Mumps Orchitis in the Post-Vaccine Era (1967–2009)

A Single-Center Series of 67 Patients and Review of Clinical Outcome and Trends

Hugo-Guillermo Ternavasio-de la Vega, MD, Mauro Boronat, MD, PhD, Antonio Ojeda, MD, Yaiza García-Delgado, MD, Alfonso Ángel-Moreno, MD, Cristina Carranza-Rodríguez, BA, Raquel Bellini, MD, Adela Francès, MD, Francisco Javier Nóvoa, MD, PhD, and José-Luis Pérez-Arellano, MD, PhD

Abstract: Since the introduction of the mumps vaccine, the age of appearance of mumps infection has shifted from children to adolescents and young adults, groups with a higher incidence of disease complications and sequelae. During the years 2000–2001, the Gran Canaria Island was part of an epidemic of mumps. In that period, our institution attended 67 cases of serologically confirmed acute mumps orchitis, the most serious complication of mumps infection in young postpubertal males. We conducted a descriptive and prospective study of this cohort and extensively reviewed the literature from 1967 (the year the first mumps vaccine was introduced) to 2009. Fifty-six patients were admitted because of general impairment and were treated with alpha-interferon. Sixty-six patients presented parotitis previous to orchitis (interval from parotitis to orchitis, 4.9 d). Orchitis was unilateral in 89.5% and bilateral in 10.4% of cases. More than 98% of patients had orchitis-associated fever. Nine patients had clinical and biochemical data showing acute mumps meningitis, and 11 had subclinical pancreatitis. The mean duration of symptoms was 4.6 days (range, 1–9). During the acute phase, more than 41% of the evaluated testes had a volume >25 mL. Acute hormonal disturbances were highly prevalent. These included decreased levels of testosterone and inhibin B with low or normal levels of gonadotropins in 35% of subjects, and, to our knowledge not previously reported, an atypical hormonal pattern consisting of low levels of free testosterone and inhibin B, along with increased measures of luteinizing hormone but low or normal follicle-stimulating hormone levels (11% of cases). During the follow-up period (mean, 331 d) a high incidence of sperm disturbance was found.

(*Medicine* 2010;89: 96–116)

Abbreviations: CRP = C-reactive protein, CSF = cerebrospinal fluid, ESR = erythrocyte sedimentation rate, FSH = follicle-stimulating hormone, LH = luteinizing hormone, MMR = measles, mumps, and rubella triple vaccine, NSAID = nonsteroidal antiinflammatory drugs, WHO = World Health Organization.

From Internal Medicine Service II (HGTV), Hospital Universitario of Salamanca, Salamanca; Endocrinology and Nutrition Section (MB, AO, YGD, FJN), and Infectious Diseases and Tropical Medicine Unit (AF, JLPA), Internal Medicine Service, Hospital Universitario Insular of Gran Canaria, Gran Canaria; Department of Medical and Surgical Sciences (MB, AAM, CCR, RB, FJN, JLPA), Health Sciences Faculty, University of Las Palmas of Gran Canaria, Gran Canaria; and Internal Medicine Service II (AAM), Clínica Puerta de Hierro, Madrid, Spain.

Reprints: Dr. Hugo Guillermo Ternavasio-de la Vega, Internal Medicine Service II, Hospital Universitario of Salamanca, 37007, Salamanca, Spain (e-mail: guillermoternavasio@gmail.com).

ISSN: 0025-7974
DOI: 10.1097/MD.0b013e3181d63191

INTRODUCTION

Mumps is a moderately to highly contagious infection that is restricted to human beings.[62] The causative agent of mumps, or epidemic parotitis, is an enveloped, nonsegmented, negative-strand RNA virus belonging to the genus *Rubulavirus,* family *Paramyxoviridae.*[4,53] The infection is transmitted by direct contact, droplet nuclei, or contaminated fomites and enters the host through the upper airway.[62,79,118] It spreads rapidly in susceptible people living in close proximity.[53] Following inoculation, the mumps virus replicates within the lymphoid and reticuloendothelial tissue of the respiratory tract.[118] A transient plasma viremia ensues late in the incubation period and leads to viral spread into organs, resulting in a systemic infection that is characterized by classical parotitis and/or extrasalivary manifestations in other organs.[62,118] Although the parotid glands are the most commonly affected organs, parotitis is not a primary or necessary step for mumps infection. The central nervous system, urinary tract, and genital organs can also be initially affected.[62] Mumps orchitis is the most common complication of mumps infection in young postpubertal males.[13,21,46] Testicular compromise is characterized by an abrupt onset of unilateral or bilateral marked scrotal swelling and pain, accompanied by constitutional symptoms and fever. Immunization programs against mumps have reduced the number of reported cases and influenced their age distribution. Since the introduction of mumps vaccine in 1967 (the year the first mumps vaccine was licensed in the United States),[58] a shift in the age of peak incidence of mumps from children aged 5–9 years, in the prevaccine era, to children and young adults aged 10–24 years has been observed.[128] Serious complications have appeared as a consequence because of the higher rate of sequelae among the older age-group. The principal complication of acute mumps orchitis is the atrophy of germinal epithelium with spermatogenesis arrest, which in turns leads to male sterility.

During the period 2000–2001, an outbreak of mumps occurred in Gran Canaria Island, in the archipelago of the Canary Islands in Spain.[63] In January 2000, the first case of a series of 67 acute mumps orchitis presented to the Infectious Diseases and Tropical Medicine Unit of the Hospital Universitario Insular of Las Palmas. During the previous several years, mumps orchitis had been only rarely seen in our institution. This sharp increase in incidence prompted us to investigate those cases and to review the literature.

We conducted the current study 1) to report the epidemiologic, clinical, and biochemical characteristics of 67 patients with mumps orchitis who were treated and followed at our institution from 2000 to 2001; and 2) to summarize the information found in the literature from case series of documented mumps orchitis.

PATIENTS AND METHODS

Study Population

From January 2000 to July 2001, 67 patients with acute mumps orchitis were treated at our unit. Diagnostic criteria for mumps orchitis were complaints of testicular pain, swelling, and tenderness at palpation during the acute illness and serologic confirmation of acute mumps infection (positive IgM with negative or positive IgG mumps antibodies).

Data Collection

A questionnaire was used at the first consultation, detailing the clinical aspects of the disease, including: age, usual place of residence, occupation, recent travels, drugs or alcohol consumption, sexual habits, possible previous contact with mumps, allergies, vaccination status (verified through regional vaccination records and personal vaccination cards), clinical manifestations (fever, parotitis, orchitis, urinary discomfort, parotitis-orchitis interval, side of parotitis and orchitis), and presence of other mumps complications (meningitis, pancreatitis). Parotitis was defined as an acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland, lasting 2 or more days. Epididymo-orchitis was defined as an abrupt onset of swelling and tenderness of the affected testicle, and inflammation of the scrotum. A general physical exam and genitalia examination (palpation, testicle volume measurement using the Prader orchidometer, and Tanner staging[87]) were carried out in all patients. The volume of testes in mL was classified as follows: <15, 15, 20, 25, >25 mL.

Laboratory Tests

Laboratory tests included hemogram (hemoglobin, white blood count and differential, platelets count), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), coagulation tests, serum enzyme levels (amylase, lipase, aspartate aminotransferase and alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, gamma glutamyltransferase), and urine analysis. Microbiology studies included blood (if fever) and urine cultures; if meningeal syndrome was present, lumbar puncture was carried out and cerebrospinal fluid (CSF) samples were processed for both bacteria and mycobacteria. Mumps-specific IgM and IgG antibodies were qualitatively detected in serum by enzyme-linked immunosorbent assay, Mumps IgM ELISA (Trinity Biotech Captia Mumps IgM, Bray, Ireland) and Mumps IgG ELISA conjugate (Wampole Laboratories Inc, Princeton, NJ). A patient was considered serologically positive for mumps when a positive IgM titer or a fourfold increase in IgG titer was observed. With the aim of evaluating gonadal function, basal determinations of gonadotropins and testicular hormones were carried out (normal values were considered as follows: free testosterone 11.5–42.5 pg/mL, luteinizing hormone 1–5 mUI/mL, follicle-stimulating hormone 1–9 mUI/mL, inhibin B 72.9–247.7 pg/mL). Luteinizing hormone (LH) and free testosterone were considered representative of steroidogenic axis and Leydig cell status, while follicle-stimulating hormone (FSH) and inhibin B (Inhibin B Dimer Assay Kit, Bionova, Madrid, Spain) were indicative of germinal axis and Sertoli cell status. Serum samples were obtained 0–7 days after the onset of clinical symptoms of mumps orchitis (mean, 3 d).

Treatment

Patients were admitted to hospital unless their general status allowed them to be treated as outpatients. All patients were treated with bed rest, elevation of the scrotum, local cooling, and nonsteroidal antiinflammatory drugs (NSAID). Antibiotics were used only in those cases in which we were not able reasonably to exclude a bacterial etiology. According to available data from the literature at that time[46,76,111,135] which showed potential benefits for preventing testicular atrophy, treatment with interferon alpha-2b was offered to all patients (Intron A, Schering Plough, 3 million IU subcutaneously every 24 h for 7 d). Before starting treatment, all patients were informed about the purpose of the study and the potential adverse effects of interferon, and informed consent was obtained. This treatment was performed with institutional review board approval. Patients were discharged as soon as their clinical status permitted.

Follow-Up

In all patients hormonal levels and semen analysis were studied 3–6 months (early recovery phase), and 12–15 months

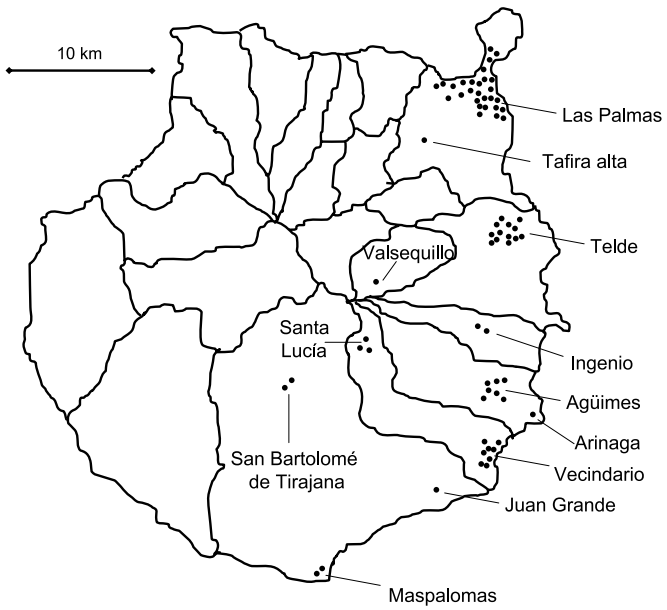

FIGURE 1. Dot density map of cases of acute mumps orchitis by cities, Gran Canaria Island, Spain.

(late recovery phase) after treatment. During follow-up, the steroidogenic function was again studied by measuring LH and free testosterone levels, while the germinal function was evaluated by FSH levels and sperm analysis. Fifteen patients (2 of them with normal gonadal function in the acute phase) agreed to be included in the follow-up.

Semen variables were assessed in seminal fluid obtained by masturbation, after at least 36 hours of sexual rest, according to World Health Organization (WHO) 1999 guidelines,[134] including sperm count (normal, over 20 million spermatozoa per mL), motility (at least 50% of observed spermatozoa moved forward normally), grade of motility (grade 1, if spermatozoa were immotile and failed to move at all; grade 2, if spermatozoa had nonprogressive motility because they did not move forward despite the fact that they moved their tails; grade 3, if spermatozoa moved forward but tended to travel in a curved or crooked motion; and grade 4, if spermatozoa had progressive motility and swam fast in a straight line), morphology (normal, if 30% or more of the observed spermatozoa had normal morphology), volume (normal, ≥2 mL), ph (normal, 7.2–7.8), levels of fructose and citrate in the sample (normal, 150–500 mg/dL and 250–750 mg/dL, respectively), liquefaction, and number of white blood cells/field. Patients with gonadal dysfunction or any alteration in sperm count (oligospermia, azoospermia), motility (asthenospermia), or morphology (teratozoospermia) were managed by us together with the endocrinology service of our institution.

