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JUVENILE PAROTITIS

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ACADEMIC DISSERTATION

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To my family.

“Tyrocinium hoe Academicum propterea vobis in grati animi pignus offero, submisse es officiosè petens me in posterum tueri, fovere, ornareqve veiitis.”

”Sen vuoksi tarjoan Teille tämän ensimmäisen akateemisen opinnäytteeni osoituksena mieleni kiitollisuudesta, pyytäen nöyrästi ja alamaisesti, että tahtoisitte minua vastedeskin tukea, suosia ja avustaa.”

Olaus Junholm: De Audiendi Sensu, 1696.
The very first otorhinolaryngological dissertation published in Finland.

CONTENTS

ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numerals I–V:

I Saarinen R, Kolho K-L, Davidkin I, Pitkäranta A. The clinical picture of juvenile parotitis in a prospective setup. Acta Paediatrica, accepted.

II Kolho K-L, Saarinen R, Paju A, Stenman J, Stenman U-H, Pitkäranta A. New insights into juvenile parotitis. Acta Paediatrica 94:1566-1570, 2005.

III Saarinen R, Kolho K-L, Lauhio A, Sorsa T, Mäki M, Laakso S, Pitkäranta A. Herpesviruses lack association with acute parotitis in children. Pediatric Infectious Disease Journal 30:1120, 2011.

IV Saarinen R, Kolho K-L, Kontio R, Saat R, Salo E, Pitkäranta A. Mandibular osteomyelitis in children mimicking juvenile recurrent parotitis. International Journal of Pediatric Otorhinolaryngology 75:811-814, 2011.

V Saarinen R, Kolho K-L, Pitkäranta A. Cases presenting as parotid abscesses in children. International Journal of Pediatric Otorhinolaryngology 71:897-901, 2007.

ABBREVIATIONS

Cl^-	Chloride ion
CMV	Cytomegalovirus
CRP	C-reactive protein
CT	Computed tomography
EBV	Epstein-Barr virus
HBO	Hyperbaric oxygen
HCO_3^-	Bicarbonate ion (Hydroxidodioxidocarbonate 1-)
HHV(s)	Human herpesvirus(es)
HHV-6	Human herpesvirus 6
HHV-7	Human herpesvirus 7
HIV	Human immunodeficiency virus
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simplex virus type 2
ICD-10	Classification on Diseases, 10^{th} revision
IgG	Immunoglobulin G
IgM	Immunoglobulin M
JRP	Juvenile recurrent parotitis
K^+	Potassium ion
MRI	Magnetic resonance imaging
Na^+	Sodium ion
NSAID	Non-steroidal anti-inflammatory drug
MMP-2	Matrix metalloproteinase 2
MMP-9	Matrix metalloproteinase 9
MMR	Measles-mumps-rubella (vaccine)
SPINK-1	Serine protease inhibitor Kazal-type 1
US	Ultrasound
VZV	Varicella-zoster virus

ABSTRACT

In parotitis, one or both of the parotid glands swell, causing pain while eating, reduced mouth opening, and in some cases fever. Before the vaccination era, mumps was the most common cause of childhood parotitis. Nowadays acute pediatric parotitis is rare, and the causative agent(s) are not fully known. It is assumed that other viruses in addition to the mumps virus are capable of causing similar symptoms. Some children develop recurrent symptoms i.e. juvenile recurrent parotitis (JRP). If symptoms are frequent, this condition can be quite life-disruptive. Fortunately, JRP often resolves in puberty. The etiology and pathophysiology of this juvenile recurrent parotid inflammation are other aspects currently not completely understood.

The aim of the present study was to assess the epidemiology, etiology, clinical picture, and outcome for pediatric parotitis at present. In addition, it addresses differential diagnosis and complications.

A group of 41 children aged ≤17 with acute parotid inflammation was collected prospectively for this study that reported clinical characteristics, treatment, outcome, and complications. Another group of 133 children was collected retrospectively with the clinical picture of their disease reported, as well. The serine protease inhibitor Kazal-type 1 (SPINK-1) genotype was tested in 88 parotitis patients, since mutation of this gene disposes to pancreatitis, and salivary glands bear some resemblance to the pancreas in function. To map the etiology of parotitis, a questionnaire recarding history of parotitis, and parotid gland -related symptoms went to 1,000 adolescents randomly selected. In addition, human herpesviruses (HHVs) from saliva samples of children with acute parotid inflammation, and from healthy controls were tested. To assess the differential diagnosis and complications of parotitis, the database of Helsinki University Central Hospital, Department of Otorhinolaryngology – Head and Neck Surgery, was searched according to ICD-10 codes in order to find all children diagnosed and treated for osteomyelitis or parotid abscess.

All prospectively studied children with acute parotitis were in good general condition, and most episodes of parotitis in childhood seem to run benign curse. Half these children were treated only with non-steroidal anti-inflammatory drugs. However, parotid symptoms have a tendency to recur in about half the cases. About 1% of the respondents to the epidemiologic survey had suffered from parotitis.

Heredity similar to pancreatitis could not be shown, since no difference emerged in the SPINK-1 genotype in children with parotitis compared to controls. HHVs seem to play no role in acute juvenile parotitis, but are instead common findings in saliva. Osteomyelitis of the head and neck region is rare, but important in differential diagnosis of children with recurrent parotid symptoms. Parotitis-related complications are rare. Parotid abscesses are multi-bacterial infections with intravenous antibiotic therapy being the cornerstone of treatment. Surgical drainage assists in recovery and does not lead to fistula formation.

In conclusion, according to this study juvenile parotitis has a frequency close to 1%, it has a tendency to recur, and in most cases the overall condition of the child is good during the infection. Osteomyelitis as a differential diagnosis must be kept in mind when treating recurrent symptoms of the parotid area. Abscesses related to parotitis are rare. The full etiology of juvenile parotitis still remains to be discovered.

TIIVISTELMÄ

Korvasylkirauhastulehduksessa poski on kipeä ja turvonnut. Suun aukaiseminen on usein rajoittunutta ja syöminen pahentaa kipua. Tautiin voi liittyä kuumetta. Ennen kattavia kansallisia rokotuksia sikotauti oli yleinen ja tavallisin korvasylkirauhastulehduksen aiheuttaja. Nykyään lasten korvasylkirauhastulehdukset ovat harvinaisia eikä kaikkia taudinaiheuttajia tunneta. Sikotautiviruksen lisäksi myös muut virukset voivat aiheuttaa korvasylkirauhastulehduksen. Osa lapsista kärsii toistuvasta korvasylkirauhastulehduksesta, jonka oireet helpottavat tai häviävät yleensä murrosiässä. Myöskään toistuvan korvasylkirauhastulehduksen etiologiaa tai patofysiologiaa ei tällä hetkellä tunneta tarkasti.

Tämän väitöskirjatyön tarkoituksena oli selvittää lasten korvasylkirauhastulehdusten epidemiologiaa, etiologiaa, taudin kuvaa ja hoitoa. Lisäksi tutkittiin erotusdiagnostiikkaa ja komplikaatioita.

Prospektiivinen tutkimusryhmä koostui 41 korvasylkirauhastulehdusta sairastavasta alle 17-vuotiaasta lapsesta. Taudinkuva, hoito ja komplikaatiot selvitettiin. Toinen tutkimusryhmä koostui 133 retrospektiivisesti kerätystä lapsesta, joiden taudinkuva ja hoito rekisteröitiin. Seriiniproteaasin estäjä Kazal tyyppi 1:n (SPINK-1) genotyyppi testattiin 88 lapselta, koska tiedetään, että tämän geenin mutaatiot altistavat haimatulehduksille. Sylkirauhasten ja haiman toiminnassa on paljon samankaltaista. Epidemiologian selvittämiseksi tuhannelle satunnaisesti valitulle nuorelle lähetettiin kysely sairastetuista korvasylkirauhastulehduksista ja muista mahdollisista korvasylkirauhasoireista. Lisäksi korvasylkirauhastulehdusta sairastavien lasten, verrokkilasten ja terveiden aikuisverrokkien syljestä testattiin herpesviruksia osana etiologisia selvittelyjä. Helsingin yliopistollisen keskussairaalan Silmä-korvasairaalan potilastietokannasta etsittiin kaikki lapset ja nuoret, jotka olivat olleet hoidossa pään ja kaulan alueen luutulehduksen tai korvasylkirauhaspaiseen vuoksi. Pään ja kaulan alueen luutulehduksen ja korvasylkirauhastulehduksen oireet voivat muistuttaa toisiaan, ja paise on korvasylkirauhastulehduksen harvinainen komplikaatio.

Kaikkien 41 prospektiivisesti tutkitun lapsen yleistila oli korvasylkirauhastulehduksen aikana hyvä. Suurin osa lasten tulehduksista parantui hyvin, vaikka noin puolet lapsista hoidettiin pelkällä tulehduskipulääkityksellä. Noin puolella lapsista korvasylkirauhastulehdus uusi. Noin joka sadannella kyselytutkimukseen osallistuneesta lapsesta oli ollut korvasylkirauhastulehdus. Tässä tutkimuksessa ei pystytty osoittamaan korvasylkirauhastulehduksissa samanlaista SPINK-1 genotyyppiin liittyvää perinnöllisyyttä kuin haimatulehduksissa. Herpesvirukset olivat yleisiä kaikkien testiryhmien syljessä, eikä yhteyttä äkilliseen korvasylkirauhastulehdukseen löydetty. Pään ja kaulan alueen luutulehdus on harvinainen, mutta tärkeä erotus-

diagnostinen vaihtoehto. Korvasylkirauhastulehduksiin liittyvät komplikaatiot ovat harvinaisia. Korvasylkirauhasen paiseet ovat usean bakteerin aiheuttamia infektioita, joiden hoidon perusta on suonensisäinen antibioottilääkitys. Paiseen puhkaisu tai avaaminen on usein välttämätöntä, eikä johda sylkifistelin muodostumiseen.

Tämän tutkimuksen perusteella lasten korvasylkirauhastulehdukset ovat luultua yleisempiä, niillä on taipumus uusiutua, ja lapsen yleistila on tulehduksen aikana yleensä hyvä. Komplikaatiot ovat harvinaisia. Toistuvia korvasylkirauhastulehduksia hoidettaessa on muistettava myös pään ja kaulan alueen luutulehduksen mahdollisuus. Kaikkia korvasylkirauhastulehduksen aiheuttajia ei tunneta.

1 INTRODUCTION

A colleague of mine suffered swollen cheeks and fever as a child eight times. Each time the doctor diagnosed mumps, and said, "Luckily you can only have this once." Her mother replied, "Well thank you doctor, we hope it is true this time." This was in the 60's. Retrospectively, it easy to say that my colleague didn't have mumps eight times. She had juvenile recurrent parotitis (JRP), which resolved by itself in puberty.

Redness, tenderness, and swelling of the parotid area, accompanied by elevated temperature, are the classical symptoms of parotitis. Chewing is painful, and opening of the mouth may be reduced. Before the vaccination era, parotitis in children was connected with paramyxovirus that caused mumps. However, since mumps has become rare in western countries – even eliminated in some places (Peltola et al., 2000) – the etiology of existing parotitis remains in part unknown. In addition, the current epidemiology of parotitis is unknown.

The clinical picture of acute parotitis is in many cases suggestive of viral infection, and therefore it is assumed that other viruses cause infection and symptoms similar to mumps. At least parainfluenza virus and adenovirus and – among herpesviruses – cytomegalovirus (CMV) and Epstein-Barr virus (EBV) (Davidkin et al., 2005), have been related to parotitis.

Bacterial infections of the parotid gland are, in most cases, secondary to some underlying condition such as reduced saliva flow, a salivary gland stone, dehydration, diabetes, or poor dental hygiene (Nusem-Horowitz et al., 1995). Viral parotid infection can predispose to bacterial invasion of the parotid gland as well. In some cases, bacterial infections can lead to more severe complications: local spread of infection, abscess formation, or generalized infection (Marioni et al., 2003).

