioma) have the potential for progressing to cirrhosis [23, 27]. All 300 subjects had manifestations of decompensated liver disease with varying degrees of cirrhosis which was the basis for their being evaluated for possible liver transplantation. This suggests that cirrhosis of the liver, irrespective of its etiology, may be the predisposing factor that was shared by the patients who had developed sialadenosis.

Initial reports dating back to the 1920s observed that sialadenosis frequently occurred in malnourished and

vitamin deficient populations [3, 4]. Subsequently, sialadenosis has been associated with eating disorders and diabetes [1, 7, 28] which have significant nutritional interactions. Since patients with these conditions as well as cirrhosis are likely develop multiple nutritional deficits, malnutrition or related metabolic complications may be the underlying pathophysiologic processes that patients with sialadenosis have in common.

The frequent association between sialadenosis and cirrhosis may also be attributed to the likelihood and possible confounding effect of patients having both liver disease and diabetes. The liver plays an essential role in the metabolic interrelationships and interdependence among glucose, glycogen, and insulin. Hepatocytes convert glucose to amino acids, fatty acids, and glycogen. Destruction of hepatocytes results in a decreased storage of glycogen, increased serum fatty acids, and decreased uptake of glucose by muscles. This results in hyperglycemia as well as insulin resistance [29]. As a consequence, diabetes can develop as a complication of cirrhosis, and occurs most frequently in patients with chronic hepatitis C and non-alcoholic fatty liver disease (steatohepatitis) [30]. Hemochromatosis is likely to affect the liver and leads to diabetes mellitus because of iron damage to the islet cells [31]. Conversely, diabetes, particularly type 2, can cause liver disease due to altered metabolism of lipids that leads to an increase in serum lipids resulting in fatty infiltration of the liver (non-alcoholic steatohepatitis [NASH]). This condition is similar to alcoholic liver disease and can progress to cirrhosis. Liver disease can also result from the hepatotoxic effects of some oral hypoglycemic drugs [31]. It is noteworthy that among the 28 subjects with sialadenosis in the present study, 13 patients (46%) (Table 1) had liver diseases that are more likely to be associated with diabetes. At the time of this study, however, we did not determine if these transplant candidates also had diabetes.

Although the pathogenesis of sialadenosis has not been established, a neuropathic process that affects the autonomic innervation of the salivary glands has been suggested [2, 9, 32–34]. This hypothesis is based on ultrastructural analyses of parotid tissue obtained from controls and patients with sialadenosis who had liver disease or diabetes [33]. Sialadenosis was associated with acinar cells that were twice as large as compared with control specimens. In addition, there was evidence of axonal and myoepithelial cell degeneration with swelling of the axon fibers and vacuolization [33]. These alterations were similar to the appearance of axons from rats that were exposed to high doses of ethanol [35]. Axonal abnormalities have also been identified by electron microscopy in diabetic rats [36].

Autonomic neuropathies develop in patients with alcoholic as well as non-alcoholic liver disease, cirrhosis, and

diabetes [37–39]. Nutritional dysfunctions that accompany these diseases, in addition to the eating disorders, may lead to neuropathy of autonomic fibers that innervate the parotid glands. This concept, first proposed in 1975, [40] could, therefore, explain the development of sialadenosis in these patients.

The diagnostic criterion for sialadenosis in this study was based on visual evidence of bilateral parotid gland enlargement. Although new technology is available for imaging the salivary glands, it has not been determined that this methodology is useful for the evaluation of sialadenosis in the absence of any structural or functional abnormalities in the glands.

The sialadenosis literature appears to have relied primarily on clinical manifestations of sialadenosis, and to ensure the validity of comparisons with the present study, the same diagnostic criteria were applied.

Conclusions

Among 28 liver transplant candidates who had sialadenosis, 17 had non-alcohol-related liver diseases. This suggests that all types of cirrhosis may contribute to the development of sialadenosis. Metabolic derangements resulting in malnutrition are common in cirrhosis and may, therefore, represent the underlying pathophysiologic mechanism for sialadenosis in patients with liver diseases as well as diabetes and eating disorders. It has been proposed that sialadenosis results from a neuropathic process that involves the autonomic innervation of the salivary glands. This neuropathy may be a complication of nutritional abnormalities that are frequently associated with sialadenosis.

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