Search Strategy

Material for the review was primarily based on journal publications identified through a comprehensive search of the English and Spanish literature using the PubMed database (National Library of Medicine, Bethesda, MD) and the Web of Science (Thomson Reuters, New York, NY). Other Internet-based resources included websites of the Health Protection Agency (London, UK) the World Health Organization (Geneva, Switzerland), the National Centre of Epidemiology of the Health Institute Carlos III of Spain (Madrid, Spain), and the United States Centers for Disease Control and Prevention (Atlanta, GA). Keywords used in the search included mumps, orchitis ("pathogenesis," "epidemiology," "diagnosis," "treatment," "vaccination," "outcomes"), testicular atrophy, and hypogonadism. The searches included all article types (that is, editorials, letters to editor, case reports, reviews, and clinical trials). Additional cases were identified through bibliographic review of these publications and were also considered when appropriate. The publication dates were 1967 to January 2009. Reports were included if they accomplished the following criteria for a diagnosis of mumps orchitis: testicular pain, swelling, and tenderness during the acute illness and unequivocal laboratory diagnosis based on any of the available methods (isolation of the mumps virus in cell cultures from biologic samples; detection of viral nucleic acid by polymerase chain reaction; and/or serologic confirmation by measurement of virus-specific IgM antibody concentration). From the included reports of mumps orchitis we recorded clinical characteristics, diagnostic studies (including study of gonadal function), final outcomes during follow-up, and treatment options as available. Thirty-two reports were excluded based on these criteria.[6,18–20,22,24,40,41,44,45,51,54,61,70,73,78,80,81,90–92,97,102,104,105,110,112,114,115,117,126,131] Forty reports (including the present report), coming from 19 countries on 3 continents (America, Europe, and Asia) and describing 609 patients, matched the criteria and were included in the analysis.[1,2,8,9,11,12,27,28,34,43,46,47,50,55,57,60,65,67–69,71,76,77,82,83,85,96,103,111,113,116,119,123,124,127,128,130,132,135]

RESULTS

Patient Characteristics

The cases of mumps orchitis herein described were part of a large outbreak of mumps infection that occurred in the autonomous community of the Canary Islands, Spain, between 2000 (4609 reported cases) and 2001 (1220 cases), which particularly affected young individuals.[63] Gran Canaria is one of the largest islands of the archipelago, and had 730,622 inhabitants according to the national census of 2001.[64] From January 2000 to July 2001, 67 patients (mean age, 19 yr; range, 14–44 yr) with severe orchitis were treated at our institution. All patients lived in Gran Canaria Island and were natives, except 1 who was from Cuba. The origin of patients is detailed in Figure 1. Most patients came from the largest cities in the island: Las Palmas de Gran Canaria (39%; 26

TABLE 1. Epidemiologic and Clinical Characteristics of 67 Patients With Acute Mumps Orchitis

Characteristic		
Age, yr, mean (range)	19.15	(14–44)
Occupation, n (%)		
Student	25	(37.3)
Worker	26	(38.8)
Unemployed	10	(14.9)
Unknown	6	(9.0)
Contact with mumps, n (%)	41	(61.2)
Length of hospital stay, d, mean (range)	3.9	(2–9)
Parotitis before orchitis, n (%)	66	(98.5)
Side of parotitis, n (%)		
Bilateral	59	(89.0)
Left	5	(7.6)
Could not remember	2	(3.1)
Parotitis at first consultation, n (%)	19	(28.8)
Parotitis-orchitis interval, d, mean (range)	4.91	(0–14)
Temperature at first consultation, °C mean (SD)	38.5	(1.0)
Side of orchitis, n (%)		
Bilateral	7	(10.4)
Left	24	(35.8)
Right	36	(53.7)
Orchitis-associated fever, n (%)	66	(98.5)
Length of orchitis, d, mean (range)	2.96	(0–16)
Length of associated-orchitis fever, d, mean (range)	4.59	(1–9)
Left testis volume at first consultation, cc, n (%)		
<15	-	-
15	1	(1.5)
20	28	(41.8)
25	7	(10.4)
>25	25	(37.3)
Unrecorded	6	(9.0)
Right testis volume at first consultation, cc, n (%)		
<15	-	-
15	1	(1.5)
20	20	(29.8)
25	4	(6.0)
>25	36	(53.7)
Unrecorded	6	(9.0)
Meningitis with abnormal LCR, n (%)	9	(13.4)
Pancreatitis involvement, n (%)	11	(16.4)
Dysuria, n (%)	4	(6.0)

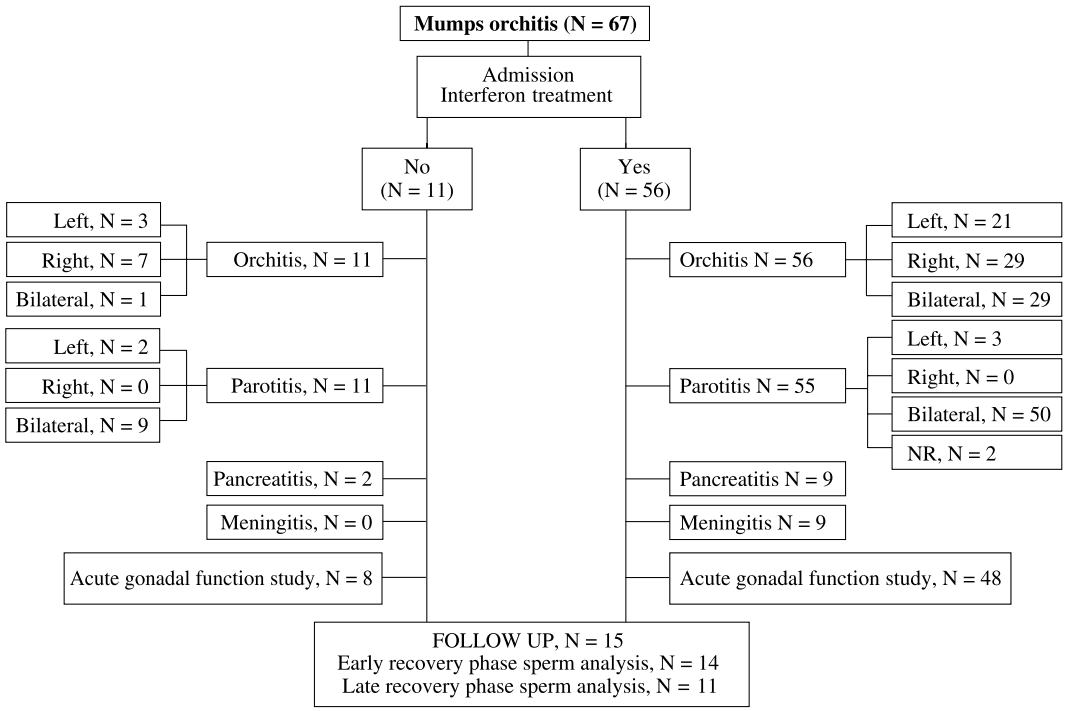

FIGURE 2. Flow chart of clinical behavior and management of 67 patients with acute mumps orchitis. NR = not remembered.

patients), Telde (19%; 13 patients), Vecindario (12%; 8 patients), and Agüimes (10%; 7 patients). All of them had received measles, mumps, and rubella vaccine at conventional doses except the aforementioned 42-year-old Cuban natural. Forty-one of the 67 patients (61%) had been in contact with a mumps-infected case (Table 1). The analysis by occupation revealed that 37% of cases were students, 15% were unemployed, in 9% occupation was unknown, and the rest (38%) were a cross-section of the employed population of the island. Other antecedents were as follows: 58 (86%) patients were single, 18 (27%) were active smokers, 4 (6%) were heavy drinkers, 3 (4.5%) admitted inhaled drug consumption, and 1 had homosexual relationships.

Because of the severity of symptoms, all patients consulted quickly: all patients were first seen within 24 hours of onset of acute orchitis. Sixty-six patients had parotitis (59 bilaterally, 5 left-sided, 0 right-sided, and 2 could not remember laterality) before the appearance of acute orchitis (Table 1 and Figure 2). At the time of the first consultation, parotitis persisted in only 19 patients (28%). Except for 1 patient, in whom orchitis started simultaneously with parotid involvement, the remainder experienced a hiatus of 1–14 days (average, 4.9 d) between the onset of parotitis and orchitis (2 reported not remembering the time of parotitis onset) (Table 1).

Orchitis Characteristics

During the acute stage, the predominant clinical picture was an abrupt onset of severe inflammatory testicular response (Figure 3), associated with increased temperature (mean, 38.5;

FIGURE 3. Acute mumps orchitis of the left testis. [Figure is reproduced in color on the *Medicine* website, www.md-journal.com.]

TABLE 2. Cerebrospinal Fluid Characteristics in Cases of Concomitant Mumps Orchitis and Meningitis

Protein (mg/dL)	Cells/μL	Mononuclear Cells (%)	Glucose (mg/dL)	Lactate (mMol/L)
50.5	10	90	66	1.7
97.8	135	90	40	3.1
104.6	150	96	59	3.3
34.8	270	92	58	2.2
55.7	30	95	94	2.1
27.7	105	98	66	1.7
58.0	585	95	94	2.1
70.0	400	90	61	2.4
164.0	900	90	48	3.2

range, 36–40°C) and varied degrees of general complaints. All patients except 1 reported fever during the orchitis course (Table 1), which persisted in 45 patients at the time of the first consultation. The orchitis was bilateral in 7 patients (10%), right-sided in 36 (53%), and left-sided in 24 (35%) (Table 1 and Figure 2). Examination of the genitalia revealed a volume of the right testis ≥25 cc in 40 (59%) patients, and a volume of the left testis ≥25 cc in 32 (47%) patients. Of the 7 patients with bilateral orchitis, 3 presented both testes ≥25 cc, 3 presented only 1 side ≥25 cc (2 right side and 1 left side), and data were not available for the remaining 1 patient. All patients had achieved full pubertal development (Tanner stage 5 in all cases). No evidence of a previous endocrine disease was noted in any of the patients.

Non-Orchitis Mumps Complications

Besides orchitis, acute meningeal syndrome was diagnosed in 9 patients (Table 1 and Figure 2). All of them were admitted and CSF samples were analyzed, showing an elevated cell count (mean, 287/μL) with a mononuclear profile (mean, 93%), mildly elevated protein concentrations (mean, 73.7 mg/dL; normal value, 15–40 mg/dL), and a mean level of glycorrhachia of 65 mg/dL (Table 2). CSF cultures for bacteria and mycobacteria were negative. According to levels of lipase, 11 patients (9 in the interferon group, 3 with concomitant meningeal syndrome) showed subclinical pancreatic involvement (Table 1 and Figure 2). Both meningitis and pancreatitis behaved as benign entities with no sequelae and responded well to supportive treatment. However, patients with these complications needed a longer hospital admission time (average, 4.33 and 5.88 days for pancreatitis and meningitis, respectively).

Laboratory Characteristics

The most remarkable laboratory findings were the levels of CRP, ESR, and prothrombin activity (Table 3). The whole cohort showed an elevated serum CRP level (mean, 12.3 [standard deviation, SD, 7.7] mg/dL; normal value, <1 mg/dL). Similarly, mean ESR was 31 mm/h (SD 17; normal value, <10 mm/h). Although mean prothrombin activity was 77% (SD 14%; normal value, 85%–100%), it was found to be remarkably below the lower normal limit in 42 (62%) patients (data not shown). All 67 serum samples obtained at admission were positive for mumps IgM antibodies, while 56 were positive for IgG antibodies (Table 3).