Some children suffer from juvenile recurrent parotitis (JRP), which in some cases can be quite life-disruptive. JRP usually resolves in puberty (Galili and Marmary, 1985, Geterud et al., 1988), but sometimes the symptoms persist into adulthood. Mostly one side is more affected, even though signs of inflammation can often be visible on both sides in imaging. The pathogenesis of JRP is not fully understood. The role of microbes in recurrent symptoms is debatable, as well as need for antibiotic treatment (Isaacs, 2002, Vinagre et al., 2003). Different kinds of theories on the pathogenesis exist including autoimmune disease, local malformations, and genetics (Reid et al., 1998).

Mandibular osteomyelitis, even more rare than JRP, can, however, have much the same symptoms. Intermittent swellings of the parotid area together with mild fever and pain can be suggestive of JRP as well as of osteomyelitis. Osteomyelitis, a more severe disease, requires quite different treatment: usually long antimicrobial

treatment and debridement, together with intensive follow-up (Dich et al., 1975, Syrogiannopoulos and Nelson, 1988 Prasad et al., 2007).

In conclusion, the aim of the present study was to assess the clinical picture, epidemiology, etiology, differential diagnosis, and complications of juvenile parotitis currently.

2 REVIEW OF THE LITERATURE

2.1 Parotid gland

The two parotid glands are situated in front of and below the ear, under the subcutis and mainly resting on the masseter muscle in close relation to the mandibular ramus (Figure 1). Parotid saliva is serose, and rich in amylase. It is present mainly when masticating, and food-odors launch the parotid salivation (Holsinger and Bui, 2007).

Two other sets of great salivary glands exist, in addition to the parotid glands: the submandibular and sublingual glands. Saliva secreted by these glands is more mucous in nature. Moreover, hundreds of little salivary glands are located under the mucosa of the mouth (Holsinger and Bui, 2007).

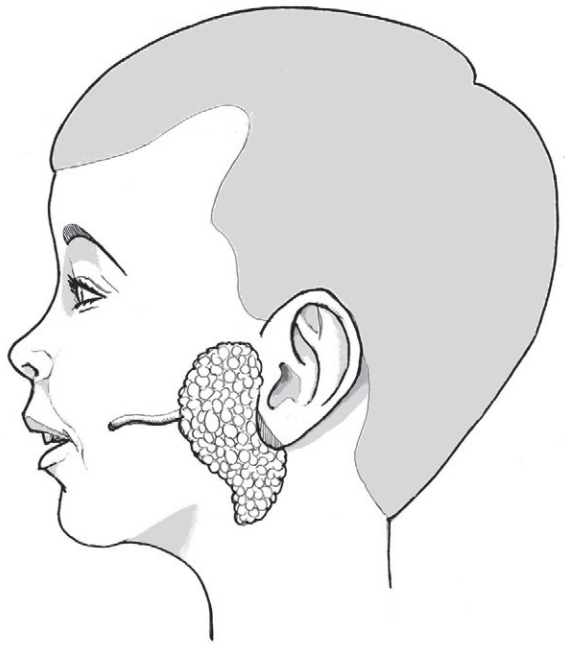

Figure 1. Child's left parotid gland situated in front of the ear and over the mandibular ramus. The parotid (Stensen's) duct runs parallel to the zygomatic bone and opens into the mouth at the level of the second upper molar. Artist: Seppo Piirainen.

2.1.1 Embryology

Development of the parotid glands begins from the oral ectodermal out-pouchings extending into the adjacent mesoderm during the sixth to eighth embryonic weeks (Holsinger and Bui, 2007). At first the branched duct buds start emerging, due to repeated epithelial bud and cleft formation. The early lobules and duct canalization appear during the second developmental stage, and in the third stage, the acini and intercalated ducts mature, whereupon the interstitial connective tissue diminishes (Gibson, 1983). A capsule forms from the ambient mesenchyme to surround the gland. The development and strengthening of the capsule continues in childhood. Development of the salivary glands is an example of branching morphogenesis, in which multicellular organs develop a complex morphology and a treelike arrangement through repetitive, self-similar branching (Jaskoll and Melnick, 1999, Holsinger and Bui, 2007).

2.1.2 Anatomy

The parotids are the largest of the salivary glands and weigh, on average, 15 to 30 g. The facial nerve emerges from the stylomastoid foramen and travels through the gland, branching into five nerves within the gland, dividing the gland into superficial and deep lobes (Figure 2). Diseases of the parotid gland may affect the facial nerve, causing partial or total paresis (Andrews et al., 1989). Facial paresis related to a parotid illness is, however, often a sign of a severe condition. The deep lobe of the parotid gland projects into the parapharyngeal space. A capsule originating from the deep cervical fascia encloses the gland. An anterior accessory parotid gland is sometimes present (Holsinger and Bui, 2007).

The glossopharyngeal nerve – ninth cranial nerve – provides parasympathetic secretory innervation to the parotid gland via the tympanic nerve (Jacobsen's nerve). The tympanic nerve – a branch of the glossopharyngeal nerve – synapses in the otic ganglion with fibers from the trigeminal nerve to form the auriculotemporial nerve, which innervates the parotid gland (Figure 2). In addition, some secretory innervation to the parotid gland is provided from the facial nerve via the chorda tympani nerve. Branches of the external carotid artery supply blood, and venous drainage is through the retromandibular vein (Figure 2). It is important to notice that, contrary to other salivary glands, a high density of lymph nodes exists within and around the parotid gland (Holsinger and Bui, 2007), and as such they are not suggestive of any pathology.

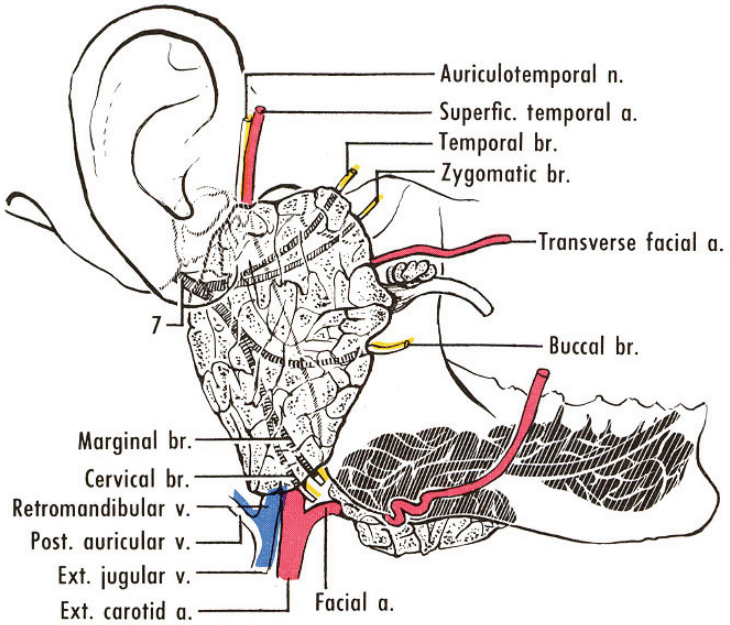

Figure 2. The facial nerve runs through the parotid gland. The blood supply is from branches of the external carotid artery, and venous drainage is through the retromandibular vein. Copyrght © O'Rahilly 2009, reprinted with permission.

Saliva from the parotid gland is secreted via the parotid duct (Stensen's duct) into to the mouth through an orifice situated approximately at the level of the second upper molar (Figure 3). The parotid duct travels parallel to the zygoma across the masseter muscle, and pierces at a sharp angle the buccinator muscle when entering the mouth. The mean diameter of the parotid duct at different points ranges between 0.5 mm and 1.4 mm, with a narrowing at the middle of the duct – the minimum width being, however, at the ostium (Zenk et al., 1998).

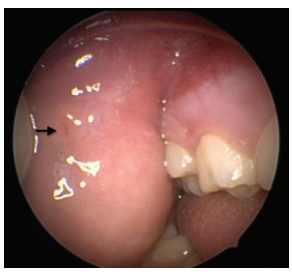

Figure 3. Papilla (arrow) of the parotid duct on the buccal mucosa at the level of the second upper molar. Photograph: Riitta Saarinen.

The basic unit of the salivary gland consists of an acinus, a secretory duct, and a collecting duct. A layer of myoepithelial cells, believed to have contractile properties and to play a role in expelling preformed secretions, surrounds each acinus. Acini are classified as serous, mucous, or mixed. Parotid glands contain mainly serous acini (Elluru and Kumar, 2005).

2.1.3 Physiology

Saliva plays many roles, such as lubrication of foods, and digestive and antibacterial functions. Saliva is also extremely important in maintenance of tooth integrity. The parotid glands secrete approximately one quarter of the total amount of saliva, but during stimulation, the role of the parotid glands enlarges, and they are responsible for one-third of all salivation. The amount of various ions in saliva varies according to the secretion rate, but K^+ concentration is always higher and Na^+ lower than in plasma. The primary secretion produced by the acini is relatively isotonic to plasma, but as the saliva flows through the ducts, Na^+ and Cl^- are reabsorbed, whereas K^+ and HCO_3^- are secreted into the fluid. Thus, with higher secretion rates, saliva concentration is more isotonic (Holsinger and Bui, 2007). In addition to electrolytes, saliva contains a complex mixture of macromolecules such as amylase, mucin 1 and 2, lysozymes, lipase, glycoproteins, trypsin, and lactoferrin (Elluru and Kumar, 2005, Holsinger and Bui, 2007).

2.2 Microbes in acute juvenile parotitis

Except for the mumps virus, the other causative agents of parotitis are not fully understood. Other viruses in addition to paramyxovirus have been related to mumps-like symptoms (Davidkin et al., 2005). Various secondary causes such as salivary stones, diabetes mellitus, or poor general condition predispose to bacterial parotitis (Nusem-Horowitz et al., 1995).

2.2.1 Mumps

Mumps or epidemic parotitis was the main cause of parotid inflammation until the 1990s in Western countries, and this still is the case in many undeveloped countries. Mumps is an acute, self-limited viral infection occurring most often in school-aged children and adolescents; it is a member of the paramyxovirus genus. Parainfluenza virus is another known member of the same genus. The mumps virus genome is composed of single-stranded RNA. Fomities and respiratory droplets transmit this virus (Pomeroy et al., 2008) for which the only natural hosts are humans (Bagg, 1996).

Parotid inflammation occurs in 60 to 70% of mumps infections, and in 95% of patients with symptoms. Parotitis is usually bilateral but can occur on one side only. Other symptoms of mumps are fever, headache, rash, pancreatitis, and orchitis. Symptoms are generally not severe in children. Males past puberty who develop mumps have about a 40% risk of orchitis, which may result in infertility or subfertility (Philip et al., 2006). Mumps is usually self-limiting, running its course before receding, with no specific treatment apart from controlling the symptoms with pain medication (Marchal and Bradley, 2007). Its incubation time is 14 to 21 days, with its most contagious period being a few days before symptoms appear.

Vaccination against mumps was introduced to the Finnish national vaccination protocol in 1982 (Measles, Mumps and Rubella vaccine, MMR vaccine), and the last outbreak of mumps in Finland was in 1987 (Peltola et al., 1994, 2008). The last indigenous transmission was diagnosed in 1996 (Peltola et al., 2000). However, what must be kept in mind is that endemic mumps still exists in Third World countries, and despite comprehensive vaccinations, recent mumps outbreaks have occurred in Western countries as well. Small outbreaks have occurred at least in North America, the United Kingdom, and Spain during the last decade (Donaghy et al., 2006, Kancherla and Hanson, 2006, Peltola et al., 2007, Barskey et al., 2009). Differing mumps vaccine strains vary in efficiency, and multiple dosing, which has been shown to be beneficial, has not been used everywhere. Waning immunity may also play a role in the mumps outbreaks (Peltola et al., 2007). Therefore, it is still important to ask the travel and vaccination history of any child with parotitis.

2.2.2 Viral parotitis other than mumps

Since children vaccinated against mumps still can experience mumps-like symptoms, we are justified in speculating that other viruses cause these infections. Adenovirus, enterovirus, EBV, human herpesvirus 6 (HHV-6), parainfluenza virus, and parvovirus have all been related to parotitis (Martinón-Torres et al., 1999, Akin et al., 2002, Davidkin et al., 2005). Davidkin et al. (2005) were able to show viral etiology in 84 (14%) of their 601 patients with mumps-like symptoms collected prospectively. Most commonly, they found EBV (7%), parainfluenza type 2 or 3 (4%), adenovirus (3%), and HHV-6 (4%, tested from children < 4 years). Akin et al. (2002) and Martinón-Torres et al., (1999), have each reported a case of complicated parvovirus-induced parotitis. Usually parvovirus infections are benign and self-limiting, with typical appearance of erythema infectiosum.