Gonadal Function

Initial hormonal studies were available in 56 of the 67 patients (48 in the interferon-treated group and 8 in the standard treatment group) (Table 4 and Figure 2). In general, some type of acute gonadal dysfunction was present in 75% of patients (n = 42). Twenty patients (35%) had decreased levels of free testosterone and inhibin B accompanied by low or normal levels of gonadotropins; 9 (16%) had low levels of free testosterone and increased levels of LH, along with normal measures of inhibin B and FSH; 6 (11%) had low levels of free testosterone and increased levels of LH, with decreased levels of inhibin B and low or normal levels of FSH; 4 (7%) had low levels of free

TABLE 3. Laboratory Data of 67 Patients With Acute Mumps Orchitis*

Characteristic		
Positive mumps IgG antibody, n (%)	56	(83.6)
Positive mumps IgM antibody, n (%)	67	(100)
Urine leukocytes, n (%)		
0	49	(73.1)
≤25	7	(10.4)
>25	2	(3.0)
Urine nitrites, n (%)	6	(9.0)
pH, n (%)		
5	32	(47.8)
6	8	(11.9)
6.5	13	(19.4)
7	2	(3.0)
8	1	(1.5)
Urine proteins, mg/dL, n (%)		
Undetectable	35	(52.2)
25	19	(28.3)
75	2	(3.0)
150	1	(1.5)
Hemoglobin, g/dL	13.81	(1.12)
Platelets, $\times 10^3$/mL	207	(60)
Leukocytes, $\times 10^3$/mL	7.91	(2.78)
Polymorphonuclear granulocytes, %	65.0	(13.9)
Lymphocytes, %	21.9	(12.5)
Monocytes, %	8.76	(3.1)
ESR, mm/h	31	(17)
CRP, mg/dL	12.33	(7.72)
Prothrombin activity, %	77.9	(14.9)
TTPA ratio	1.24	0.22
Lactate dehydrogenase activity, IU/L	204.6	(88.4)
Aspartate aminotransferase activity, IU/L	38.6	(56.2)
Alanine aminotransferase activity, IU/L	51.6	(56.3)
Alkaline phosphatase activity, IU/L	86.1	(40.0)
Gamma glutamyltransferase activity, IU/L	40.0	(61.3)
Amylase activity, IU/L	143.7	(131.4)
Lipase activity, IU/L	266.0	(342.0)
Free testosterone, pg/mL	9.97	(7.02)
Inhibin B, pg/mL	96.96	(57.01)
FSH, mUI/mL	5.55	(4.86)
LH, mUI/mL	6.33	(4.41)

*All values are expressed as mean (SD) unless indicated.

TABLE 4. Acute Hormonal Profile in 56 Patients With Mumps Orchitis

LH/Testosterone Axis*		FSH/Inhibin B Axis*		Total (n = 56)	
LH	**FT**	**FSH**	**IB**	**No.**	**%**
N	N	N	N	14	25.0
↑	↓	↑	↓	4	7.1
N	N	↑	↓	3	5.3
↑	↓	N	N	9	16.1
N or ↓	↓	N or ↓	↓	20	35.7
↑	↓	N or ↓	↓	6	10.7

Abbreviations: FT = free testosterone, IB = inhibin B, N = normal, ↓ = decreased, ↑ = increased.

*Normal values for adults: FT = 11.5–42.5 pg/mL; LH = 1–5 mUI/mL; FSH = 1–9 mUI/mL; IB = 72.9–247.7 pg/mL.

testosterone and inhibin B, with increased concentrations of both LH and FSH; 3 (5%) had low levels of inhibin B and high levels of FSH, along with normal values of free testosterone and LH; finally, 14 (25%) had a normal hormonal profile.

Treatment

Fifty-six patients were hospitalized because of high fever, severe testicular pain, general compromise, and/or suspicion of associated complication (specifically, meningitis). Eleven patients were treated ambulatorily because of their good clinical status. Among inpatients, the treatment with interferon was initiated 0–9 days (mean, 2.8 d) after orchitis onset. The mean temperature at admission was 38.5°C. The average interval between start of treatment (interferon plus standard treatment) and resolution of fever and symptoms and hospital discharge was 3.9 days (range, 2–9 d). No adverse reactions were observed among patients treated with interferon. All 56 admitted patients were discharged home with significantly improved symptoms and without fever. Among the 11 ambulatory patients, who received standard treatment only, the mean temperature at first consultation was 37.8°C. None of them required hospitalization.

Because it was impossible to rule out a bacterial origin for symptoms, 4 patients were also treated with antibiotics. They complained about dysuria, but urine culture was negative in all cases. One of the 45 febrile patients at admission had a single positive blood culture (*Staphylococcus epidermidis*), which was considered a contaminant.

Follow-Up

Fifteen patients (mean age, 19.6 yr) agreed to take part in the follow-up study (mean total follow-up, 331 d) (Table 5 and Figure 2). Of these, 14 (93%) were evaluated in the early recovery phase (mean follow-up, 113 d) and 9 (60%) in the late recovery phase (mean follow-up, 418 d). Ten of the followed patients provided sperm samples to be analyzed both in the early and late recovery phases, while 5 patients contributed only 1 sperm sample (4 in the early recovery phase and 1 in the late recovery phase). In all cases acute orchitis had been unilateral (6 left-sided, and 9 right-sided). Gonadal function during acute phase had been assessed in 13 of the 15 subjects who participated in the follow-up survey. Of these, 5 patients had presented decreased levels of free testosterone and/or inhibin B accompanied by low or normal levels of gonadotropins (Table 5, Patients 5, 6, 8, 12, 14), 4 had low levels of free testosterone and increased levels of LH, together with decreased levels of inhibin B and low or normal levels of FSH (Table 5, Patients 3, 11, 13, 15), 1 had low levels of free testosterone and increased levels of LH, along with normal measures of inhibin B and FSH (Table 5, Patient 9), and 3 had shown no gonadal dysfunction (Table 5, Patients 2, 4, 7).

Table 6 displays the characteristics of the sperm samples. As shown, samples collected in the early recovery phase (n = 14) had a lower mean sperm count/mL, a lower mean volume of total ejaculate, and a lower mean sperm count/total ejaculate when compared with late-recovery phase samples (n = 11). The high proportion of oligospermic patients in both phases was remarkable. Only 1 sample showed a complete lack of spermatozoa during the early recovery phase (Table 5, Patient 5, and Table 6). Other sperm disturbances were as follows: asthenospermia (>18% of patients in each follow-up period), teratospermia (1 sample in late recovery phase), incomplete liquefaction, and presence of white cells in 9 samples from the early phase (64%) and in 3 samples from the late phase (27%) (Table 6).

At the end of the follow-up, 11 patients had evidence of isolated germinal function impairment proven by decreased sperm count with concomitant normal levels of FSH (Table 5, Patients 2, 4, 6, 7, 8, 9, 12, 14) or elevated levels of FSH (Table 5, Patients 5, 11, 13); 1 patient had evidence of both steroidogenic and germinal function compromise (Table 5, Patient 3) showing decreased levels of testosterone and oligospermia, respectively.

Data from 10 patients with repeated sperm analyses throughout follow-up showed that 80% had persistent oligospermia at the end of evaluation (Table 5, Patients 2–4, 6, 7, 11, 13, 14). Among the rest of the initially oligospermic patients, 1 developed asthenospermia and decreased vitality (Table 5, Patient 1), and 1 became normal (Table 5, Patient 15). Regarding the spermatozoa motility, all 3 patients with asthenospermia at the time of the first spermiogram recovered normal motility in the last evaluation (Table 5, Patients 3, 13, 15). None of the studied patients showed isolated hormonal disturbances without concomitant sperm impairment. The most severe spermatogenesis disturbance took place in a 26-year-old man with evidence of secondary hypogonadism (in the acute phase) (Table 5, Patient 12). The late recovery phase spermiogram (not available in the early phase) displayed oligoasthenoteratozoospermia and decreased vitality, accompanied by atrophic changes (<15 cc) in his affected left testis. Only 2 patients achieved normal hormonal and sperm profiles in their last evaluation (Table 5, Patients 10, 15).

Data on testicular volume were available for 61 patients in the acute phase, 31 in the early recovery phase, and 14 in the late recovery phase (Table 7). In accordance with the presence of a severe inflammatory process during the acute phase, 41% of left and 59% of right evaluated testes showed a volume >25 cc. During recovery phases, testes presented a trend to normalize volume: only 1 patient showed a persistently enlarged left testis in the early recovery phase. Although atrophy is a pathologic concept, it is usually used to describe any diminution of size of the testis on physical examination. During the follow-up period 7 patients developed testicular atrophic changes (2 left sided, and 5 right sided), 4 of them reaching testes volume <15 cc before 6 months of follow-up (early recovery phase). Because no testis showed a volume <15 cc during the acute phase, atrophic changes attributable to previous causes were discarded. Seven testes displayed a loss of turgor at the end of evaluation (data not shown). Clinically, there was no loss of hair, alteration in libido, or change of voice to indicate an endocrine dysfunction.

TABLE 5. Gonadal Function and Sperm Analysis in 15 Patients With Acute Mumps Orchitis and Follow-Up

Patient	IFN	Age (yr)	Side of Orchitis	Fever (d)	Total Follow-Up (d)	Acute Hormonal Function				Early Recovery Phase (3–6 mo)				Late Recovery Phase (12–15 mo)			
						FT*	LH*	FSH*	IB*	FT*	LH*	FSH*	Sperm Analysis	FT*	LH*	FSH*	Sperm Analysis
1	Y	19	L	2	392	NR	NR	NR	NR	17.97	4.25	5.18	Oligospermia	NR	NR	NR	Asthenospermia, decreased vitality
2	Y	19	L	5	382	NR	9.28	5.55	80.2	NR	2.29	7.00	Oligospermia	16.33	5.55	7.46	Oligospermia
3	Y	21	R	4	262	4.9	9.67	7.11	29.5	9.13	21.80	36.67	Oligospermia, asthenospermia	4.93	8.75	24.92	Oligospermia
4	Y	18	L	3	550	20.9	4.8	5.10	98.7	9.50	3.30	6.90	Oligospermia	34.08	4.69	5.42	Oligospermia
5	Y	19	L	5	96	4.3	2.03	3.15	92.1	12.80	7.51	16.57	Azoospermia	13.30	8.25	9.37	NR
6	Y	21	R	5	514	19.4	5.35	6.62	63.3	19.39	5.35	6.62	Oligospermia	NR	NR	NR	Oligospermia
7	Y	20	L	8	428	16.7	8.66	2.68	112.7	18.14	5.77	5.98	Oligospermia	NR	NR	NR	Oligospermia
8	N	19	R	NR	98	24.5	6.72	5.01	23.83	26.30	4.29	3.88	Oligospermia	NR	NR	NR	NR
9	Y	18	R	5	93	7.87	7.33	4.77	97.5	14.30	4.05	5.93	Oligospermia	11.00	2.41	2.45	NR
10	Y	18	R	3	102	NR	NR	NR	NR	26.00	3.96	4.78	Normal	25.48	3.46	3.88	NR
11	Y	23	R	6	382	3.1	9.5	7.80	4.33	17.05	5.29	9.36	Oligospermia	18.58	7.60	9.60	Oligospermia
12	Y	26	L	3	566	3.5	4.2	3.10	122.5	3.61	4.25	3.06	NR	20.60	6.55	5.52	Asthenospermia, oligospermia, teratospermia, decreased vitality
13	Y	18	R	6	262	5.1	10.9	5.88	14.1	15.43	5.49	9.06	Oligospermia, asthenospermia	31.22	4.90	9.10	Oligospermia
14	Y	16	R	5	514	8.4	2.07	2.91	79.5	18.52	3.67	9.49	Oligospermia	22.52	2.60	6.47	Oligospermia
15	Y	19	R	7	329	9.53	6.47	0.81	67.9	20.60	2.99	4.72	Oligospermia, asthenospermia	22.40	2.81	4.06	Normal

Abbreviations: See previous tables. IFN = interferon treatment, Y = yes, N = no, L = left, R = right, NR = not recorded.

*Normal values listed in Table 4.

TABLE 6. Characteristics of Sperm Samples of Patients With Acute Mumps Orchitis During Follow-Up*

	Early Recovery Phase Samples (3–6 mo) (n = 14)		Late Recovery Phase Samples (12–15 mo) (n = 11)	
	No.	(%)	No.	(%)
Sperm count				
Mean spermatozoa/mL (million/mL)	8,083,470		37,022,222	
Mean total spermatozoa (million/total ejaculate volume)	32,466,957		159,231,111	
Oligospermia	12	(85.7)	7	(63.6)
Azoospermia	1	(7.1)	-	-
Asthenospermia	3	(21.4)	2	(18.2)
Grade of motility, mean				
Grade 1 (%)	35		34	
Grade 2 (%)	10		11	
Grade 3 (%)	39		40	
Grade 4 (%)	9		15	
Teratozoospermia	-	-	1	(9.10)
Oligoasthenospermia	3	(21.4)	-	-
Oligoasthenoteratozoospermia	-	-	1	(9.10)
Mean volume, mL	3.85		4.23	
Incomplete liquefaction	2	(14.3)	3	(27.2)
Presence of white cells	9	(64.3)	3	(27.2)
Abnormal pH	1	(7.1)	1	(9.10)
Mean fructose, mg/mL	225		286	
Mean citrate, mg/mL	321		402	
Interval orchitis/semen analysis, d (range)	113	(46–295)	418	(262–566)

*All values are expressed as number and %, unless indicated.

It was impossible to carry out comparative studies of the cohorts regarding interferon treatment because of the small and asymmetric size of the groups.

DISCUSSION

The series herein described was part of a large outbreak of mumps in the Canary Islands in 2000–2001. The origin of the initial case is unknown. The most affected age-group was young adults aged 14–44 years, many of whom were college students.

During mumps infection, the parotid glands are the most commonly affected organ.[53,62,118] They are involved in 70%–95%[62,118] of all cases of mumps. Pain and swelling of the salivary glands are the most frequent symptoms,[47] usually progressing over 2–3 days and taking an average of 7 days (range, 2–14 d).[28,47,62,71,90] In the current series, almost 90% of patients had bilateral parotitis, which was still apparent in 28% at first evaluation (Table 1). Bilateral parotid compromise has been reported in the literature in 53%–90% of cases.[47,62,118] Although parotitis is the clinical hallmark of mumps, it is estimated that up to 50% of mumps infections are subclinical.[47] Indeed, in almost one-third of all cases of mumps, extrasalivary manifestations are seen in the absence of parotitis.[105,118] The rate of complications ranges between 0 and 35%.[47,132]

Orchitis

Although mumps infection can affect a wide range of ages,[29,34,115] mumps orchitis is an entity classically linked to adolescents or young adults, and its occurrence is rare before 10 and after 50 years of age.[13,21] The mean age of our patients is similar to that reported in most other series[2,11,12,21,27,28,46,68,76,83,127,135] (Table 8). Anecdotal cases of acute mumps orchitis

TABLE 7. Testes Volume of Patients With Acute Mumps Orchitis During Acute Phase and During Follow-Up

Volume (mL)	Acute Phase (No. of Patients = 61)				Early Recovery Phase (No. of Patients = 31)				Late Recovery Phase (No. of Patients = 14)			
	Left Testis		Right Testis		Left Testis		Right Testis		Left Testis		Right Testis	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<15	-	-	-	-	1	3.2	3	9.7	2	14.3	5	35.7
15	1	1.6	1	1.6	7	22.6	6	19.3	3	21.4	3	21.4
20	28	45.9	20	32.8	11	35.5	10	32.3	4	28.6	2	14.3
25	7	11.5	4	6.5	11	35.5	12	38.7	5	35.7	4	28.6
>25	25	41.0	36	59.0	1	3.2	-	-	-	-	-	-

TABLE 8. Clinical Manifestations of 609 Patients With Acute Mumps Orchitis Since 1967, Present and Previous Reports

First Author, Year (Ref.)	No. of Patients	Country	Age, yr (Range)	Side of Orchitis, (No. of Patients)					P-O Interval (d)	Fever (d)	Other Manifestations (No.)		
				B	U	R	L	NM			P	ME	Pa
Atkinson, 1967[8]	1	USA	3	-	1		1	-	1	5	1	-	-
Bartak, 1973[11]	54	Czechoslovakia	(16–37)	-	54	-	-	-	NM	NM	-	-	-
Adamapoulos, 1978[2]	27	Greece	29	16	11	-	-	-	NM	NM	-	-	-
Falk, 1980–1982[47]	14	Canada	NM	-	-	-	-	NM	NM	NM	14	-	-
Baandrup, 1984[9]	1	Denmark	38	-	-	-	-	NM	NM	NM	1	-	-
Wharton, 1986[132]	10	USA	NM	-	-	-	-	NM	NM	NM	10	2	1
Shulman, 1987–1988[116]	19	Israel	NM	3	11	4	7	NM (5)	8.5 (7–10)	NM	19	-	-
Kaplan, 1988[71]	15	USA	NM	-	-	-	-	NM	NM	NM	14	1	2
Erpenbach, 1990[46]	4	Germany	22 (20–24)	4	-	-	-	-	5 (3–8)	3 (2–4)	4	-	-
Manson, 1990[85]	1	USA	18	-	1	1		-	7	4	1	-	-
Ku, 1990–1997[76]	21	Korea	16 (13–28)	6	15	-	-	-	5.9 (2–11)	2–5.4	21	-	-
Tarantino, 1990–1998[123]	12	Italy	(14–34)	1	11	2	9	-	NM	NM	12	-	-
Hersh, 1991[57]	5	USA	NM	-	-	-	-	NM	NM	NM	5	-	-
Yeniyol, 1992–1995[135]	18	Turkey	23 (17–29)	-	18	10	8	-	5 (2–7)	3.5 (3–4)	18	-	-
Jiménez, 1993–2005[67]	4	Spain	16.5	-	-	-	-	NM	NM	NM	4	4	-
Kuczyk, 1994[77]	1	Germany	30	-	1	-	1	-	No	4	-	-	-
Rüther, 1995[111]	1	Germany	16	-	1	1	-	-	6	2	1	-	-
Vicari, 1995[127]	24	Italy	27 (21–35)	-	-	-	-	NM	(0–7)	NM	12	-	-
Casella, 1995–1996[27]	11	Switzerland	32 (17–55)	2	9	5	4	-	10 (2–21)	3.6 (3–5)	9	-	-
Visser, 1995–1996[128]	35	Spain	NM	-	-	-	-	NM	NM	NM	35	-	-
Kalaydjiev, 1997–1998[68]	74	Bulgaria	(12–50)	-	-	-	-	NM	NM	NM	74	-	-
Başekim, 1998[12]	11	Turkey	20 (18–22)	2	9	7	2	-	5 (3–8)	NM	11	-	-
López, 1998[83]	8	Spain	(15–19)	2	6	-	-	-	NM	NM	-	-	-
Tecle, 1998–2000[124]	22	Lithuania	20	-	-	-	-	NM	NM	NM	22	1	-
Lin, 1999[82]	1	Taiwan	39	1	-	-	-	-	NM	NM	1	-	-
Ternavasio, 2000–2001(PR)	67	Spain	19 (14–44)	7	60	36	24	-	4.9 (0–14)	4.6 (1–9)	66	9	11
Kalaydjiev, 2001[69]	21	Bulgaria	NM	-	-	-	-	NM	NM	NM	-	-	-
Horiguchi, 2002[60]	1	Japan	26	1	-	-	-	-	7	NM	1	-	-
Jalal, 2004[65]	1	UK	16	-	1	1	-	-	14	NM	1	-	-
Niizuma, 2004[96]	7	Japan	22 (12–36)	-	-	-	-	NM	NM	NM	-	-	-
Sartorius, 2004[113]	1	Sweden	NM	-	-	-	-	NM	NM	NM	1	-	-
Philip, 2004–2005[103]	25	UK	23 (15–38)	3	22	-	-	-	5.2 (4–11)	NM	25	-	-
Harling, 2005[55]	2	UK	NM	-	-	-	-	NM	NM	NM	2	-	-
Spanaki, 2004–2005[119]	2	Greece	NM	-	-	-	-	NM	NM	NM	2	-	-
Emerson, 2005–2006[43]	5	Ireland	NM	-	-	-	-	NM	NM	NM	1	-	-
CDC, 2006[34]	21	USA	NM	-	-	-	-	NM	NM	NM	-	-	-
Gerstel, 2006[50]	17	Spain	NM	-	-	-	-	NM	NM	NM	-	-	-
Waxman, 2006[130]	27	USA	NM	-	-	-	-	NM	NM	NM	-	-	-
Castilla, 2006–2007[28]	17	Spain	19 (16–30)	-	-	-	-	NM	NM	NM	17	-	-
Abdelbaky, 2008[1]	1	UK	18	-	1	1	-	-	8	1	1	-	-

Abbreviations: NM = not mentioned, B = bilateral, U = unilateral, R = right-sided, L = left-sided, P-O interval = parotitis-orchitis interval, P = parotitis, ME = meningo-encephalitis, Pa = pancreatitis, PR = present report.

have been described in children.[8] Since 1967, the year the mumps vaccine was introduced in the United States,[58] massive vaccination campaigns using measles, mumps, and rubella triple vaccine (MMR) have shifted the age of appearance of mumps[25,28,30–32,34,56,57,71,103,113] from children to young adults, a period where the development of mumps complications, such as orchitis, is more frequent.[47] In fact, the incidence of bilateral orchitis has been found to be 2 times higher in young adults than in adolescents (29% vs. 13%, respectively).[11] Apart from the severity of the symptoms, the clinical picture is similar in children, adolescents, or adults.[47,53,71] The predisposition to gonadal involvement among postpubertal individuals suggests that certain hormonal factors might promote the tropism of mumps virus toward testicular cells. The LH- or FSH-receptors, whose expression is

up-regulated by the rise of circulating gonadotropins levels during puberty, could be a binding site for mumps virus, but this statement is totally speculative.

Mumps virus has affinity for the glandular epithelium.[62] The direct viral attack on testicular tissue leads to severe periductal interstitial edema, congestion, separation of the seminiferous tubules, and a profuse perivascular lymphocytic infiltration in the interstice.[2,5,46] The pathologic picture has been described as a mild to intense lymphocytic infiltration, sparing Sertoli and Leydig cells.[5,85] The glandular cells of the germinal epithelium may become involved with edema and overflow of the inflammatory reaction from the interstitial tissues.[62,118] Since the process is often of a patchy nature, the inflammatory process may resolve and not be followed by later atrophic changes.[85] However, if the reaction has been extensive and intense, the healing course may include atrophy of the germinal epithelium. In this case, the damage to the seminiferous tubules is due to the increased temperature and intratesticular pressure caused by edema and a firm, inelastic tunica albuginea, which offers resistance.[18,74,95,127] This situation can lead to necrosis, atrophy of the germinal epithelium, and hyalinization of the seminiferous tubules, all of which lead to atrophy of the testes and stop the spermatogenesis.[2,5,46,62,135]

After the central nervous system, testes are the most frequent sites of compromise in complicated mumps infection. Epididymo-orchitis is reported to affect 3%–38% of postpubertal male patients with mumps.[13,34,47,71,105,124] Orchitis manifests usually 3–10 days after parotitis[12,27,46,76,85,103,116,135] (Table 8), although intervals of up to 6 weeks have been reported.[62] Epididymo-orchitis may also precede the onset of parotitis or may indeed occur without prior parotid involvement.[85,105,118] In the largest historical series that we know of (132 cases of mumps orchitis), comprising both pre- and post-vaccine eras, mumps orchitis followed parotitis in 64% (n = 84) of cases, preceded parotitis in 3% (n = 4), began simultaneously with parotitis in 2% (n = 3), and occurred without parotitis in 8% (n = 11) of cases.[13] In the current series the mean parotitis-orchitis interval was 5 days, and only 1 patient had a simultaneous beginning of parotid and testicular complaints.