Human herpesviruses (HHVs) – herpes simplex virus type 1 (HSV-1), varizella-zoster virus (VZV), CMV, EBV, HHV-6 and human herpesvirus 7 (HHV-7), - are known pathogens of the respiratory tract (Zerr et al., 2005, Liljeqvist et al., 2009) with high saliva concentrations during acute infection. However, HHVs have also been detected in saliva of those who are asymptomatic. Speculation as to their role

in upper respiratory tract infections is therefore of special interest. Even though EBV and HHV-6 have been related to parotitis (Davidkin et al., 2005), the true role of herpesviruses in pediatric parotitis is unclear.

HHV-6s are frequent findings in child and adult saliva, HHV-6B being the variant most often encountered (Caserta et al., 2004, Pereira et al., 2004, Zerr et al., 2005). Its transmission is speculated to occur via saliva as well (Rhoads et al., 2007). Zerr et al. (2005) showed that HHV-6 infects the majority of children by the age of two. They concluded that most children are symptomatic during the primary infection, and the HHV-6 levels in saliva remain high at least for 12 months thereafter. The role of human HHV-7, a genetic relative of HHV-6, is more controversial (Caserta et al., 2004).

EBV causes infectious mononucleosis and is associated with many other respiratory tract pathologies: mucosal lesions, lymphoid and epithelial malignancies, and periodontitis (Slots et al., 2006). EBV resides in B-lymphocytes, and the salivary glands are considered a site of EBV production in the oropharynx (Morgan et al., 1979). Akaboshi et al. (1983) have suggested that EBV might be of importance in the pathogenesis of JRP. Over 80% of the population in developed countries is infected with EBV before adulthood.

HSV-1 is present in the saliva of asymptomatic children and adults as a result of occasional viral reactivation (Spicher et al., 2001, Liljeqvist et al., 2009), whereas herpes simplex virus 2 (HSV-2) is not a respiratory tract pathogen. The occurrence of CMV and of VZV in saliva is less studied. Todoroki et al. (2006) associated a case of neonatal suppurative parotitis with congenital CMV infection. It has to also be kept in mind that new viruses are constantly found, and viruses play multiple roles in various diseases; it is therefore possible that more will be discovered about viral involvement in future.

2.2.3 Parotitis associated with human immunodeficiency virus (HIV) infection

Parotid gland enlargement occurs in up to 10% of HIV-positive patients (Soberman et al., 1991, Mandel and Witek, 2001, Gaitan-Cepeda et al., 2002). In children, other salivary glands are often involved as well, causing xerostomia, which affects the homeostasis of the mouth (Pinto and De Rossi, 2004). Dave et al. (2007) suggest that parotid lesions in HIV-positive patients can be divided into three categories: persistent generalized lymphadenopathy, benign lymphoepithelial cysts, and benign lymphoepithelial lesions. In most cases, parotid swelling is secondary to multiple lymphoepithelial cyst formation, which is otherwise rare (Shaha et al., 1993). Cystic parotid enlargement is therefore suggestive of HIV infection, especially in children (Dave et al., 2007). Lymphoepithelial lesions pose a bigger risk of transforming into lymphoma (Sato et al., 2002) than do other types of lesions. Parotid enlargement in HIV can also be diffuse in nature, as in juvenile recurrent parotitis.

2.2.4 Bacteria

Bacterial infections of the parotid gland are more common in adults than in children (Laskawi et al., 2006), in many cases being related to some underlying condition like weak general condition, diabetes mellitus, or poor dental hygiene (Nusem-Horowitz et al., 1995, Stong et al., 2005). Obstruction to salivary flow also disposes to bacterial involvement. Pus may be discharged from the parotid duct. The bacteria encountered are typical of oral flora, and mixed infections are common. *Staphylococcus aureus, Streptococcus pneumonia*, and *Haemophilus influenzae* have been among the most common pathogens in suppurative parotitis (Giglio et al., 1997, Stoesser et al., 2012), together with anaerobic bacteria in adults (Brook, 2003).

Mycobacterium tuberculosis causes parotid infections on rare occasions, and usually the symptoms of the parotid region are accompanied by systemic symptoms such as cough, malaise, and fever (Chatterjee et al., 2001, Suleiman, 2001). Another rare cause of parotitis is meliodosis, endemic in parts of Southeast Asia, caused by *Burkholderia pseudomallei* found in soil and water (Lumbiganon et al., 2011). In a recent paper from Cambodia, Stoesser et al. (2012) found 74% of their 39 pediatric parotitis patient's cultures positive for *Burkholderia pseudomallei* emphasizing the importance of this pathogen on certain areas. How et al., (2005) reported an incidence of 0.68 / 100,000 of pediatric meloidosis in Malyasia with 15% of the affected children presenting with parotitis as their first symptom.

Neonatal suppurative parotitis is an uncommon condition most often associating with *Staphylococcus aureus*, although case-reports also describe *Staphylococcus epidermis* (Chevalier and Jadcherla, 2002), *Streptococcus pyogenec* (Herrera-Guerra and Osguthorpe, 2010) and anaerobic bacteria (Brook, 2001) induced suppurative neonatal parotitis. Only some 40 reports of this rare entity appeared in the English literature over recent decades (Spiegel et al., 2004). Neonates with acute suppurative parotitis require hospitalization and intensive follow-up, together with intravenous antibiotic therapy. Prematurity, dehydration, and male gender are considered the main risk factors (Spiegel et al., 2004, Özdemir et al., 2011, Decembrino et al., 2012).

Table 1. Studies describing clinical features and outcome of juvenile parotitis and juvenile recurrent parotitis.

Reference	Number of patients Gender	Age, mean (range) m = months y = years	Aim of the study	Conclusions	Follow-up, mean (range) m=months y=years
Geterud et al. 1988. Ann. Otol. Rhinol. Laryngol.	25 Boys, 18	6.5 y (2.5–16 y)	To evaluate long-term outcome of JRP.	In most patients, symptoms disappear by age 22 independent of treatment given.	(3 y or more)
Zou et al.1990. Chin. Med. J.	102 Boys, 58	5.4 y (2.5–14 y)	To evaluate clinical picture, and outcome of JRP.	URIs may dispose to JRP. Many patients have long symptom-free periods.	7 y (1–23y)
Ericson et al. 1991. Ann. Otol. Rhinol. Laryngol.	20 Boys, 12	7.2 y (3 m–16 y)	To evaluate clinical picture, and outcome of JRP.	Congenital malformations and oral infections contribute to JRP. URIs and autoimmune causes play no role in JRP.	(7–22 y)
Leerdam et al. 2005. J. Paediatric. Child. Halth	53 Boys, 37	8 y (1.5–16 y)	To evaluate clinical presentation, diagnosis, and management of JRP.	JRP has a biphasic age distribution, male predominance; antibiotics play no role in treatment; Sjögren's syndrome and immune deficiency should be screened.	Retrospective
Sitheeque et al. 2006 Int. J. Paediatr. Dent.	26 Boys, 15	8.4 y (2.5–16 y)	To evaluate clinical presentation, and sialographic, and ultrasonographic features of JRP.	JRP has a slight male predominance; sialography and ultrasound are useful tools in diagnosis.	–
Stong et al. 2006. Int. J. Pediatr. Otorhinolaryngol.	21 Boys, 8	6.5 y (6 m–15 y)	To evaluate clinical picture and management of parotis in children.	Pediatric parotitis is rare, admission should be reserved for those with a co-morbidity, leucocytosis, or fever; imaging is unnecessary unless, suspicion of abscess.	5 y

JRP = Juvenile recurrent parotitis. URI = Upper respiratory infection.

2.3 Juvenile recurrent parotitis

Juvenile recurrent parotitis (JRP) is an infrequent condition of unknown etiology (Baurmash, 2004). The peak onset of symptoms is at around four to six years, and the symptoms usually resolve after puberty (Ericson et al., 1991, Miziara and Campelo, 2005). Leerdam et al. (2005) showed a biphasic age distribution at two to five years and at ten years (Table 1). It has been speculated that development of the immune system and growth of the parotid capsule contribute to the JRP resolution (Zou et al., 1990). However, in some cases the symptoms persist into adulthood (Chitre and Premchandra, 1997, Baurmash, 2004). Recurrent episodes of parotid swelling and pain can be life-disruptive, even though the overall condition of the patient remains good (Figure 4). In most cases, only one side is affected, but the symptoms may be bilateral (Shacham et al., 2009). Male dominance has been reported (Arrieta and McCaffrey, 2005, Leerdam et al., 2005). The main criterion for establishing the JRP severity is frequency of recurrence.

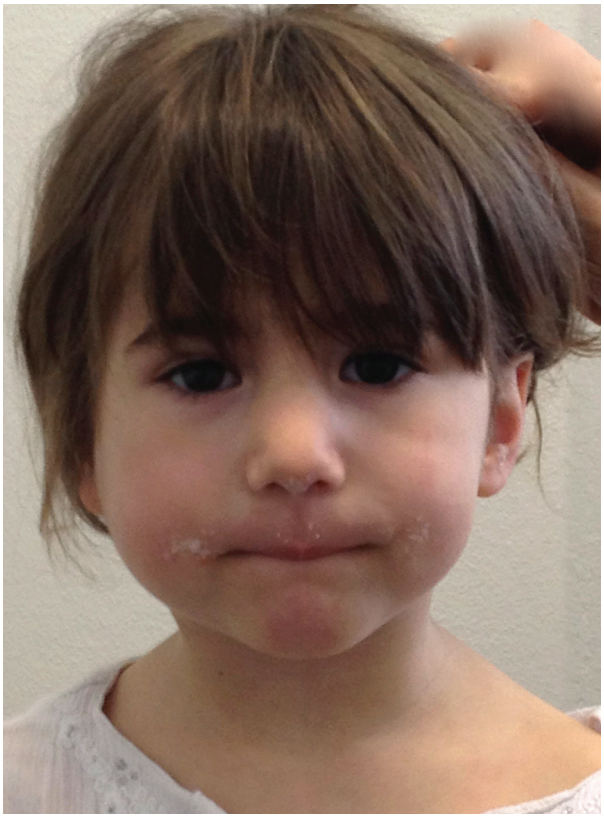

Figure 4. A 3-year-old girl presenting with acute symptoms of right-sided recurrent juvenile parotitis: right parotid enlargement, pain and mild fever. Photograph: Riitta Saarinen.

2.3.1 Etiology

Among theories on etiology, none has proven to be solid. Etiology may, in fact, be multifactorial. It has been suggested that allergy, congenital parotid malformations, infections, and genetic inheritance dispose to JRP (Giglio et al., 1997, Reid et al., 1998, Wittekindt et al., 2000, Vinagre et al., 2003, Fazekas et al., 2005, Leerdam et al., 2005). Some suggest that JRP is a local manifestation, or early presentation of autoimmune diseases (Friis et al., 1983). JRP has been related to common variable immune deficiency (Nguyen and Green, 2009), to IgG3 subclass deficiency (Marsman and Sukhai, 1999), and considered a precursor of Sjögren's syndrome (Flaitz, 2001, Munro and Allen, 2003, Houghton et al., 2005, Baszis et al., 2012).

Hara et al. (1992) diagnosed Sjögren's syndrome in three (5,1%) of their 59 recurrent parotitis patients but found autoantibodies transiently present in 12 (20%), and therefore recommended screening for underlying systemic immune disorders for children with late onset of JRP. Fazekas et al. (2005) showed selective IgA deficiency in 22% of their 23 JRP patients, different from the cumulative prevalence of IgA deficiency in healthy population of 0.3% ($P < 0.001$). Shkalim et al. (2004) have reported a JRP patient with selective IgA deficiency without any accompanying autoimmune disease as well. Frati et al. (2011) recently reported a case of eosinophilic parotitis and recommended cytological assessment when patients with parotitis of uncertain origin are evaluated.

From the clinical point of view, in the acute phase of JRP, the saliva is often milky and viscous with semisolid material, and molecular alternations in parotid saliva of JRP patients have been reported (Ericson and Sjoback, 1996a). Saliva analyses show an increase in albumin, lactoferrin, and kallikrein concentrations (Tabak et al., 1978, Ericson and Sjöback, 1996b,). Recently, Morales-Bozo et al. (2007) demonstrated higher overall protein concentration, increased matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9) concentrations, altered mode of protein diffusion, and higher frequency of some polypeptide bands in JRP, speculating that parotid saliva analysis could lead us to the foundation of the disease. Even more recently, they concluded that the levels of MMP-2 and MMP-9 could be useful in evaluating the degree of glandular damage and the efficiency of medical trials (Morales-Bozo et al., 2008).

Even though Akaboshi et al. (1983) found some evidence of possible EBV involvement in JRP, and Giglio et al. (1997) have cultured *Streptococcus pneumoniae* and *Haemophilus influenzae* in their JRP patients, others have concluded that most likely there exists no microbial etiology behind recurrent symptoms, and therefore the treatment can be symptomatic (Isaacs, 2002, Vinagre et al., 2003, Leerdam et al., 2005). Vinagre et al. (2003) tested JRP patients for adenovirus, respiratory syncytial virus, parainfluenza virus, influenza virus, CMV, HSV, EBV, and mumps. Because viral infections were detectible in only seven (14%) among 50 cases, they concluded that the main respiratory and oropharyngeal viruses are not the cause of acute episodes of JRP (Table 2).

Table 2. Pathogens in acute parotitis and juvenile recurrent parotitis reported in the literature.

Reference	Number of patients / controls	Age years (Range) Gender	Acute / Recurrent Parotitis	Pathogens studied	Pathogens found Study group / controls	Conclusions
Akaboshi et al. 1983	34 / 40	– (2.0–12) Boys, 19	Recurrent	*EBV	*EBV antibodies suggestive of a persistent carrier in 29 cases (85%) / None had EBV antibodies suggestive of a persistent carrier	*EBV may associate with JRP
Giglio et al. 1997	56 / 20	6.1 (2.0–11) Boys, 36	Recurrent	Bacteria	91% positive: *S. pneumoniae, H. influenzae, Moraxella catarrhalis, Viridans streptococcus* / *65% positive: Moraxella catarrhalis, Viridans streptococcus*	*S. pneumoniae,* and *H. influenzae* associate with JRP
Nusem-Horowitz et al. 1995	20	4.4 (9d–14y) Boys, 13	Acute	Bacteria	10 cases of suppurative parotitis, of which 40% positive: *Bacteroides fragilis, Staphylococcus aureus, Klebsiella* species	–
Vinagre et al. 2003	70 / 20	5.6 (1.0–12) Boys, 29	Recurrent	*Adenovirus, enterovirus, RSV, parainfluenza virus, influenza virus, CMV, HSV, mumps	*14% positive: CMV, enterovirus, influenza virus A, mumps / 10% positive: mumps	Viruses do not associate with JRP
**Davidkin et al. 2005	601	– (1.6–19) Boys, 373	Acute	*EBV, adenovirus, enterovirus, parainfluenza virus, parvovirus, HHV-6	*14% positive: EBV, adenovirus, enterovirus, parainfluenza virus, parvovirus, HHV-6	Various viruses may cause mumps-like symptoms

*RSV = respiratory syncytial virus, CMV = cytomegalovirus, HSV = herpes simplex virus, EBV = Epstein-Barr virus, HHV-6 = human herpesvirus 6.
**Acute mumps was excluded in an earlier phase of the study.

The development of miniature endoscopes has made intra-ductal investigation of the salivary glands possible. The main findings in endoscopic investigation are in the parotid duct: dilatations and strictures, a whitish appearance of the ductal layer, and lack of normal blood vessels (Nahlieli et al., 2004, Shacham et al., 2011). Fibrotic plaques are often visible. Like other imaging methods, endoscopy of the non-symptomatic side, often reveals signs of inflammation, as well. Studies on glandular tissue from patients with JRP have shown lymphocytic infiltrates and lymphoid follicles around dilated interlobular ducts (Ussmuller and Donath, 1999).

2.3.2 Genetics

Reid et al. (1998) have described a family with four members affected with JRP, and others have also reported families in which two siblings or members of more than one generation were affected leading to speculation about possible genetic inheritance as a predisposing factor for JRP (Galili and Marmary, 1985, Sitheeque et al., 2007).

Recently, what has been recognized is that children and adolescents with chronic pancreatitis have a high (23%) incidence of mutations in the serine protease inhibitor Kazal-type 1 (SPINK-1) (Pfützer et al., 2000, Witt et al., 2000 Chen et al., 2001, Drenth et al., 2002). SPINK-1 has functional importance in the pancreas as it inhibits proteolytic trypsin activity and tissue destruction. Pfützer et al. (2000) concluded that SPINK-1 mutations act as disease modifiers, altering the phenotypic expression of pancreatitis. N34S and P55S SPINK-1 mutations are, however, mostly found in patients with idiopathic pancreatitis without any family history of the disease (Witt et al., 2000). According to a study by Lempinen et al. (2005) prevalence of the N34S mutation of SPINK-1 is 2.6% and of the P55S mutation 1.3% among the Finnish blood donors, which is more frequent than reported elsewhere. The pancreas and salivary glands have similarities in function, making it therefore tempting to speculate that chronic juvenile parotitis and recurrent pancreatitis might share genetic similarities as well.

2.4 Radiological imaging of the parotid gland

Ultrasound (US) is a readily available, non-invasive, and reliable tool for salivary gland imaging (Sitheeque et al., 2007, Sodhi et al., 2011). It is useful as the initial diagnostic method for various pathologies of the neck. It visualizes lymph nodes, salivary glands, and the thyroid as well as other soft tissue structures well. In addition, US can aid in surgical procedures such as abscess incision (Gritzmann et al., 2003) or needle aspiration. With US, the findings suggestive of parotitis are multiple hypoechoic areas, heterogeneous echogenicity, and in many cases, sialectasis (Sitheeque et al., 2007). In their review article Sodhi et al. (2011) conclude that high resolution US remains the first-line imaging modality for evaluation of the parotid gland in pediatric patients.

If further diagnostics is needed, magnetic resonance imaging (MRI) is the best choice in children, since computer tomography (CT) exposes patients to radiation. In addition, MRI is superior to CT in demonstrating soft-tissue changes (Reinert et al., 1999). MRI sialography is a new method in salivary diagnostics, enabling a three-dimensional view of the salivary ductal system without contrast media (Wittekindt et al., 2000, Gadodia et al., 2011). MRI sialography is non-invasive, and possible to use during acute infection as well, but unfortunately the availability of MRI sialography is limited.

Sialography with intra glandular contrast media has been the standard in salivary gland imaging, but nowadays non-invasive methods have replaced it (Rubaltelli et al., 1987, Encina et al., 1996, Shimizu et al., 1998). In addition Shimizu et al. (1998) concluded that US is more sensitive than sialography in both primary and recurrent parotitis. Findings most suggestive of parotitis in sialography are multiple sialectasias. In addition, sialendoscopy can serve as a diagnostic tool as well as a treatment modality (Capaccio et al., 2008).

2.5 Management of parotitis

Treatment modalities for acute parotitis include symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs), milking of the gland, sialogogues (Isaacs, 2002, Fazekas et al., 2005), and antibiotics. However, stimulating salivary flow by milking in the acute phase may be impossible due to pain, and the role of antibiotics is controversial. It is possible that a significant proportion of primary parotid infections are of viral origin (Davidkin et al., 2005). In JRP, the microbe etiology behind the recurrent symptoms is even more controversial, and some researchers favor symptomatic treatment (Isaacs, 2002, Vinagre et al., 2003, Leerdam et al., 2005). However, antibiotics for the acute phase of JRP are still often the choice (Arrieta and McCaffrey, 2005, Sitheeque et al., 2007), even with no clear evidence of their benefits (Isaacs, 2002), since it is speculated that reduced glandular function with reduced salivary flow predisposes the gland to oral pathogens emerging via the parotid duct.

Treatment of JRP consists of relieving the acute symptoms and preventing reoccurrences. Bowling et al. (1994) did a double-blind study on rabbits to demonstrate acinar atrophy after intra-glandular tetracycline therapy, concluding that tetracycline would be effective in JRP-symptom reduction. Even oral-appliance positioning has been tried to treat JRP, since one of the hypothesis is that dental malocclusion with mandibular misplacement may be a causative agent through unbalanced masticatory muscles (Bernkopf et al., 2008). Nowadays, watchful waiting has become a common practice in JRP, because the condition is known often to resolve in puberty (Geterud et al., 1988, Ericson et al., 1991, Isaacs, 2002). In addition to this spontaneous recovery in puberty, JRP has also been shown to improve with time (Zou et al., 1990, Miziara and Campelo, 2005,). It has also been speculated that treatment type has no impact on long-term outcome (Geterud et al., 1988).

Table 3. Representative studies of treatment of juvenile recurrent parotitis.

Reference	Number of patients Gender	Age, mean (range) years	Treatment modality	Given treatment	Outcome	Follow-up, mean (range) m=months y=years
*Galili and Marmary 1986	22 Boys, 14	4.0 (0.5–8.0	Sialography	Contrast medium	Decreased symptoms in 86%	–
*Wang et al. 1998	16 Boys, 10	– (16–58)	Canalization	Methyl violet 1%	2 relapses No relapse after 2nd treatment	– (0.5–7.0 y)
Nahlieli et al. 2004	26 Boys ,14	7.0 (2.5–13)	Sialendoscopy	Saline and 100 mg hydrocortisone	No relapse	– (4.0–36 m)
Antoniades et al., 2004	27 Boys, 16	– (8.0–65)	Canalization	Penicillin, saline, or both	2 relapses No relapse after 2nd treatment	– (1.0–14 y)
Quenin et al. 2008	10	– (1.8–13)	Sialendoscopy	Saline	One relapse	11 m (2.0–24 m)
Katz et al. 2009	840 Boys, 437	4.5 (0.5–14)	Canalization	Iodinated oil	12 symptom-free months on average (range 6–18)	5.5 y (2.0–9 y)
Shacham et al. 2009	70 Boys, 43	– (1.0–14)	Sialendoscopy	Saline and 100 mg hydrocortisone	13 relapses + 1 recurrent relapse	12 m (6.0–36 m)

No study had a control group.
*Intention of treatment was to introduce gland atrophy.

2.5.1 Sialendoscopy and intra glandular lavage

In 1986 Galili and Marmary showed that patients with JRP who underwent sialography had, at least to some extent, relief of their symptoms. Most likely the symptoms decreased due to enlargement of the ductal system and lavage of the debridement. Thereafter, various substances such as saline, methyl violet, and cortisone have been applied to lavage parotid glands of JRP patients (Wang et al., 1998, Nahlieli et al., 2004) (Table 3). Intra-ductal treatment of chronic sialadenitis with penicillin and saline has been tried in adolescents and adults with promising preliminary results (Antoniades et al., 2004). Recently Katz et al. (2009) have treated their pediatric parotitis patients with iodine sialography and report no recurrences of symptoms in children treated after the first episode, and an average one-year symptom-free interval in patients treated after two or multiple episodes. They conclude that the antiseptic influence of iodine was capable of reducing their patient's' symptoms for as many as 98%. However, they report no control group, but compare their findings to the frequency of symptoms before their treatment.

Development of miniature endoscopes has made it possible to visualize the inside-gland appearance of juvenile parotitis in addition to intra-glandular treatment (Figures 5a, 5b, and 5c). Recently, sialendoscopy has become a common preventive treatment modality (Nahlieli et al., 2004, Quennin et al., 2008). Sialendoscopy is minimally invasive: an endoscope with a diameter from 0.8 to 1.1 mm is introduced into the parotid duct via the papilla. For most children, however, this procedure needs to be done under general anesthesia. Nahlieli et al (2004) were the first to report endoscopic treatment of JRP patients. They treated 26 symptomatic JRP children with sialendoscopy, saline lavage, and 100 mg intra-ductal hydrocortisone administered through the endoscope under visual control with good results. All children were symptom-free during the 4 to 36 months' follow-up. However, two developed symptoms on the contralateral side. The pitfall of the study was the absence of a control group. Others have also reported good results from endoscopic treatment and ductal dilatation, although these studies lack a control group as well (Leerdam et al., 2005, Shacham et al., 2009, Martins-Carvalho et al., 2010). In any case, endoscopes have brought new aspects to the treatment and diagnosis of JRP.