The clinical presentation of our patients did not differ from the classical description referred to in the literature. A clinical course that ranges from mild testicular discomfort and swelling to an abrupt start of severe testicular pain and a three- to fourfold increase in the normal size of the testis, accompanied by prostration, high fever, headache, and severe constitutional symptoms, generally in parallel with gonadal involvement, is systematically mentioned.[62,75,90,118] Symptoms usually progress for 2–3 days and resolve within 1 or 2 weeks after defervescence, although residual testicular tenderness can persist for longer than 2 weeks in 20% of cases.[62,118]

Clinical estimation of testicular volume using the Prader orchidometer is useful in clinical practice and has been used in the research setting.[76] Ku et al[76] measured the testicular volume of 21 patients with acute mumps orchitis and found a mean testicular volume of 19.2 and 18.1 mL for the right and left side, respectively. In the same study, 8 of the 44 measured testes (18.2%) reached a volume ≥25 mL. Ultrasound studies performed during the acute phase showed edema, decreased testicular echogenicity, thickness of the scrotal wall, hydrocele, a greater volume and vascularity of the affected testis and epididymis, decreased resistivity indexes of intratesticular arteries, and spontaneous flow of testicular veins.[12,123] Tarantino et al[123] measured the testicular volume in 12 patients with acute mumps orchitis (9 left-sided, 2 right-sided, 1 bilateral). The mean volume of the left testicles by ultrasound was 18.5 ± 3.12 cm^3, whereas the mean volume of the right testicles was 14.9 ± 1.33 cm^3 in that study.[123] In another series of 11 patients with acute mumps orchitis, the volumes of the affected testes ranged between 15.2 and 47.5 mm^3 (mean, 27.2 mm^3)—that is, 1.75–3.27 (mean, 2.45) times the volume of normal testes.[12] Up to 59% of testes measured in our study during the acute phase presented a volume ≥25 mL, which represents more than 3 times the estimation of Ku et al.[76] The measurement of testicular volume was performed with a Prader orchidometer, a semiquantitative method, which is obviously less precise than ultrasonography because of the implicit subjectivity of the method and the interference of surrounding tissues. For instance, Basekim et al[12] found a mean thickness of 5.2 mm (range, 3.7–7.5 mm) of scrotal skin of the affected testes using ultrasound. Neither Ku et al[76] nor we used ultrasound, so it is impossible to exclude complications (such as hydrocele) or to quantify the grade of participation of the epididymis and skin in testicular enlargement.

The different impact of uni- or bilateral testicular involvement on the risk of sterility has been profusely discussed in the literature. Location of testicular damage was available in 280 of the 609 patients mentioned in mumps orchitis reports. Forty-eight (18%) presented bilateral orchitis and 232 (82%) presented unilateral orchitis (29% right-sided, 24% left-sided, 47% not mentioned). Data were not available in 329 cases (Table 8).

Other Non-Orchitis Mumps Complications

Central Nervous System Involvement

The most severe complication of mumps infection in childhood, meningo-encephalitis, which appears in 250/100,000 cases, is the primary justification for routine childhood immunization.[27] Although the mumps virus is one of the most frequent viral causes of acute lymphocytic meningitis,[42] there are conflicting opinions regarding the frequency of central nervous system involvement in mumps.[6,110] Common symptoms of meningo-encephalitis in acute mumps infection include headache (40% of patients), neck stiffness (32%–40%), and confusion (18%).[47,105,132] Historical data show that, in routine examination of CSF from patients with mumps parotitis, pleocytosis was found in 56% of cases, although 50% of these had no signs or symptoms of central nervous system involvement.[10] Because of its high frequency, some authors have suggested that meningeal compromise should be considered as an integral part of the disease.[107] Others have considered that the mumps virus is primarily neurotropic and that involvement of the parotid glands occurs as a secondary complication.[110] Beyond these considerations, the general view is that mumps meningitis is a benign condition rarely giving rise to sequelae.[6,27,62,67] As in other studies, neurologic sequelae did not occur in our patients. Regarding the concurrent appearance of mumps orchitis and meningo-encephalitis, data are scarce.[6,13,67,132] In a large retrospective survey of mumps infection in England and Wales before the vaccination era,[6] simultaneous neurologic involvement (meningitis or encephalitis) was observed in 71 of 404 (17.5%) cases of mumps orchitis. Another smaller retrospective Spanish study[67] on the prevalence of mumps meningitis showed concomitant mumps orchitis in 4 of 12 (33%) male patients. Finally, the involvement of the central nervous system in a larger series of mumps orchitis was notoriously lower (4.5%), although the authors recognized a possible underestimation.[13] Clinical acute meningitis was present in 13% of our patients, with a CSF profile similar to that previously mentioned.[53,62,67] A mean parotitis-meningitis interval of 8.4 days has been reported,[67] but central nervous system infection may precede parotitis[90] by as many as 10 days,[110] or may manifest itself up to 2 weeks after the appearance of parotitis.[62] On the other hand, the simultaneous onset of

orchitis and meningitis, and a 4-day delay in the appearance of orchitis after meningitis have been described.[62,67]

Pancreatic Involvement

Pancreatitis arises in about 0.3%–5% of mumps infections, mostly subclinically or with a mild course,[6,13,34,47,62,90,132] and usually resolves in 3–7 days.[90] Mumps pancreatitis may cause epigastric pain and increased serum levels of lipase or pancreatic amylase isoenzyme.[53] Abdominal pain associated with mumps infection is frequent (11%–50%)[105,132] and can occur without a definite diagnostic of mumps pancreatitis, suggesting that the real incidence of this complication is underestimated. In our series, 16% of patients showed increased levels of lipase, but no patient had clinical data of pancreatitis.

Laboratory Characteristics

The elevated levels of biochemical markers of systemic inflammation is a remarkable finding in the current study. Such elevation has been scantly mentioned in the literature.[96,121,122] Strati et al[121,122] demonstrated that CRP is elevated above 0.8 mg/dL in more than 90% of mumps orchitis cases. On the other hand, only 10% of mumps meningitis and mumps pancreatitis showed such elevation of CRP. In another study, CRP levels were analyzed in patients with meningitis and orchitis induced by mumps virus, and a significantly higher CRP concentration was found in mumps orchitis patients.[96] Because clinical findings in acute orchitis are nonspecific, the elevation of CRP levels is eventually used to decide the need for antibiotic treatment. In this sense we are in agreement with Niizuma et al,[96] who pointed out that if elevation of CRP was definitely recognized as a manifestation of mumps orchitis, administration of antimicrobial agents would be avoided in many cases. Although leukocytosis has been commonly found in orchitis-, meningitis-, or pancreatitis-complicated mumps,[62,90,118] our patients showed a normal mean leukocyte count.

Fifty percent of patients in our study had prothrombin activity below the usually accepted lower limit of normality (80%). Moreover, prothrombin activity fell below 60% in 11% of patients. This coagulation disturbance was found in 30% of patients from 1 series of mumps meningitis, in which 4 patients developed concomitant orchitis.[67] Although prothrombin activity impairment may be a biochemical feature of acute mumps infection, it seems to be mild and transient, in light of the fact that none of our patients showed clinical signs of coagulopathy.

Treatment

In the current study, 83% of patients required admission because of general compromise, severe orchitis, or other concomitant mumps complication (specifically, meningitis). The admission rate due to mumps orchitis is difficult to specify in the literature. Most reviewed series of mumps infection do not refer to the need for admission because of gonadal compromise.[2,11,34,50,55,57,69,111,116,124,127,128,132]

There is a general idea that hospital admission for mumps infection is uncommon.[47] Few mumps orchitis series[12,13,21,27,46,67,68,71,96,103,123,135] mentioned the hospital admission time (Table 9). Our patients remained hospitalized a similar time (mean, 3.9 d, range 2–9 d) as those described in the literature, whose mean time varied from 1 to 7 days (range, 1–9 d).[46,47,103,135] In our series, the stay of patients who suffered complications (pancreatitis or meningitis) was longer than the stay of patients who had only testicular involvement. In comparison, Falk et al[47] found that the mean length of stay for mumps pancreatitis (4.4 d) and for mumps meningitis (4 d) were shorter than for mumps orchitis (5 d). Finally, there are reports of cases with as long as 14 days of admission because of mumps complications.[60]

Mumps orchitis is still a rare disease, thus data detailing therapeutic strategies mostly consist of case reports[1,60,82,85,111,113] or short series.[27,46,68,69,76,103,116,127,135] Currently the general opinion is that mumps orchitis management is purely symptomatic, and treatment should be based on alleviating symptoms.[56,62,118] Although there are no relevant clinical trials, most authors recommend conservative measures (bed rest, scrotal elevation, local cold, and NSAID).[1,8,27,62,68,69,76,77,80,85,103,116,135] Other treatments have been evaluated since 1967, mainly with the aim of preventing testicular atrophy and subsequent sterility after mumps orchitis.[2,46,68,76,111,127,135]

Seventeen of 40 reviewed studies explicitly mentioned the treatment administered to patients (Table 9). Fourteen studies referred to the use of some kind of classical treatment (bed rest in 12, scrotal elevation in 11, NSAID in 10, local cold in 6), whereas 10 series included alternative treatments (alpha-interferon in 6, systemic steroids in 3, leuprolide acetate in 1). Surgical maneuvers were needed in 3 of 609 patients in the literature (scrotal exploration to exclude torsion and abscess in 3 and tunica vaginalis resection in 1).[27,103] Routine use of antibiotics was mentioned in 4 studies,[27,67,85,103] whereas 2 studies reported administration of antibiotics under suspicion of bacterial infection.[76,127]

The use of systemic standard and specific anti-mumps immunoglobulins, diethylstilbestrol, and steroids therapy has been proposed to prevent testicular atrophy after mumps orchitis.[37,40,41,54,61,94,97] However, none of these regimens has been definitely demonstrated to be effective. What is more, besides the fact that there is no evidence that treatment with steroids produces more rapid resolution of the orchitis or prevents subsequent atrophy,[118] steroids can decrease testosterone concentrations, and can decrease concentrations of FSH and LH, which could facilitate, rather than alleviate, testicular atrophy.[2,79] In animal models it has been shown that acute stimulation with gonadotropin hormones induces vascular disturbance in the testis similar to those caused by inflammation, consisting of accumulation of intravascular polymorphonucleate leukocyte, leukocyte migration, abnormal leakage in postcapillary venules, and tissue edema.[15–17,38,59] Based on these findings, the gonadotropin-releasing-hormone-agonist leuprolide has been proposed as an option in the treatment of postpubertal acute orchitis of diverse etiologies.[127] Currently, surgical interventions (that is, incision of the tunica albuginea) are seldom, if ever, recommended.[79,118]

In early 1990s, Erpenbach and colleagues[46] suggested that interferon treatment could be beneficial to prevent sterility after bilateral mumps orchitis. Although the mechanism by which interferon could prevent late complications of mumps orchitis was unknown, the authors suggested a direct antiviral effect by interrupting the transcriptase-induced virus replication. Damage in testicular tissue seems to occur in the first 4 days of infection.[135] Administering interferon treatment early in the course of the disease could influence the process. So, the beneficial effect of interferon could be based on the prevention of intratesticular damage and severe inflammatory edema.[46] Since then, other short series have supported the use of alpha-interferon to prevent testicular atrophy and infertility, not only for bilateral mumps orchitis, but also for unilateral disease.[76,111,135]

In the aforementioned study by Erpenbach,[46] 4 patients were evaluated by clinical examination, testicular ultrasonography, scrotal scintigraphy, and spermiograms before and after treatment with alpha-interferon. Testicular pain and scrotal swelling disappeared within 2–4 days (median, 3 d) of treatment; testicular volume returned to normal after 12–20 months, with no evidence

TABLE 9. Therapeutic Options in 609 Patients With Mumps Orchitis Since 1967, Present and Previous Reports