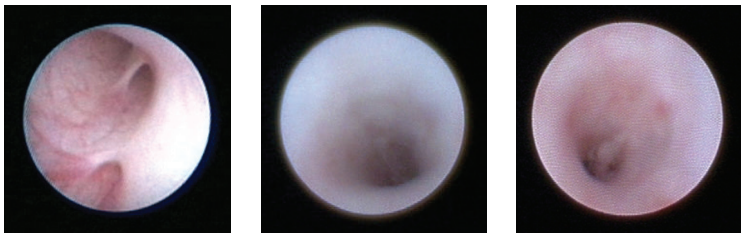

Figure 5. Sialendoscopy view of a normal parotid duct (a). In juvenile recurrent parotitis, avascular ductal wall (b and c) with typical fibrin plaques (c). Photographs: Riitta Saarinen.

2.5.2 Surgical treatment

Tympanic neurectomy has been a method for treating chronic parotitis (Benedek-Spat and Szekely, 1985, Vasama, 2000). Part of the nerve lying across the cochlear promontory is removed via a tympanic approach. Most of the neural innervation of the parotid gland occurs via the tympanic nerve (Jacobson's nerve), and therefore cutting off its fibers diminishes glandular activity and leads to atrophy. But since JRP is usually self-limiting in puberty, a wait-and-see policy has replaced tympanic neurectomy in young patients. In addition, because some nerve fibers travel to the parotid gland via the corda tympani nerve, then cutting solely the tympanic nerve does not always result in the desired outcome. Concurrent cutting of the corda tympani improves the results but may affect permanently the sensation of taste.

Ductal ligation has been used to initiate glandular atrophy, as well (Chitre and Premchandra, 1997, Baurmash, 2004), and parotidectomy for treatment of frequent JRP has also been described (Moody et al., 2000, Orvidas et al., 2000, Laskawi

et al., 2006). However, parotidectomy is quite a radical procedure, and should be reserved only for extremely severe and prolonged cases when other treatments provide no relief. Encounters with the facial nerve occur during surgical procedures in the parotid area.

2.6 Differential diagnosis and complications

Other diseases of the head and neck area may mimic symptoms of parotitis and must be taken into account. In addition, on rare occasions, infection of the parotid gland may lead to dangerous complications.

2.6.1 Differential diagnosis

Lymphadenitis and cellulitis are common infections of the head and neck. Especially in children, lymphadenitis is often related to viral respiratory tract infections and tonsillitis. Unilateral lymphadenitis is often a sign of bacterial infection, so uncommon pathogens such as toxoplasmosis, cat-scratch disease, and atypical mycobacterial infection must be considered in addition to more frequent *Streptococcus* and *Staphylococcus* infections. Insect bites and allergic reactions may cause a similar redness and tenderness of the affected area, but these conditions lack other signs of infection.

2.6.1.1 Mandibular osteomyelitis

Mandibular osteomyelitis in children is rare. Pediatric osteomyelitis is most often of hematogenous origin, but can also result from local infection or trauma or be secondary to vascular insufficiency. In mandibular and maxillar osteomyelitis, a tooth follicule is the potential origin of the infection (Schuknecht et al., 1997, Prasad et al., 2007, Pigrau et al., 2009).

Osteomyelitis is classically divided into three forms: acute, subacute, and primary chronic. The chronic form differs from the others by its prolonged symptoms, ones lasting more than four weeks. At present, primary chronic osteomyelitis is considered a distinct disease, representing a chronic non-suppurative inflammation (Baltensperger et al., 2004). It seems that the mandible in particular is susceptible to the chronic form of osteomyelitis (Prasad et al., 2007). Moreover, acute osteomyelitis may on some occasions become a chronic disease, and chronic osteomyelitis may result in variable sclerosis and deformity of the affected bone (Ducic, 2008). Often no microbes can be cultured from bone, and surgery is ineffective (Eyrich et al., 2003). In addition, a chronic multifocal form of osteomyelitis occurs in children and adolescents, mainly affecting the metaphyses of the long bones; but other parts

of the skeleton, as well as other organs may be concomitantly affected (Otsuka et al., 1999, Girschick et al., 2007, Monsour and Dalton, 2010).

In acute osteomyelitis, bacteria or other microorganisms are embedded in a suppurative inflammation with various inflammatory factors and leucocytes also present. Eventually the process leads to obliteration of the vascular canals and to tissue necrosis. Avascular segments of dead bone, sequestra, can continue to collect bacteria despite antibiotic treatment. Increased osteoclastic activity at the edge of the inflammation produces bone loss and localized osteoporosis (Lew and Waldvogel, 2004). The bacterium most often encountered in osteomyelitis is *Staphylococcus aureus* (Vinod et al., 2002).

For suspected bone involvement in infection, panoramic radiography, CT, and MRI can serve as imaging modalities. Ultrasound is not suitable for bone imaging. CT can be considered the gold standard for imaging cortical bone defects and calcifying periosteal reactions and bone sequestra (Schuknecht et al., 1997). MRI can, to some extent, also evaluate bone structures (Lee et al., 2003). In a pediatric population, MRI is especially valuable because of its lack of ionizing radiation.

Osteomyelitis should be treated intensively, and usually long courses of antibiotics are needed. However, some evidence, especially in children, speaks for the efficiency of shortened courses of antibiotics (Peltola et al., 1997, Vinod et al., 2002, Malcius et al., 2005), but no clear consensus exists (Weichert et al., 2008). As adjuvant therapy, debridement of the infected area is often beneficial, and sometimes more radical surgery is also necessary (Montonen et al., 1993, Eckardt et al., 1994). Despite intensive therapy, healing of osteomyelitis can be problematic. Adjuvant treatment options include hyperbaric oxygen (HBO) therapy (Aitasalo et al., 1998, Lentrodt et al., 2007). Recently, bisphosphonate treatment for chronic osteomyelitis has shown promising results in cases resistant to conventional therapy (Soubrier et el., 2001, Yamazaki et al., 2007, Gleeson et al., 2008, Simm et al., 2008).

2.6.1.2 Actinomycosis

Anaerobic, gram-positive *Actinomyces* causes granulomatous infection, which in many cases turns into a chronic disease. The infection travels through tissue borders, affecting soft tissue as well as bone (Bennhoff, 1984, Stewart et al., 2005). Its diagnosis is based on sulfur-granules seen in tissue samples. *Actinomyces* is part of the normal oral flora, and in the orofacial area, the origin of the infection is likely to be dental (Ohlms et al., 1993, Sharkawy, 2007). The symptoms are often fluctuant and subtle: the overall condition of the patient remains good (Yenson et al., 1983, Robinson et al., 2005).

In most cases, a permanent cure requires bone debridement and long antibacterial treatment, but there is no clear consensus as to the ideal therapy (Bartkowski et al., 1998, Robinson et al., 2005). *Actinomyces* species are usually

susceptible to penicillin, clindamycin, and tetracycline, all of which should penetrate well into bone (Smego and Foglia, 1998). Other organisms may complicate the infection. Bartowski et al. (1998) report a series of 15 patients with mandibular actinomycosis, of which three had a single reoccurrence; all were treated surgically, and the antibiotic treatment ranged from three weeks to one and half months. Robinson and colleagues reported in 2005 four juvenile cases of osteomyelitis of the mandible caused by *Actinomyces*, and recommended three-month antibiotic treatment, with repeated debridement in any case of relapse. According to others, even longer courses of antibiotics and a more radical surgical approach may be necessary (Friduss and Maceri, 1990, Ohlms et al., 1993).

2.6.1.3 Other causes of parotid swelling

Masseter hypertrophy, which results from constant clenching, bruxism, or gum chewing, can be mistaken for parotid enlargement (Mandel and Surattanont, 2002). A first branchial cleft cyst is an infrequent malformation of the parotid area that can lead to recurrent swelling and infections. An infected branchial clef cyst may present as an abscess of the parotid gland. However, the symptoms usually re-emerge, and a cure can only result from surgery (Triglia et al., 1998, Daniel et al., 2003).

Frequent vomiting in bulimia can cause parotid swelling, and in obese people the glands are often constantly swollen (Touyz et al., 1993, Bozzato et al., 2008). Pneumoparotitis resulting from air being forced through parotid duct also occurs in children, although rarely (Goguen et al., 1995). Parotid neoplasia is rare in children, but must be taken under consideration, if the swelling of the gland is constant or a lump appears. Pleomorphic adenoma is the most common benign lesion of the parotid gland in children, with malignancy also a possibility (Orvidas et al., 2000, Daniel et al., 2003). Bilateral recurrent parotitis can also be a single sign of pediatric Sjögren's syndrome (Baszis et al., 2012) or sarcoidosis (Surattanont et al., 2002).

2.6.1.4 Complications

Bacterial parotitis is a potentially life-threatening disease, since the parapharyngeal space lies in close contact with the parotid gland, and the inflammation can spread, causing fasciitis (Marioni et al., 2003), deeper head and neck abscesses (Cmejrek et al., 2002, Kishore et al., 2004), Lemiere's syndrome, or mediastinitis. Parotitis may lead to facial nerve paresis (Andrews et al., 1989, Martinón-Torres et al., 1999, Stoesser et al., 2012).

2.6.1.5 Parotid abscesses

One rare complication of acute suppurative parotitis is a parotid abscess. In adults it is often related to poor oral hygiene, long-term debility, and reduction in salivary flow (Brook, 2003). However, such an abscess can also appear in relatively young and fit adults with no history of oral pathologies (Nusem-Horowitz et al., 1995, Ganesh and Leese, 2005,). In children, few reports exist of parotid abscesses. Ductal stones are rare in children, which supports the finding that parotid abscess formation is in most cases of non-obstructive origin (Ganesh and Leese, 2005).

The symptoms of a parotid abscess include marked swelling of the angle of the jaw, and pain while eating. Regional lymphadenitis may occur, as well as purulent secretion from the parotid duct. The treatment includes broad-spectrum intravenous antibiotics, good oral hygiene, and adequate hydration. If an abscess has formed, surgical drainage is advisable (Brook, 2003).

Various bacteria are involved in the parotid inflammation process: *Staphylococcus aureus, Streptococcus pneumonia, Haemophilus influenza,* and anaerobic bacteria. (Giglio et al., 1997, Brook, 2003, Ganesh and Leese, 2005,). One case-report even describes a candida parotid abscess (Even-Tov et al., 2006). Tuberculosis of the parotid gland is rare even where the disease is endemic; patients usually have long-duration swelling of the parotid gland together with systemic symptoms such as cough, fever, and weight loss (Chatterjee et al., 2001, Suleiman, 2001).

Surgical drainage is usually necessary in curative treatment of an abscess (Brook, 2003), but the development of efficient antimicrobial treatment has shifted the initial treatment towards more conservative direction. Surgical methods include quite radical procedures such as multiple drainage incisions or raising a full posterior-based flap as in parotidectomy. But it seems that in most cases, a smaller procedure is sufficient (Ganesh and Leese, 2005), especially when modern imaging techniques can assist in the procedure accompanied by broad-spectrum antibiotic therapy.

3 AIMS OF THE STUDY

The purpose of this study was to understand the current clinical picture, epidemiology, etiology, differential diagnosis, and complications of pediatric parotitis.

Specific aims were:

1. To determine the clinical characteristics of juvenile parotitis in a prospective and a retrospective setup, and to map its epidemiology.
2. To determine the possibility of SPINK-1 mutations as a factor predisposing to juvenile parotitis.
3. To assess whether herpesviruses (HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, or HHV-7) are etiological factors in pediatric parotitis.
4. To assess the differential diagnosis between juvenile parotitis and mandibular osteomyelitis.
5. To asses the parotid abscess as a complication of parotitis.

4 SUBJECTS AND METHODS

The study consists of five studies, all conducted at Helsinki University Central Hospital, a tertiary care hospital covering about 1.4 million inhabitants, at the Department of Otorhinolaryngology - Head and Neck Surgery, and at Children's Hospital.

4.1 Patients and controls

Study I
All consecutive pediatric patients (n=44) with a primary diagnosis of acute parotitis admitted between 2005 and 2010 were recruited for this prospective study of juvenile parotitis. Three patients were excluded due to incorrect primary diagnoses (described in Study IV). A control group comprised 38 sex- and age-matched children.

The type and duration of symptoms were recorded together with clinical findings, treatments given, history of previous episodes of parotitis, family history of parotitis, and imaging methods. Laboratory investigations included C-reactive protein (CRP), blood leukocyte count, serum amylase, and serum trypsinogen 2. SPINK-1 genotype was determined, and any purulent excretion from the parotid duct was sampled for bacterial culture. Mumps antibodies type IgG and IgM were determined from saliva of parotitis patients (n=22) and of 34 age- and sex-matched control children who came for an elective otorihinolaryngological surgery, were healthy at the moment and had no history of parotitis. To map the recurrence of parotitis, all children with a primary episode of parotitis at recruitment were telephoned a year after the study was closed.

Study II
Clinical records of all children admitted to Helsinki University Central Hospital, Department of Otorhinolaryngology between 1995 and May 2003 due to swelling of the parotid gland were reviewed retrospectively, with 142 children and adolescents with parotid swelling successfully traced. Two children of non-Finnish origin were excluded due to inadequate communication, and seven children had parotid-related symptoms instead of true parotitis. This produced a total of 133 children and adolescents. Treatment given, outcome, recurrences, blood leukocyte count, CRP, and imaging methods were recorded. A postal questionnaire covered possible recurrences, and familial cases of parotitis, or pancreatitis, and children were asked to give a blood sample for determination of mutations in the SPINK-1 gene.

Questionnaires filled in by guardians of 48 children admitted for elective surgery served as controls. Forty-seven patients agreed to SPINK-1 status testing. For the SPINK-1 study another control group of 39 children admitted to our clinic for elective surgery was collected. The results were contrasted, in addition to the control group, also to figures in a recent study by Lempinen et al. (2005) on the prevalence of N34S and P55S mutations among Finnish blood donors.

Study III

Thirty-five saliva samples, obtained in the acute phase, of children (boys 19) aged 17 years or younger (median age 7.6, range 2.6-17) with acute parotitis were analyzed for HHVs (HSV-1, HSV-2, VZV, CMV, EBV, HHV-6 and HHV-7). From age- and sex-matched children who came for an elective otorhinolaryngological surgery, were healthy at the moment, and had no history of parotitis came 34 control samples. Another control group comprised ten healthy adult dental hygienists with excellent oral and dental status.

Study IV

Three patients with osteomyelitis of the mandible, ones excluded from Study I, were included in this study together with three other children with osteomyelitis diagnosed and treated earlier. All these six children had initially been treated as JRP patients. Diagnostic codes according to the Classification on Diseases, 10th revision (ICD-10), for parotid illnesses and osteomyelitis were included in the data base search of the Helsinki University Central Hospital Department of Otorhinolaryngology – Head and Neck Surgery to find all pediatric patients with osteomyelitis treated between 1998 and 2009.

Study V

The diagnostic codes for parotid illnesses and for abscesses in the head and neck region were included in the data base search of the Helsinki University Central Hospital, Department of Otorhinolaryngology – Head and Neck Surgery, according to the ICD-10 involving all patients aged ≤17 treated between 1996 and 2005 at our institute. Review of the patient charts revealed ten children with parotid abscesses within this time period. Clinical data recorded included age, gender, site of the disease, laboratory results, imaging, drainage methods, length of hospitalization, bacteria, antibiotics used, and outcome, as well as other illnesses of importance such as parotitis, anomalies, and general health.

4.2 Methods

4.2.1 Saliva sample

A 2-ml saliva sample stimulated by parafilm chewing was attempted in the acute phase by all patients and control children participating in Study I, but due to reduced salivary flow in acute infection, and the lack of co-operation from some children, the total number of saliva samples (0.1–2 ml) was 35 in the parotitis and 34 in the control group. Analyses of HHVs were possible for all samples, and mumps antibodies of class IgM and IgG were possible for 22 parotis and 34 control samples.

4.2.2 Herpesvirus analyses

A total of 35 saliva samples from children with acute parotitis, 34 control samples from healthy controls, and ten adult control samples were analyzed with the Prove-it™ Herpes TubeArray system and Prove-it™ Advisor software (Mobidiag Ltd, Finland) for HSV-1 and 2, VZV, CMV, EBV, and HHV-6 and -7. DNA extraction was with the automated extraction device EasyMAG and Generic 2.0.1 program according to manufacturer's instructions (bioMérieux, France). After the polymerase chain reaction (PCR), the amplicons were subjected to hybridization onto TubeArray, following the Prove-it™ Herpes protocol 2.0 (Jääskelainen et al., 2008).

4.2.3 SPINK analysis

Blood samples were tested for mutations in the SPINK-1 gene encoding the Kazal-type trypsin inhibitor. N34S and P55S mutations of SPINK-1 were analyzed as described by Lempinen et al. (2005).

4.2.4 Mumps antibodies

Mumps IgM and IgG antibodies in saliva were measured by the capture enzyme immunoassay (EIA) test (Microimune Ltd, England) according to manufacturer's instructions (Warrener and Samuel, 2006). The cut-off optical density value of the antibody positivity was set for the negative controls (for IgM mean x 1.4 and for IgG mean x 2).

4.2.5 Epidemiologic survey

A questionnaire about general health, vaccination history, verified diagnoses of parotitis, and possible parotitis-related symptoms and diagnoses of parotitis in

close family members was sent to 1,000 children aged 13 living in the district of Helsinki University Central Hospital. They were randomly drawn from the Finnish national population register. The age group of 13 years was chosen, since according to Study II, the first episode of juvenile parotid symptoms occurs at a median age of six, but towards adulthood other causes, such as bacterial infection and ductal stones, start to predominate. If the first invitation to the questionnaire survey had no response, the questionnaire was re-mailed. Children were asked to fill in the questionnaire together with their parents.

4.2.6 Statistical analyses

The Mann-Whitney U-test and Spearman's rank correlation test served for non-parametric comparisons, and Fisher's exact test for other comparisons. Differences were considered significant at a p-value <0.05.

4.3 Ethics

The institutional ethics committee approved all study protocols. Guardians and the children, if old enough, signed a written informed consent. The studies were conducted according to the Declaration of Helsinki and good clinical practice.

5 RESULTS

5.1 Clinical picture of juvenile parotitis (I, II)

The clinical prospective study on juvenile parotitis included 41 patients (26 boys) aged ≤17 years (median 6.2, range 2.0–17). All patients had acute symptoms of parotitis: swelling and pain in the parotid area. The mean duration of acute symptoms before the first visit was 2.0 days (range 0.5–7.0) (Table 4). All children practiced good dental hygiene and had no concomitant illnesses. They all claimed to have been vaccinated according to the national vaccination protocol including the MMR vaccination. Analysis of IgM and IgG type antibodies showed no acute mumps. (Study I)

CRP was elevated in 28 (68%) patients (median 13 mg/l, range 5.0–170), but only 13 children had CRP values over 40; 11 patients (27%) had an elevated blood leukocyte count (median 11.5 E9/l, range 5.0–20.8). Serum amylase values were elevated in 30 of 38 (79%) cases (median 261 U/l, range 24–1220, not determined n=3) (Table 4a). Six children with normal serum amylase reported recurrent symptoms. None of the patients had elevated serum trypsinogen values. In 8 cases (20%) purulent secretion came from the parotid duc; bacterial culture showed *Haemophilus influenzae* in one case and normal oral flora in the rest. (Study I)

In 17 children (41%) temperatures exceeded 38°C. In 20 cases (49%), the diagnosis was based on clinical symptoms and elevated serum amylase value, and in 21 other cases the diagnosis was verified by an US examination, which showed enlarged, hypoechoic parotid gland and reactive intra-glandular and regional lymph nodes in all parotitis patients. Some cases revealed signs of sailenctasia. All those children with a previous episode of parotitis had their diagnosis verified by US. Of the 41, 34 children were treated as outpatients and 7 (17%) were hospitalized. All admitted patients received antibiotics, as did 13 outpatients. Intra-venous cefuroxime was the choice for admitted patients, and cephalexin for those treated as outpatients except in 2 cases with amoxicillin and clindamycin. Twenty-one children (51%) received symptomatically non-steroidal anti-inflammatory drugs (NSAIDs) only (Table 4b).

Table 4a. Characteristics of 41 children with acute parotitis.

	Age Years	Duration of symptoms Days	Temperature °C Fever ≥ 38°C	Blood Leukocyte count E9/l Normal range 4.5–13 E9/l	C-reactive protein mg/l Normal range < 5 mg/l	Serum Amylase U/l Normal range 30–110 U/l n=38
Median	6.2	2.0	37.2	11.1	13	261
Range	2.0–17	0.5–7.0	35.5–39.2	5.0–20.8	5.0–170	24–1220
Raised value (%)	–	–	17 (41)	11 (27)	28 (68)	30 (79)

Table 4b. Characteristics of patients treated with antibiotics and without antibiotics.

	Children treated with antibiotics N=20	Children treated without antibiotics N=21
Temperature °C Range (median) Number of patients with temperature ≥ 38°C [%]	37.0–39.0 (38.0) 11 [55]	35.5–39.2 (37) 6 [29]
Blood Leukocyte count E9/l Normal range 4.5–13 E9/l Range (median) Raised value [%]	6.8–20.8 (12.6) 8 [40]	5.0–15.5 (9.1) 3 [5]
C-reactive protein mg/l Normal range < 5 mg/l Range (median) Raised value [%]	5.0–170 (43.5) 17 [85]	5.0–63 (9) 11 [55]
Serum Amylase U/l, n=19 Normal range 30–110 U/l Range (median) Raised value [%]	24–1114 (273) 15 [79]	40–1220 (256) 15 [79]

Study II found 133 children and adolescents with parotitis (median age at admission 8.0 years, range 1–19, 82 boys), 10% of whom had an associated ailment. Their first episode of parotitis had occurred at a median age of 6.0 years. The diagnosis was confirmed by US in 88% (97 of 110) of the children undergoing this examination, and bilateral changes in US appeared in 17% (12 of 71) of the 71 cases presenting with unilateral symptoms. Mean CRP level was 34 mg/l (range 2–121, n=59) and mean blood leucocyte count 10.2 E9/l (range 3.5–21, n=53). Oral antibiotics were prescribed for 78% (104 of 133) of the children and 15% (16 of 104) of them were treated intravenously because of suspicion of a severe infection.

In Study I, 12 children (29%) had experienced a previous episode of parotitis (2–13 episodes, median 4), and 2 (4.8%) had had prolonged (30 and 45 days) intermittent parotid symptoms. A year after the end of recruitment for the study, the

children who were included during a primary episode of parotitis were telephoned for follow-up data. Of the 22 (76%) reached, 5 (23%) had had a recurrent parotitis. Thus, in Study I, the recurrent parotitis involved 19 (46%). In Study II, recurrent symptoms occurred in 57% (76 of 133) of the cases, of whom about half (38 of 76) had had four or more episodes of parotitis. Young age at the first episode of parotitis indicated increased likelihood of a reoccurrence ($p<0.0001$). In Study I, the total follow-up time from the first episode ranged from 1 to 6 years, comparable to those with no recurrences in Study II. In Study II, the mean follow-up ranged from 0.7–15 years being 5.7 years for those with only one parotitis episode significantly longer for those with recurrent symptoms (mean 7.0 years).

5.2 Epidemiology (I)

Of the 728 (73%) children (358 boys) returning the epidemiologic survey, 64 (8.8%) reported a chronic illness requiring medication, and 714 (98%) claimed that they were vaccinated against mumps.

Of the respondents, 14 children (1.9%, 5 boys) reported having experienced parotitis, and 5 (0.7%, 1 boy) of them reported recurrent symptoms. All these children claimed that they were vaccinated against mumps. However, of the 14 children, 6 had not seen a physician for their parotid symptoms, and therefore the accuracy of the diagnosis is questionable. Thus, of the 728 children, 8 (1.1%) in this survey had had a verified parotitis. Of the 5 reporting recurrent symptoms, 3 children reported two episodes of parotitis, 1 reported three episodes and 1 reported ten episodes. Twenty-three children (3.2%) named a first-degree family member with symptoms suggestive to parotitis but only 1 of these 23 children had himself-experienced parotid symptoms.