First Author, Year (Ref.)	No. of Patients	Admitted Patients, No.	Mean Length of Stay, d (Range)	Classical Treatment				Alternative Treatment, Dose	Surgery, No.	Antibiotic
				Bed Rest	Local Cold	Scrotal Elevation	NSAID			
Atkinson, 1967[8]	1	NM	NM	Y	-	Y	-	-	-	-
Bartak, 1973[11]	54	NM	NM	-	-	-	-	-	-	-
Adamapoulos, 1978[2]	27	NM	NM	Y	Y	-	Y	Prednisolone, 30 mg/24 h, 4–7 d	-	-
Falk, 1980–1982[47]	14	4	5	-	-	-	-	-	-	-
Baandrup, 1984[9]	1	1	NM	-	-	-	-	-	-	-
Wharton, 1986[132]	10	NM	NM	-	-	-	-	-	-	-
Shulman, 1987–1988[116]	19	NM	NM	Y	Y	Y	Y	-	-	-
Kaplan, 1988[71]	15	4	5 (1–9)	-	-	-	-	-	-	-
Erpenbach, 1990[46]	4	4	7	-	-	-	Y	Interferon alpha 2B, 3 MU SC/12 h, 7 d	-	-
Manson, 1990[85]	1	1	7	Y	-	Y	Y	-	-	Y
Ku, 1990–1997[76]	21	21	NM	Y	-	Y	-	Interferon alpha 2B, 3 MU SC, 7 d	-	Y*
Tarantino, 1990–1998[123]	12	12	NM	-	-	-	-	Prednisone, 20–30 mg/24 h, 5 d	-	-
Hersh, 1991[57]	5	1	NM	-	-	-	-	-	-	-
Yeniyol, 1992–1995[135]	18	18	7	Y	Y	Y	-	Interferon alpha 2B, 3 MU IV/12 h, 7 d	-	-
Jiménez, 1993–2005[67]	4	4	NM	-	-	-	-	-	-	-
Kuczyk, 1994[77]	1	1	NM	Y	-	Y	Y	-	-	Y
Rüther, 1995[111]	1	NM	NM	-	-	-	-	Interferon alpha 2A, 6 MU SC/24 h, 5 d	-	-
Vicari, 1995[127]	24	NM	NM	-	Y	Y	Y	Leuprolide acetate depot 3.75 mg every 27 d, 3 mo	-	Y*
Casella, 1995–1996[27]	11	11	6 (3–8)	Y	Y	Y	Y	-	1	Y
Visser, 1995–1996[128]	35	NM	NM	-	-	-	-	-	-	-
Kalaydjiev, 1997–1998[68]	74	74	NM	Y	-	Y	-	Methylprednisolone 1–1.5 mg/kg per d, 2–18 d	-	-
Başekim, 1998[12]	11	11	NM	-	-	-	-	Interferon alpha 2B, doses not mentioned	-	-
López, 1998[83]	8	NM	NM	-	-	-	-	-	-	-
Tecle, 1998–2000[124]	22	NM	NM	-	-	-	-	-	-	-
Lin, 1999[82]	1	NM	NM	-	-	-	-	-	-	-
Ternavasio, 2000–2001[(PR)]	67	56	3.9 (2–9)	Y	Y	Y	Y	Interferon alpha 2B, 3 MU SC/24 h, 7 d	-	Y*
Kalaydjiev, 2001[69]	21	NM	NM	-	-	-	-	-	-	-
Horiguchi, 2002[60]	1	1	14	-	-	-	-	-	-	-
Jalal, 2004[65]	1	NM	NM	-	-	-	-	-	-	-
Niizuma, 2004[96]	7	7	NM	-	-	-	-	-	-	-
Sartorius, 2004[113]	1	NM	NM	-	-	-	-	-	-	-
Philip, 2004–2005[103]	25	25	1.9 (1–4)	Y	-	Y	Y	-	2	Y
Harling, 2005[55]	3	NM	NM	-	-	-	-	-	-	-
Spanaki, 2004–2005[119]	2	NM	NM	-	-	-	-	-	-	-
Emerson, 2005–2006[43]	5	NM	NM	-	-	-	-	-	-	-
CDC, 2006[34]	21	NM	NM	-	-	-	-	-	-	-
Gerstel, 2006[50]	17	NM	NM	-	-	-	-	-	-	-
Waxman, 2006[130]	27	NM	NM	-	-	-	-	-	-	-
Castilla, 2006–2007[28]	17	NM	NM	-	-	-	-	-	-	-
Abdelbaky, 2008[1]	1	1	NM	Y	-	-	Y	-	-	-

Abbreviations: NM = not mentioned, Y = yes, MU = million units, SC = subcutaneously, IV = intravenously.

*If bacterial infection was suspected.

of testicular atrophy; ultrasonography showed a complete regression of the intratesticular damage and edema from 3–6 days (median, 4 d) of hospital admission to 6 months after treatment; the increased perfusion rate that had been seen during the acute phase became normal in the scrotal scintigraphy performed 3–6 months after treatment; and, finally, 75% of patients who presented oligoasthenospermia before treatment, were normospermic after 6 months.[46]

In a randomized trial comparing interferon with standard treatment in 21 patients with either unilateral or bilateral mumps orchitis, Ku et al[76] found that patients treated with systemic interferon showed a significant difference in the duration of symptoms (interferon-treatment group, mean 2.5 [SD 0.5] d; standard-treatment group, mean 3.9 [SD 1.5] d; $p < 0.05$). No significant differences were found in relation to scrotal swelling. Regarding sperm characteristics, sperm count returned to normal after treatment with interferon, while it persisted low in 50% of standard-treated patients. Moreover, there was a greater tendency to sperm motility recovery in the interferon group.[76] However, patients treated with standard treatment more often recovered normal sperm morphology during follow-up than patients in the intervention group.[76]

Yeniyol et al,[135] with the goal to evaluate prospectively the effectiveness of intravenous alpha-interferon in preventing testicular atrophy, performed testicular biopsies in 18 postpubertal men with clinical data of acute unilateral mumps orchitis. Clinical symptoms (fever, pain, tenderness and swelling of the testes) receded within 3–4 days after interferon was started. Interferon was not completely successful in preventing testicular atrophy because almost 40% of patients presented evidence of total atrophy of seminiferous tubules on testicular biopsies performed during follow-up. Although to our knowledge this is the only study that evaluated the impact of interferon treatment on pathologic alteration in mumps orchitis, the lack of a control group minimizes the value of its results.[135]

Other authors used ultrasonography and Doppler ultrasonography to evaluate testicular damage in 11 patients with acute unilateral mumps orchitis treated with interferon.[12] Ultrasonographic and color Doppler ultrasonographic distortions observed during the acute phase of the disease began to improve in the third day, and were completely normalized 3 months after therapy. Although the unaffected testis was used as a control, a comparative evaluation with normal subjects would have been desirable, because an asymptomatic compromise of the contralateral side cannot be completely excluded.[12]

In the current series, 56 patients were admitted to hospital and treated with interferon, which to our knowledge is the largest series using alpha-interferon as treatment for acute mumps orchitis. Unfortunately, participation in follow-up was sparse, and only 1 of 11 patients treated symptomatically and 14 of 56 patients treated with interferon could be evaluated afterwards. However, some conclusions can be drawn. At the end of follow-up (3–15 mo), most patients treated with interferon showed some kind of hormonal (64%) or sperm (85%) impairment (Table 5). Only 2 patients (14%) could be considered completely free of sequelae. The only patient treated conservatively showed, in the same way, sperm and hormonal disturbances. The high incidence of hormonal and sperm disturbances seen in our study are in disagreement with early reports supporting the use of interferon in acute mumps orchitis.[46,76,111]

Although no severe adverse reactions were reported with the use of interferon in literature series,[12,46,76,135] its benefits seem to be, at least, controversial. The use of alpha-interferon (and other treatments) to prevent fertility impairment after acute mumps orchitis must be evaluated in clinical trials, probably in an epidemic context, to achieve sufficient number of patients. Clinical, hormonal, ultrasonographic, and pathologic data as well as sperm characteristics during acute and recovery phases should be examined to establish the real effect of the intervention treatment in the outcome of the disease.

In summary, although some treatments for mumps-related acute orchitis have been proposed in recent years, the most successful therapy is still prophylactic vaccination.

Follow-Up

The most important complication of mumps orchitis is the risk of testicular atrophy, which takes between a couple of months and 1 year after the infection, and may lead to infertility.[46] The exact mechanisms of fertility impairment are not entirely understood.[68] Moreover, the frequency of infertility after acute mumps orchitis is also a matter of discussion. It was previously mentioned that 30%–50% of involved testes undergo some degree of testicular size diminution,[75,90,118] although infertility after mumps orchitis is generally linked to severe bilateral orchitis.[2–4,53,79,118,131] Impaired fertility is estimated to occur in about 13% of patients.[27] Most authors agree that among those with bilateral involvement, absolute infertility is rare, although some authors place it between 30% and 87%.[88,135] On the basis of a supposedly higher incidence of atrophy and sterility after mumps orchitis, other authors have assayed different treatments to preserve fertility.[18,37,40,46,54,70,76,111,127,135] Finally, it has also been speculated that male infertility can occur after mumps infection without mumps orchitis.[95]

The controversies around the effect of mumps orchitis on gonadal function are the consequence of small sample sizes, bias in the selection of cases, and the absence of baseline data for comparison.[62] Furthermore, we note that a wide variety of terms, which are not necessarily synonyms, is erratically used to describe organic (orchitis, atrophy) and functional (sperm impairment, infertility) testicular damage from mumps infection. For instance, "testicular atrophy" is frequently used to define any reduction in testicular size.[103] So the incidence of testicular atrophy can vary widely according to the method of assessment: clinical inspection, orchidometers, or ultrasounds. Likewise, even when orchidometers are used, the accuracy in determining testicular volume is imprecise. Although ultrasonography is more exact, it is often performed during the acute episode, when testes are swollen. In the case of unilateral involvement, it is usual to assume the fairly reasonable, but not necessarily true, premise that both testes were originally of equal size before orchitis.[103] In the same way, patients are unlikely to have a previous semen analysis to evaluate the effects of orchitis on germinal function.[103] Finally, atrophy of the testis subsequent to orchitis is probably noted inconsistently and is dependent on the severity of the atrophy, the concern of the patient, and the level of clinical record maintained by the examiner.[13]

Clinical Study

Clinical signs of testicular damage (reduced testicular volume, tenderness, and often loss of turgor) are observed in 20%–50% of patients 1–4 months after bilateral or unilateral orchitis.[11,103] Moreover, 25%–70% of patients have some degree of atrophy of the affected testes, but severe atrophy is rare.[11,18,53] Thirteen percent of patients with bilateral orchitis may develop subfertility.[53] Bartak[11] found persistent poor fertility at follow-up in many patients who had no signs of testicular atrophy. In the aforementioned study of Ku et al,[76] the authors found clinical signs of atrophy in 3 of 21 patients (14%) during a mean follow-up of 19.5 months (range, 9 to 58 mo). It is remarkable that 18 of

44 measured testes (41%) showed a volume of less than 15 mL in the same study. In our series, 6.5% and 25% of the testes evaluated showed a volume of less than 15 mL during early (3–6 mo) and late (12–15 mo) recovery phases, respectively. The higher rate of testes below 15 mL found by Ku et al could be attributed to the longer follow-up time.

Among cases with favorable outcome, Doppler ultrasound performed during the early follow-up period showed that vascularity decreases after the third day and disappears almost entirely on the seventh day.[12] Different series showed an occurrence of atrophy up to 12.5% during 1–20 months of ultrasound follow-up.[12,46,123,127]

Hormonal Study

Hormonal data on gonadal function disturbance during the acute phase were highly prevalent among our patients. Up to 75% of studied patients showed some type of testicular dysfunction, which widely exceeds the 47% mentioned by Ku et al.[76] The determination of inhibin B, not measured in previous studies, undoubtedly contributed to the detection of a greater number of cases with hormonal abnormalities. Because of initial testicular damage in acute mumps orchitis, hypergonadotropic hypogonadism would be the a priori expected endocrine dysfunction. On the contrary, a great proportion of our cases showed depressed levels of testicular hormones along with low or inappropriately normal serum concentrations of gonadotropins, indicating an acute alteration in the regulation of the hypothalamic-pituitary axis. Ku et al[76] also reported data relating to secondary hypogonadism (decreased levels of testosterone and normal levels of gonadotropins) in 33% and primary hypogonadism (decreased levels of testosterone and increased levels of gonadotropins) in 14% of patients in their series. Acute systemic diseases are known to be associated with the suppression of gonadotropin secretion. Fever, cytokines, and stress hormones could be responsible, acting upon the hypothalamus or the pituitary.[72] An additional explanation could come from the high frequency of central nervous system compromise associated with mumps infection. Finally, there is evidence of some kind of local regulatory mechanism in the pituitary controlling gonadotropin secretion where activins and follistatin, 2 hormones closely related to the inhibin B action, could play a role that is incompletely understood.[39,93]

Primary impairment of the LH/testosterone axis (decreased levels of testosterone and increased levels of LH) was the second most frequent gonadal disturbance found in the acute phase in our study, not only in an isolated way but also together with data of apparent failure of FSH secretion, thus conforming an unforeseen mixed pattern of hypogonadism (see below). Although the consequences of mumps orchitis on the seminiferous tubules of the testis are well documented,[118,135] Leydig cell function disturbances, both in the acute phase and during recovery, are less well understood and remain a matter of controversy.[2,62] It has been generally sustained that Leydig cell function is preserved more or less intact after recovery from mumps.[5,79,120] Adamopoulos et al[2] studied Leydig cell function in 27 men during the acute phase of mumps orchitis (11 unilateral, 16 bilateral); they found a lower mean testosterone concentration both before and after human chorionic gonadotropin administration compared to values observed in a control group of healthy euspermic men. Blunted testosterone levels were accompanied by significantly increased basal concentrations of FSH and LH in the group with orchitis. During the recovery phase (10–12 mo after the acute phase) basal testosterone concentrations returned to normal, while mean basal FSH and LH concentrations remained significantly increased compared to values found in control subjects.[2] The authors suggested that Leydig cell function is early and permanently impaired in certain subjects, even if this is not enough to produce a clinical hypergonadotropic hypogonadism. The deleterious effects of the acute phase of mumps orchitis on Leydig cell function are strengthened by another report[3] that showed a low mean plasma production rate of testosterone and elevated serum gonadotropin concentrations after testicular atrophy due to mumps orchitis. On the contrary, however, other authors have found no hormonal disturbances during the acute and follow-up periods of mumps orchitis.[46,111,135] Finally, Ku et al[76] referred to only transient impairment in hormone levels during acute orchitis: decrease of testosterone levels in 47% of patients and restoration to normal hormonal concentrations in a mean of 20 months of follow-up. In our series, 5 patients with acute data of Leydig cell compromise were followed (1 with isolated impairment of the LH/testosterone axis and 4 with the mentioned associated pattern of germinal compromise). Four of them showed a tendency to normalization during the follow-up period (Table 5, Patients 9, 11, 13, 15). In a general way we can affirm that the Leydig cell function was acutely affected but showed a tendency to be restored during follow-up.