5.3 Heredity of juvenile parotitis (I and II)

In Study I, of the 41 children, 1 girl (2%) with recurrent symptoms was positive for the N35S SPINK-1 mutation, and 2 children (5%) had a close family member with a history of parotitis. In Study II, 47 of 133 patients agreed to testing of the SPINK-1 genotype. Of these 47 children, 3 had a heterozygous N34S mutation, and 1 had a heterozygous P55S mutation. Thus, 8.5% of the tested children had a SPINK-1 mutation, which made them not significantly different from the control group. Among controls were two N34S mutations in 39 children. In Study II, the questionnaire about parotitis, parotid-related symptoms, and parotitis in the close family was returned by 67% (89 of 133) of the families. Of these families 22% reported parotid-related symptoms in the close family, whereas the families of the controls significantly less frequently reported parotid symptoms.

5.4 Human herpesviruses in acute parotitis (III)

All 35 samples from the children with acute parotitis were positive for HHVs. HHV-6 was identified in 34 (97%) samples, of which 32 were positive for HHV-6B, 1 was positive for both HHV-6A and HHV-6B, and 1 for HHV-6A alone; 29 (83%) samples contained multiple herpesviruses, with 14 (40%) cases being double detection of HHV-6B plus HHV-7; 9 (26%) samples gave triple detection of HHV-6B and HHV-7 plus either EBV or VZV or HSV-1; and 2 (6%) samples had four herpesviruses: HHV-6B, EBV, and CMV plus either HHV-7 or VZV.

Of the 34 samples from the control children, 97% were positive for HHVs, with HHV-6 the most frequent finding. HHV-6B appeared in 28 (82%) samples (difference from patients non-significant, Fisher's exact test) but HHV-6A only in 1; 23 (68%) samples contained HHV-6 and some additional herpesvirus(es) (difference from patients non-significant, Fisher's exact test). The majority of the findings were double detection of HHV-6B plus HHV-7 (21%) or HHV-6B plus EBV (17%). In addition, in 5 (15%) samples, three or four various herpesviruses occurred simultaneously. In 7 (21%) samples, only one virus, HVV-6 or HVV-7, was identified.

Of the 10 adult samples, all were positive for herpesviruses. HHV-6 appeared less frequently than in the children with acute parotitis (p-value<0.05, Fisher's exact test). Multiple HHVs including EBV and HSV-1 occurred in 9 (90%) samples (difference from patients non-significant, Fisher's exact test). In 1 sample, HHV-7 was the only finding. VZV was undetected in any of the control samples.

5.5 Differential diagnosis (IV)

The database search provided 6 children (aged 5–17 years, 1 boy) presenting with mandibular osteomyelitis initially diagnosed as recurrent parotitis over a period of 12 years. All the children had a primary diagnosis of JRP; the data-base search with osteomyelitis as a primary diagnosis provided negative results.

Each child had had an acute onset of symptoms, after which each had developed recurrent swelling and pain in the parotid region. They had received short courses of antibiotics and NSAIDs for any recurrent symptoms. The first symptoms had occurred at a mean age of 9.5 years (range 5–13, median 11). A US investigation during one acute phase had shown no clear signs of parotid inflammation. MRI led to the correct diagnosis, revealing edema and chronic changes in the bone structure typical for osteomyelitis. All children practiced good dental hygiene, and their general health was excellent.

The diagnostic delay for osteomyelitis ranged from 1.5 months to 6 years (mean 24 months). The mean duration of symptoms after the correct diagnosis was 18.5

months (range 3 months to 4 years), and mean follow-up was 37 months (range 6 months to 4 years). Blood leukocyte count was within normal limits in every case, CRP levels ranged from 3 to 30 mg/l and erythrocyte sedimentation rates were from 6 to 28 mm/h.

One child had multifocal disease affecting both the mandible and the ipsilateral clavicle. In all cases, a biopsy was taken for histological evaluation and bacterial culture. Two cases required debridement, and four children each had one wisdom tooth on the affected side removed (Table 5).

In three cases, *Actinomyces* was cultured from a bone sample, and in one case the culture showed structures resembling actinomyces. In addition, *Streptococcus viridans* occurred in three cases and *Fusobacterium* in one case. Four cases had more than one pathogen, and in two, bacterial cultures were negative (Table 5). All children received lengthy antibiotic treatment. In addition, two children with severe disease received hyperbaric oxygen treatment, which, however, had no clinical effect on the disease course.

One boy suffered a relapse after a 6-month symptom-free period, and bisphosphonates were introduced to his treatment, producing promising preliminary results by 6 months. All children, except this one boy, have been symptom-free during follow-up (range 6 months to 4 years, median 37 months). Three patients are considered cured, since they have been symptom-free for over two years.

Table 5. Characteristics of six children with osteomyelitis first diagnosed as recurrent juvenile parotitis.

Patient	Age years/ Gender	Duration of symptoms before / after diagnosis m=months, y=years	Bacteriology	Tooth removal / Debridement	Antibiotic therapy after diagnosis of osteomelitis m=month	Follow-up / Outcome m=months, y=years
1	5/F	2.5 y / 6 m	*Actinomyces, Fusobacterium, Streptococcus viridans*	No / No	Penicillin 3 m	6 m / Symptom-free
2	11/F	18 m / 3 m	*Actinomyces turicencis, Fuco-bacterium, Streptococcus viridans*	d38 / No	Penicillin 3 m	10 m / Symptom-free, mouth-opening mildly reduced
*3	13/M	1.5 m / 4 y	*Actinomyces, Enterococcus faecalis, Candida albicans*	d38 / Yes	Penicillin 3 m, amoxicillin + flukonazole 4 m, meropenem	4 y / Symptoms persist
4	17/F	6 y / 5 m	*Actinomyces type of bacteria, Propionibacterium acnes, Streptococcus viridans and anginosus*	d38 / No	Amoxicillin 40 days	24 m / Cured
5	10/F	12 m / 24 m	Negative cultures	No / No	Ciprofloxacin and rifampicin 2 m, ciprofloxacin 3 m	6 y / Cured
*6	11/F	10 m / 25 m	Negative cultures	d38 / Yes	Clindamycin + cephalexin 3 m, rifampicin and levofloxacin 2 m	5 y / Cured

*Children who received hyberbaric oxygen (HBO) in addition to other treatment.

5.6 Complications (V)

Records for 10 children (median age 10 years, range 2.2–16.8, 5 boys) suffering from a parotid abscess during a 10-year time-period were retrieved. This indicates an annual incidence of 0.067 cases per 100 000 inhabitants aged ≤17 (Table 6).

Four children had suffered from parotitis or parotid-related symptoms during the preceding 6 to 24 months. One girl had suffered from a single episode of parotitis, one boy and one girl had had recurrent parotitis within 2 previous years, and another boy had a history of mild swellings of the parotid region without detailed diagnosis.

All patients had similar symptoms prior to admission: mild to moderate fever, swelling of the parotid region, cellulites, and pain. None had bilateral symptoms or symptoms of septic infection nor had any history of oral pathology. The general health of all patients was good.

Two girls (aged 2.2 and 5.9) were diagnosed with first brachial cleft cysts and later underwent superficial parotidectomy; one of these two had a recurrence of

a cyst infection before the operation. None of the others had any recurrence of an abscess during follow-up. However, one boy who had suffered from recurrent parotitis prior to the abscess had two mild parotid infections afterwards as well.

All children had received per oral antibiotic treatment before hospitalization and bacterial culture. Duration of antibiotic treatment ranged from 7 to 15 days, and 8 children developed the abscess during the treatment and 2 just after. Bacterial cultures were positive for *Haemophilus influenzae* (n=3), and one each for *Streptococcus pneumonia*, *Proteus mirabilis*, and *Mycobacterium tuberculosis*. In three, bacterial culture was negative, and for one, no culture was performed (Table 6).

The girl with *Mycobacterium tuberculosis* infection was of African origin. She developed a large parotid abscess, which, when needle aspirated twice under ultrasound guidance, yielded 20 ml and 40 ml of pus. A surgical incision was made as well, but she did not react as expected to the surgical and antibiotic treatment. A pus-sample culture finally revealed *Mycobacterium tuberculosis*. Her infection had affected her lungs, as well. She recovered well whit proper treatment.

In nine cases US was the initial diagnostic method, and in one case MRI. In seven cases, the abscess was drained, and three experienced spontaneous rupture. Two girls each had a fistula formed after spontaneous rupture, with frequent secretion from it. Both girls were diagnosed with a first branchial cleft anomaly, and treated with superficial parotidectomy later. Needle aspiration guided by US in four cases drained the abscess. In two cases, a surgical incision was required before the permanent cure. All surgical procedures were performed under general anesthesia and did not lead to fistula formation. There occurred no need for more radical surgery in the acute phase.

In addition to drainage, all patients received broad-spectrum intravenous antibiotic therapy. In most cases, antibiotics comprised a combination of metronidazole with penicillin or cefuroxime. Length of hospitalization ranged from 2 to 9 days, median 5.4. All children were symptom-free after a few months except for the two girls with first brachial cleft fistulas.

Table 6. Characteristics of 10 children with a parotid abscess

Age Years	Gender	Side R=right L=left	Temperature °C Fever ≥ 38°C	C-reactive protein mg/ml Normal range < 5 mg/ml	Blood Leukocyte count E9/l Normal range 4.5-13E9/l	Bacteria	Intra-venous antibiotics	Drainage
2.2	F	R	37.8	10	20.7	Negative	Metronidazole and penicillin	Spontaneous, Branchial cyst
2.3	M	R	37.8	38	18.2	Negative	Metronidazole and cefuroxime	Needle aspiration and incision
5.9	F	L	38.0	47	20.8	*Haemophilus influenzae*	Clindamycin	Spontaneous, Branchial cyst
8.2	M	L	Unmeasured	12	7.8	Unknown	Metronidazole and cefuroxime	Needle aspiration
9.3	M	L	37.2	12	11.1	*Streptococcus pneumoniae*	Metronidazole and cefuroxime	Needle aspiration
10.0	M	R	37.0	95	12.4	*Haemophilus influenzae*	Cefuroxime	Spontaneous
10.8	F	R	37.8	56	12.7	*Haemophilus influenzae*	Metronidazole and cefuroxime	Incision
11.1	F	R	38.0	92	8.0	*Mycobacterium tuberculosis*	Treatment for tuberculosis	Needle aspiration and incision
11.1	F	L	Unmeasured	Unmeasured	7.6	*Proteus mirabilis*	Metronidazole and amoxicillin	Incision
16.8	M	R	38.1	79	8.1	Negative	Cefuroxime	Incision

6 DISCUSSION

Pediatric parotitis not associated with mumps is a rare disease, and most studies dealing with it comprise small numbers of patients, are retrospective, and lack control groups. There are many case reports based on which, not many conclusion can be made. The number of recent (2000–2012) papers in English on pediatric parotitis other than mumps is only 56. This study comprised a relatively large group of 41 pediatric parotitis patients, and assessed them systematically. The retrospective study comprised an even larger group of 133 children.

6.1 Clinical picture of juvenile parotitis

The clinical picture of juvenile parotitis in this study featured viral infection in most cases: the overall condition of these children was good, the bare majority had no fever and there was no purulent excretion from the parotid duct. Most of the patients had low blood leukocyte values as well. Whereas Stong et al. (2006) reported leukocytosis in 46% of their patients, in the present study leukocytosis was found in only 27% of the patients. In the acute phase, the CRP elevation was more frequent, but high values were rare. In Study II, leukocyte and CRP values were usually only moderately elevated. Determination of the serum amylase value served as an additional tool in the diagnostic work-up in Study I, since 79% of the patients showed an elevated value. For some reason, amylase is often forgotten in clinical work, even though in acute parotid inflammation it rises (Scully et al., 1981, Ericson and Sjoback, 1996b,).