As described above, it was noteworthy that measures of FSH were low or normal in 6 patients with Leydig cell dysfunction during the acute phase, in spite of concurrently diminished levels of inhibin B (Table 4). This atypical pattern entails an early injury of both Leydig cells, with compromise of the steroidogenic function, and the whole germinal axis, as evidenced by the lack of response of FSH to the fall of inhibin B levels. Similar discordances between inhibin B and FSH levels have been eventually observed in other clinical settings, namely among men under evaluation for infertility of different etiologies,[129] but, to our knowledge, they have not been previously described in subjects with acute orchitis. Unfortunately, we were able to follow only 4 of 6 patients with this atypical pattern. Early, during the recovery phase (3–6 mo) the atypical hormonal profile varied in all 4 aforementioned patients. Three of them (Table 5, Patients 3, 11, 13) developed oligospermia and elevated values of FSH, both of which persisted unchanged until the end of follow-up. In the fourth case (Table 5, Patient 15), who had oligospermia but with normal serum levels of FSH, the sperm count turned to normal values at the end of follow-up.

The explanation for this atypical hormonal pattern remains elusive. It would be plausible that other inhibin-related peptides or its fragments, not detected by the specific inhibin B assay, were liberated to systemic circulation from destroyed testicular tissue. High amounts of these peptides might exert a negative feed-back upon the secretion of FSH by the pituitary gonadotroph cells or, alternatively, they could interfere with the immunoassay by taking up the capture antibody, giving artificially low values for inhibin B. Finally, a speculative question emerges about the possibility that the atypical pattern we describe here could be a hormonal profile associated with mumps infection and, if so, in the future it should facilitate the study of different causes of acute orchitis by means of a specific hormonal study.

Sperm Study

Sterility, the most frightening complication of mumps orchitis in adults, was evaluated by means of sperm studies by some case reports[65,77,82,111] and several series[11,46,76,83,116,127] including the current one (Table 10). The series included data on 145 patients, who were followed for 3–58 months. The most frequently reported characteristics were sperm count, motility, and morphology.

The reported incidence of oligospermia at the end of follow-up fluctuated between 0 and 45% (Table 10). Few cases of complete lack of spermatozoa were reported[82] (1 of them in the present study), but azoospermia is probably underestimated. Our

TABLE 10. Studies Performed During Evolution in 609 Patients With Acute Mumps Orchitis Since 1967, Present and Previous Studies

First Author, Year (Ref.)	No. of Patients	Study			Follow-Up; Time; Study	Outcome Comments
		Volume	Hormones	Sperm		
Atkinson, 1967[8]	1	N	N	N	N	
Bartak, 1973[11]	54	N	N	Y	Y; 3,6,12 mo; spermiogram	Oligospermia (3.6%), teratospermia (74%), asthenospermia
Adamapoulos, 1978[2]	27	N	Y	N	Y; 3–5 and 10–12 mo; hormones	Impaired response to HCG, increased concentrations of basal FSH and LH
Falk, 1980–1982[47]	14	N	N	N	N	
Baandrup, 1984[9]	1	N	N	N	N	
Wharton, 1986[132]	10	N	N	N	N	
Shulman, 1987–1988[116]	19	N	N	Y	Y; 40–60 wk; spermiogram, ASA	Teratospermia (61%), asthenospermia (15%)
Kaplan, 1988[71]	15	N	N	N	N	
Erpenbach, 1990[46]	4	Y	Y	Y	Y; 12–20 mo; hormones, spermiogram, US	Edema, intratesticular damage before treatment (75%); normal during follow-up; oligoasthenospermia before treatment (75%); normospermia after treatment (100%)
Manson, 1990[85]	1	N	N	N	Y; 3 wk; testicular size	Normal size
Ku, 1990–1997[76]	21	Y	Y	Y	Y, 19.5 mo (range 9–58 mo); testicular size, hormones, spermiogram, mumps virus titers	Atrophic testes (3, standard group); transient hypogonadism (14% primary, 33% secondary); oligospermia (50%, standard group), asthenospermia (30%, interferon group; 50%, standard group), teratospermia (23%, interferon group; 12%, standard group).
Tarantino, 1990–1998[123]	12	Y	N	N	Y; 3,6,9,12,15 d, 1 mo; US	Normal US findings
Hersh, 1991[57]	5	N	N	N	N	
Yeniyol, 1992–1995[135]	18	Y	Y	N	Y; 1 yr; hormones, bilateral testicular biopsy	Atrophy in seminiferous tubules (38% total atrophy, 16% partial atrophy, all of the affected side)
Jiménez, 1993–2005[67]	4	N	N	N	N	
Kuczyk, 1994[77]	1	Y	N	Y	Y; 3 mo; US, spermiogram	Normal size, normospermia, hypoechogenic pattern of the affected testicle
Rüther, 1995[111]	1	Y	Y	Y	Y; 6 mo; clinical findings, US, scintigraphy, spermiogram	
Vicari, 1995[127]	24	Y	N	Y	Y; 1,2,3 mo during treatment 3, 6 mo posttreatment; ASA, spermiogram, US	Atrophic testicles (3, not treated patients); oligospermia (45%, standard treatment group); asthenospermia (>53% in all groups); teratospermia (54%, standard treatment group); higher seminal white blood cell concentration in standard treatment group
Casella, 1995–1996[27]	11	N	N	N	N	
Visser, 1995–1996[128]	35	N	N	N	N	
Kalaydjiev, 1997–1998[68]	74	N	N	N	N	
Başekim, 1998[12]	11	Y	N	N	Y; 3 and 7 d, 3 mo; US	Normal US finding
López, 1998[83]	8	N	N	Y	Y	Oligoasthenospermia (37%)
Tecle, 1998–2000[124]	22	N	N	N	N	
Lin, 1999[82]	1	Y	Y	Y	Y; 10 yr; testicular size, hormones, spermiogram	Bilateral atrophy (right 5 mL, left <5 mL, Seager orchidometer); primary hypogonadism; azoospermia. Successful TESE and ICSI

(Continued on next page)

TABLE 10. *(Continued)*

First Author, Year (Ref.)	No. of Patients	Study			Follow-Up; Time; Study	Outcome Comments
		Volume	Hormones	Sperm		
Ternavasio, 2000–2001[PR]	67	Y	Y	Y	Y; 3–6 and 12–15 mo; testicular size, hormones, spermiogram	13 Atrophic testicles, diverse degrees of gonadal dysfunction; description of an atypical pattern of hormonal behavior; sperm abnormalities: azoospermia-oligospermia (80%), asthenospermia (13%), teratospermia (7%), decreased vitality (13%)
Kalaydjiev, 2001[69]	21	N	N	N	N	
Horiguchi, 2002[60]	1	N	N	N	N	
Jalal, 2004[65]	1	N	N	Y	Y; 14, 40, 84 d; ASA, spermiogram	Day 14, normospermia; day 40, oligoasthenoteratozoospermia; day 84, asthenospermia. Positive ASA in seminal fluid
Niizuma, 2004[96]	7	N	N	N	N	
Sartorius, 2004[113]	1	N	N	N	N	
Philip, 2004–2005[103]	25	Y	N	N	Y; 4 mo; clinical findings	Testicular abnormalities in 4 patients (persistent pain, change in consistency, reduction in size, and significant atrophy)
Harling, 2005[55]	3	N	N	N	N	
Spanaki, 2004–2005[119]	2	N	N	N	N	
Emerson, 2005–2006[43]	5	N	N	N	N	
CDC, 2006[34]	21	N	N	N	N	
Gerstel, 2006[50]	17	N	N	N	N	
Waxman 2006[130]	27	N	N	N	N	
Castilla 2006–2007[28]	17	N	N	N	N	
Abdelbaky, 2008[1]	1	N	N	N	N	

Abbreviations: N = no, Y = yes, ASA = anti-sperm antibodies, US = ultrasound, HCG = human chorionic gonadotropin, TESE = testicular sperm extraction, ICSI = intracytoplasmic sperm injection.

study presented the highest incidence of sperm count disturbance (azoospermia-oligospermia) at the end of follow-up among the reviewed series, 80% (12 of 15 followed patients). However, subjects with more aggressive symptoms of orchitis could have been more receptive to participate in the follow-up investigation, as they were especially concerned about chronic sequelae of orchitis. This fact could have contributed to overestimating the prevalence of testicular dysfunction. An abnormality of the sperm motility was found in between 0 and 53% of patients in the literature. In this case, our series has one of the lowest rates of asthenospermia (13% of followed patients). Teratospermia rate was reported in up to 61% of cases. The incidence in our patients was lower (7% of followed patients).

Although sperm abnormalities appear to be frequent, historical reports have indicated that fathering a child is still possible after severe bilateral orchitis.[112] Currently, because of the rapid progress in high-technology-assisted reproduction, new techniques, such as Testicular Sperm Extraction and Intracytoplasmic Sperm Injection, provide a chance for paternity even in azoospermic patients with postpubertal mumps orchitis,[82] so the current concepts about infertility after mumps orchitis should be taken cautiously.

Pathologically, atrophic testes after orchitis may show varying degrees of arrest of spermatogenesis, reduced number of germ cells in seminiferous tubules, increased thickness of the basement membrane, and peritubular fibrosis. Bilateral and extensive damage of the testes can led to severe oligospermia and even azoospermia (7%–13% of cases), but they do not necessarily cause a complete absence of spermatozoa in the testes,[82,118] because some focal areas of normal seminiferous tubules preserve the spermatogenesis.[76,82,120] Yeniyol et al[135] found arrest of the spermatogenesis in 44% and some degree of atrophy in 38% of patients (total atrophy in 7 patients and partial atrophy of the seminiferous tubules in 3 patients) who underwent bilateral testicular biopsies 1 year after unilateral or bilateral acute mumps orchitis.

It has been mentioned that, in cases of severe bilateral orchitis, testicular atrophy may lead to hypergonadotropic hypogonadism.[82] But, why does hypogonadism appear in unilateral mumps orchitis? Is it possible that local inflammation with an increase of temperature also affects the spermatogenesis in the contralateral testis and leads to hypogonadism? The hypothesis of the high local temperature is a possible explanation for the appearance of hormonal and sperm disturbances in acute unilateral mumps orchitis.

Fever, one of the most characteristic symptoms associated with mumps infection and mumps orchitis, appears abruptly in the range of 39–41°C.[118] Parotitis-associated fever, reported in almost 80% of patients with parotitis,[132] usually abates over 5 days in the vast majority of cases (range, 1–14 d) with the resolution of symptoms.[21,62,71,118] Data about length of orchitis-associated fever are sparse. A mean time of 3.0–3.6 days (range, 2.0–5.4 d) has been described.[27,46,76,135] Our patients exceeded in 1 day the higher reported mean length of fever[27] (Table 8).