Half the children in Study I received symptomatic treatment only, and had an excellent outcome, supporting the fact that antibiotics should not be an automatic part of treatment; the recommended treatment of parotitis has traditionally included antibiotics even with little evidence of their benefit (Isaacs, 2002). In this study the infection parameters were somewhat lower in those children treated symptomatically (Table 4b), but based on this, it is impossible to state precise norms as to when symptomatic treatment is adequate. The most conservative approach towards antibiotics is wise in frequent episodes of JRP, the other end of the spectrum being neonates suffering from parotitis, as well as children with purulent secretion from their parotid duct who always require intensive treatment. In many cases, diagnosis can be based on the typical clinical picture and elevated serum amylase, but ultrasound is of assistance, especially if the diagnosis is unclear or a complication is suspected.

Only 17 of 22 children and 20 of 35 control children had in their saliva detectable levels of IgG-type mumps antibodies, even though all children were assumed to be

vaccinated against mumps. The mumps vaccine virus is the weakest immunogen of the MMR vaccine components, so antibody formation may result in low antibody levels (Davidkin et al., 1995). In addition, antibody levels wane over time, and in general, total IgG antibody levels in saliva are lower than in serum. However, none of the children had high levels of IgM antibodies, suggesting that there were no acute mumps infections among these children. In any case, mumps must be included in the differential diagnosis since it is still endemic in many places, with outbreaks reported among vaccinated populations (Kancherla and Hanson, 2006). Of the respondents to the epidemiological study, 98% reported being vaccinated against mumps (MMR), which represents a high national vaccination coverage (Dorell et al., 2011, Vandermeulen et al., 2008).

In clinical evaluation, the possibility of another underlying disorder has to be kept in mind. Stong et al. (2005) found a relevant co-morbidity in 7 (33%) of their 21 parotid patients, whereas in our study only one child had a predisposing co-morbidity. Parotid gland enlargement is associated with such conditions as HIV infection, occurring in up to 10% of these patents. Typically, benign lymphoepithelial cysts are found in HIV-associated parotid gland enlargement (Dave et al., 2007). In our series, one boy who presented with repeated parotid swelling was later diagnosed as HIV-positive. However, he did not present with the typical findings of lymphoepithelial cyst related to HIV, and his symptoms were basically unilateral. Therefore, the suspicion of HIV did not rise, and his diagnosis was delayed. Since the incidence of HIV has increased, the possibility of HIV even in a pediatric population must be remembered.

6.2 Epidemiological speculations

According to the epidemiological study, eight (1.1%) of 728 adolescents had had a parotitis with verified diagnosis. In addition, six others claimed having suffered from parotitis-type symptoms. Thus, the frequency of juvenile parotitis may possibly reach 1.9% (range 1.1–1.9%). Of these 14 adolescents in total, five reported recurrent symptoms. This is in line with the results of Studies I and II, which show recurrences in nearly half the cases. According to Study II, early onset of symptoms raises the likelihood of reoccurrences. The literature has no clear reports on recurrence frequency. In this study, no clear predisposing factor (clinical, laboratory or imaging findings studied) was found that could predict recurrence. It can thus be concluded that pediatric parotitis seems not to be so rare after all, and reoccurrences are common.

6.3 Heredity of juvenile parotitis – anything new?

Since mutations of the SPINK-1 gene may predispose to juvenile pancreatitis (Drenth et al., 2002), and since the structure and function of salivary glands bear a resemblance to the pancreas, this study speculated the possible role of SPINK-1 mutations in recurrent juvenile parotitis. However, only one child (2.0%) with acute parotid symptoms in Study I, and four (8.5%) in Study II with parotid symptoms were found to be positive for a N34S or P55S mutation. These findings were not statistically significant. Studies shown that 2.6% of Finnish blood donors are positive to N34S mutation and 1.3% to P55S (Lempinen et al., 2005), and in our control group 5.1% of the children were positive for either of these mutations. The number of children in this study is, however, too small for definitive genetic evaluation.

None of the children in Study I reported a history of parotitis in close family members, but interestingly, in Study II, 22% of the respondents did. Therefore, possible heredity of JRP deserves further study.

6.4 Have herpesviruses a role in juvenile parotitis?

The role of HHVs in pediatric parotitis arouses speculation, with some evidence as to their involvement (Davidkin et al., 2005). Nonetheless, the present study was unable to show significant differences in HHV occurrence in the saliva of children with acute symptomatic parotitis compared with that in healthy children or adults. However, what was unexpected was that HHVs are indeed frequently present in saliva. HHVs were detectable from almost every saliva sample; even from asymptomatic subjects, and in many cases multiple viruses were evident. The only statistically significant difference between the study groups was that children's saliva seemed more often to contain HHV-6 than did adults'.

HHV-6 is known to infect children, the primary infection and reactivation possibly both being asymptomatic (Caserta et al., 2004, Zerr et al., 2005). HHV-6 was a common finding in both the pediatric parotitis group (97%) and the pediatric control group (82%), and seemed not to associate with parotitis symptoms. In adults, HHV-6 occurred in the majority (60%) of the samples as well, but statistically was less common in adults than in children. HHV-7 was also a frequent finding in all three groups. VZV appeared in 5.7% of the children with acute parotitis but in none of the control samples. However, that the difference in VZV was not statistically significant may relate to the relatively low number of subjects.

HSV-1 is present in the saliva of asymptomatic children and adults as a result of occasional viral reactivation (Spicher et al., 2001, Liljeqvist et al., 2009). The findings of this study supported this with HSV-1 in 2.8% of pediatric parotitis, in

8.8% of pediatric controls, and in 10% of adult controls. HSV-2, on the other hand, not being a respiratory tract pathogen, was predictably absent from all samples.

In addition to respiratory tract infections and mucosal lesions, EBV has been associated with periodontitis in adults, (Slots et al., 2006) and is therefore an important pathogen in oral diseases. Davidkin et al. (2005) found elevated IgG and IgM antibodies to EBV in 7% of their 601 pediatric patients with mumps-like symptoms. The present study was unable to show any statistically significant difference in EBV rates between the parotitis and control groups.

Even though this study was unable to show any relation between HHVs and parotitis, it can be speculated that perhaps the primary HHV infection presents as parotitis whereas reactivation does not. Most children suffer from HHV-6 infection by the age of two (Zerr et al., 2005), earlier than the first peak onset of parotitis (Study II). On the other hand, VZV infects children at approximately that same age. In this study VZV appeared in few parotid patients but in none of the control patients. Most children are infected by EBV by the age of 12, which is approximately the time after which juvenile parotitis becomes rare (Study II).

6.5 The importance of osteomyelitis in differential diagnosis

Acute osteomyelitis is a potentially life-threatening disease. Recurrent juvenile parotitis, on the other hand, is a benign condition usually resolving after puberty. In these series, although their ultrasound tests were negative in the acute or subacute phase of parotid swelling, all children received the diagnosis of JRP. Based on this experience, MRI should be scheduled for children whose diagnosis of JRP has not been verified. The diagnosis of primary parotitis may be clinical.

There were five female cases of osteomyelitis in this study even though male predominance has been reported (Weichert et al., 2008). Symptoms of osteomyelitis seemed to occur in the prepubertal years, somewhat later than the typical onset of JRP (Study I and II). An unerupted wisdom tooth was suspected to be the origin of the osteomyelitis in two cases, whereas the other cases had no clear predisposing factor. Overall prognosis was good, as after a mean follow-up of 37 months, five of six children were symptom-free. Altogether, the symptoms of the children in this study are suggestive of a primary chronic form of osteomyelitis (Baltensperger et al., 2004) rather than acute osteomyelitis: the overall condition of the children was good, and infection parameters were low. In osteomyelitis, symptoms of the infected area tend to be sustained over time, whereas in JRP the child is completely symptom-free between periods of swelling.

Few papers report on actinomycosis in children. Here three of the six children who underwent biopsies were culture-positive for *Actinomyces* known to be a

causative agent in osteomyelitis (Robinson et al., 2005, Stewart et al., 2005), and in this study it was also the most common bacterium. However, according to the literature the most common causative agent is *Staphylococcus aureus* (Vinod et al., 2002), and therefore the antibiotics chosen, as first-line treatment should cover this pathogen. Streptococci and gram-negative bacteria, as well, are encountered. A sample for bacteriology should be obtained, when possible. In addition to conventional therapy, two of the six children were treated with adjuvant HBO therapy with disappointing results. Others have reported more beneficial results from HBO treatment in osteomyelitis (Aitasalo et al., 1998, Lentrodt et al., 2007). Since osteomyelitis is a rare entity, the number of subjects in studies is bound to be low, making it difficult to reach a consensus on treatment of choice.

Another recent adjuvant therapy for osteomyelitis with promising results involves bisphosphonates (Gleeson et al., 2008, Simm et al., 2008, Landesberg et al., 2009). One child in Study IV, with persistent recurrent symptoms received three pamidronate infusions as an adjunct therapy with promising preliminary results. It is still too early to evaluate the final outcome. The role of bisphosphonates in the treatment of difficult osteomyelitis is most likely going to expand, but again, since osteomyelitis is a rare entity, gaining solid data is difficult.

Based on this study, osteomyelitis is definitely highly important in the differential diagnosis of JRP.

6.6 Parotid abscess – a rare complication

Parotid abscesses represent only a small portion of parotid infections. Ten children with an abscess during a ten-year period were traced. Four of them had suffered from a previous parotitis or from parotid-related symptoms. One of them had a single episode of parotid inflammation, whereas the others had recurrent parotid symptoms. This supports the fact that a parotid abscess can emerge without other salivary gland pathology. On the other hand, what must be remembered is that other pathologies of the region may dispose to abscess formation. In this study, two girls had first branchial cleft cysts and later underwent superficial parotidectomy. First brachial cleft cyst is a low-incidence anomaly that can lead to fistula formation and result in frequent suppuration of the parotid gland. A permanent cure requires surgical treatment (Triglia et al., 1998).

All ten children had received per oral antibiotic treatment before hospitalization and bacterial culture. Eight developed the abscess during treatment, and two children a few days afterwards. Of five positive bacterial cultures, four showed common pathogens, and *Mycobacterium tuberculosis* appeared in one. When treating infections not responding to treatment as expected to, the possibility of

tuberculosis must be kept in mind, even though tuberculosis of the parotid gland is rare, even where the disease is endemic. The girl with *Mycobacterium tuberculosis* infection in Study V was originally from an endemic region. The possibility of HIV infection behind parotid symptoms must also be kept in mind.

When an abscess has formed, surgical drainage is considered necessary (Brook, 2003). Methods include quite radical procedures such as multiple drainage incisions or raising a full posterior-based flap as for parotidectomy. But it seems that in most cases quite a small procedure is sufficient (Ganesh and Leese, 2005). None of this study's patients needed radical drainage procedures, which may lead to poor wound healing, saliva fistula formation, and poor cosmetic outcome and therefore should be avoided.

Facial nerve paresis has been reported in relation to parotid abscesses (Smith and Hartig, 1997) in adults. None of the children developed facial nerve dysfunction due to either the infection or surgery. Spread of a parotid infection may cause severe complications (Marioni et al., 2003, Kishore et al., 2004) such as mediastinitis, but luckily the present series included no mediastinitis nor other spread of infection.

6.7 Future aspects

The causative agents of acute pediatric parotitis or JRP are unclear. A possible viral involvement in acute parotitis especially deserves future research. On the other hand, the factors possibly predisposing to JRP would be interesting to reveal. Treatment of JRP is definitely worth future study since, although the disease is usually self-limiting, the frequent symptoms can be life-disruptive. It will, however, be somewhat challenging to collect a sufficiently large controlled study group for a prospective treatment trial.

7 CONCLUSIONS

1. Juvenile parotitis shows a frequency of about 1%, and the parotid symptoms have a tendency to recur in almost half the cases. In many cases, the episodes of parotitis in childhood are isolated symptoms in the parotid area with a benign course not necessitating antibiotic therapy.
2. This study found no correlation between SPINK-1 mutations and juvenile parotitis.
3. Human herpesviruses (HHVs) are frequent findings in saliva but seem to play no role in juvenile parotitis.
4. Mandibular osteomyelitis may present with similar symptoms to those of juvenile recurrent parotitis, and is therefore important in differential diagnosis.
5. Parotid abscesses in children are multi-bacterial infections not necessarily related to other parotid gland pathologies. Intravenous antibiotic therapy is the cornerstone of the treatment, but surgical drainage assists in recovery and should not lead to fistula formation.
6. Serum amylase is frequently elevated in acute parotitis and is a useful diagnostic tool in clinical work.

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