Moreover, 20 patients of our series (30%) exceeded 5 days of fever during acute orchitis.

It was affirmed that there is no evidence that the mumps virus directly affects the seminiferous epithelium. Most likely the infectious process is limited to the interstitial area of the testes, and the damage to the seminiferous tubules is related to increased temperature and intratesticular pressure secondary to the edema in the interstitial area.[120] Although fever usually abates over 5 days in the vast majority of cases,[118] the damage of the seminiferous tubules may start earlier in the course of the disease.[135]

Many studies have shown that high scrotal temperature or any febrile illness is associated with transient decrease of spermatozoa concentration,[23,26] increase in the percentage of abnormal spermatozoa,[26,48] and increase in the percentage of immotile spermatozoa.[26,84] Carlsen et al[26] showed that sperm count was significantly affected by fever during meiosis and the postmeiotic period (spermatogenesis), and that impairment of motility and morphology of spermatozoa occurred during spermatogenesis, when spermatids undergo the morphologic changes to become mature germinal cells. Moreover, sperm quality was increasingly affected with increasing number of days of fever.[26] Recovery of sperm motility and morphology following a febrile episode seems to occur faster (~30 d) than recuperation of sperm count (~60 d).[26,84,109] Systemic infections, as well as infections of genital accessory organs, may be associated with transient (or at times even permanent) diminution of sperm output, possibly due to subclinical testicular disease.[26,48,120] Damage to seminiferous epithelium in testicular ectopia is thought to be, at least in part, secondary to elevated environment temperature.[120] Finally, a possible relationship could exist between the hypothalamic centers regulating temperature homeostasis and the abnormalities of gonadotropin-releasing-hormone secretion in the hypothalamus.

The role of the humoral immunity against spermatozoa, through the production of sperm antibodies, has been previously studied[65,68] according to several hypothetical mechanisms: 1) due to "breaks" in the blood-testis barrier and leakage of sperm, the inflammation of the testis causes autoimmunization with sperm antigens; 2) the attachment of the mumps viruses to the sperm surface (serving as haptens), leads to the production of sperm antibodies, and 3) the antigenic mimicry between the mumps virus and human spermatozoa causes the production of cross reacting antibodies in the course of disease. However, diverse authors have proven that the presence of anti-sperm antibodies does not play a role in the etiology of mumps orchitis or in the subsequent infertility.[66,68,69,116]

Predisposing Causes for Mumps Outbreak in the Canary Islands

A mumps vaccine, consisting of an attenuated version of the Jeryl-Lynn strain, was licensed in the United States in 1967, and its use quickly led to marked decreases in mumps incidence in that country.[4,31] In 1973 the monovalent vaccine against mumps was first licensed in Spain, but the vaccination rate was low. The notification of mumps cases to the national system of Diseases of Obligatory Declaration was initiated in Spain in 1982.[63] Cases of mumps have diminished since 1985, when the national immunization program against measles, mumps, and rubella was consolidated. Since 1995 the program has covered more than 90% of the population in all Spanish autonomous communities.[63,106] Before 1985, the number of reported cases of mumps was about 215,000/year (annual mean incidence of 560 cases/100,000 inhabitants). Since then, mumps cases have experienced a gradual decrease of more than 95%, in spite of undergoing 5 epidemic waves.[7]

Mumps vaccine was introduced into the routine immunization schedule in Spain in 1981, together with measles and rubella vaccines at 15 months of age. Later, in 1995, a second dose of MMR was recommended between 11 and 13 years of age. In 1999 the age of administration of the second dose was moved to 3–6 years. Currently, in the national immunization program, the first dose of MMR vaccine is given at 12–15 months and the second dose at 3-6 years of age.

At the beginning of the immunization program 2 mumps vaccines were originally used in Spain, those containing the Jeryl-Lynn and the Urabe Am9 strain.[7,106] The more reactive Urabe strain[101] was used in Spain until it was withdrawn in 1992 due to an unacceptable risk of aseptic meningitis, although that risk was, indeed, considerably lower than the risk associated with natural mumps infection.[7,56] The Rubini strain was gradually introduced nationwide along with the Jeryl-Lynn strain,[7,106] and both strains were administered interchangeably between 1993 and 1999 in the vast majority of autonomous communities. The low effectiveness of the Rubini vaccine was proven in outbreak settings, not only in Spain[25,106,128] but also in other European countries.[14,35,49,52,89,98,108,125] The extremely high (>93%) Rubini strain vaccine coverage reached in some epidemic places supported the idea of the low immunogenic potential of the strain.[106] As a consequence, Spain's Ministry of Public Health and Consumer Affairs has restricted the use of the Rubini strain since 1999 to those children allergic to a component of other vaccines.[7,106]

In the Canary Islands, a region with a high rate of atopy, the Rubini vaccine was especially used between 1995 and 1998.[7] In 2001 the WHO recommended that mumps vaccines containing the Rubini strains should not be used in routine national immunization programs.[133] During the 4-year period 1998–2001, several mumps outbreaks were reported in Spain.[25,106] Particularly, in 2000 almost 50% (4609) of the 9282 mumps cases reported from all around the country came from the Canary Islands. Later, the incidence in the Canary Islands dropped (1220, 176, and 124 cases, respectively, for years 2001, 2002 and 2003)[63] (Table 11).

The effectiveness of a second dose of MMR vaccine has been proven during outbreak settings.[33] Moreover, indigenous mumps was eliminated from Finland in 1996 through high and sustained coverage with 2 doses of MMR vaccine.[30,99,100] Although it is desirable to achieve the implantation of 2 doses of MMR vaccine, it is also pertinent to remark that 2 doses are not 100% effective in preventing mumps. Post-licensure studies of the Jeryl-Lynn mumps vaccine have demonstrated that 1 dose of mumps or MMR vaccine is approximately 80% effective and 2 doses are approximately 90% effective in preventing mumps disease.[4,33,36,56,62] Moreover, in an outbreak in the United States in 2006, most cases (96%) were reported in persons who had

TABLE 11. Cases of Mumps in Spain and the Canary Islands, 2000–2007

Year	Spain No.	Canary Islands No.
2000	9282	4609
2001	7767	1220
2002	4515	176
2003	1667	124
2004	1526	96
2005	2458	68
2006	6885	75
2007	10,343	452

received 2 doses of MMR vaccine.[29] The cases of acute orchitis (in the setting of a mumps outbreak) herein described occurred partly because of the presence of susceptible individuals in cohorts who received a second dose of MMR vaccine between 1995 and 1998 with the Rubini strain, even though this group had received a different vaccine strain in the first MMR dose. This hypothesis is supported by epidemiologic findings of the fifth epidemic wave of mumps in Spain since the introduction of mumps vaccine.[7] Because of the higher incidence observed in Spain during 2006 and 2007,[7,25,28,50] studies were carried out to characterize the affected population. The analysis showed that 46% of cases were aged between 15 and 24 years,[7] a cohort that included people never vaccinated, people vaccinated with just 1 dose, and the cohort of people vaccinated between 1993 and 1999, the period of use of the Rubini strain. The vaccine effectiveness, estimated by the screening method, also showed a decrease in the cohorts vaccinated from 1993 to 1999 (Rubini strain).[7] Although it seems that the low effectiveness of the Rubini strain could be the most important factor in the development of the Canary Islands outbreak, it is not enough to explain all cases. So, probably no single factor caused the outbreak, but instead, smaller contributions by multiple factors acted in concert to cause it.

Other possible contributors to mumps outbreaks were mentioned in several studies,[4,22,27,29–32,34,36,53,56,62,86,101,117] including inadequate levels of vaccination; primary vaccine failure (no seroconversion after vaccination as a result of immaturity, age-related or genetic primary vaccine failure) or secondary vaccine failure (waning immunity); antigenic differences between the outbreak and vaccine strains; increased risk of transmission associated with environment (schools, colleges), which facilitates the transmission through respiratory and oral secretions; inherent limitations in mumps protective immunity; misdiagnosis of infection; delayed recognition and diagnosis of mumps cases (young inexperienced physicians); failure to report the cluster of illnesses in a timely manner; less effectiveness of the vaccine in preventing asymptomatic infection or atypical mumps than in preventing parotitis, so that people with asymptomatic or mild disease might contribute to transmission; improper storage of the vaccine (that is, disruption of the cold chain, exposure to light, or delayed use) resulting in reduced vaccine potency; the conception of mumps as a "harmless childhood disease" and the parents' fear of possible side effects from the vaccination. Cohen et al[36] have suggested that waning immunity may occur and the level of vaccine effectiveness may decrease with time since vaccination, because young adults (aged 18–24 yr) have most commonly received their most recent dose of mumps-containing vaccine 6–17 years ago.[34]

Study Limitations

Several limitations are recognized in this study. First, as we did not conduct an analytical study, it was not possible to identify risk factors or transmission routes. Second, although the study design is a prospective one, the sparse adherence to follow-up limits the conclusions about the effectiveness of alpha-interferon treatment and the true prevalence of long-term sequelae of the disease on fertility and endocrine function. Third, because the cases developed in the Canary Islands, the review included local and regional as well as international series from the English and Spanish literature. However we cannot exclude that remarkable contributions from studies written in other languages may have been missed.

Conclusions

To our knowledge the current series represents the largest study in Spain, and one of the largest in the literature, and includes the greatest number of patients treated with systemic alpha-interferon to prevent sterility after mumps orchitis. Interferon treatment has been effective in some short studies; however, the indication in the prevention of testicular atrophy is controversial. More studies with a prospective design and including a larger number of patients are necessary to evaluate the effectiveness of therapies in the prevention of testicular atrophy and sterility after mumps orchitis. We contribute here a broad clinical, hormonal, and sperm study. We conclude that gonadal function impairment is highly prevalent among patients with acute mumps orchitis. Moreover, to the best of our knowledge, we describe for the first time an atypical mixed pattern of decreased levels of testosterone with increased levels of LH along with decreased levels of both inhibin B and FSH, which can contribute to the understanding of gonadal dysfunction accompanying acute mumps orchitis. The current report also provides comprehensive information about mumps orchitis in the post-vaccine era, including epidemiologic, clinical, therapeutic, and follow-up studies and outcomes of 609 patients.

REFERENCES

1. Abdelbaky AM, Channappa DB, Islam S. Unilateral epididymo-orchitis: a rare complication of MMR vaccine. *Ann R Coll Surg Engl*. 2008; 90:336–337.
2. Adamopoulos DA, Lawrence DM, Vassilopoulos P, Contoyiannis PA, Swyer GI. Pituitary-testicular interrelationships in mumps orchitis and other viral infections. *Br Med J*. 1978;1:1177–1180.
3. Aiman J, Brenner PF, MacDonald PC. Androgen and estrogen production in elderly men with gynecomastia and testicular atrophy after mumps orchitis. *J Clin Endocrinol Metab*. 1980;50:380–386.
4. Anderson LJ, Seward JF. Mumps epidemiology and immunity: the anatomy of a modern epidemic. *Pediatr Infect Dis J*. 2008;27: S75–S79.
5. Andrada JA, von der Walde F, Hoschoian JC, Comini E, Mancini E. Immunological studies in patients with mumps orchitis. *Andrologia*. 1977;9:207–215.
6. Anonymous. A retrospective survey of the complications of mumps. *J R Coll Gen Pract*. 1974;24:552–556.
7. Anonymous. Situacion de la parotiditis en Espana. Actualizacion 2008. [Instituto de Salud Carlos III Centro Nacional de Epidemiologia Espana Web site]. June, 2008. Available at: http://www.isciii.es/htdocs/centros/epidemiologia/pdf/Informe_Parotiditis_CNE_junio_2008.pdf. Accessed January 12, 2009.
8. Atkinson JE, Bass HN. Mumps orchitis in a 3-year-old child. *JAMA*. 1968;203:892.
9. Baandrup U, Mortensen SA. Fatal mumps myocarditis. *Acta Med Scand*. 1984;216:331–333.
10. Bang HO, Bang J. Involvement of the central nervous system in mumps. *Acta Med Scand*. 1943;113:487–505.
11. Bartak V. Sperm count, morphology and motility after unilateral mumps orchitis. *J Reprod Fertil*. 1973;32:491–494.
12. Basekim CC, Kizilkaya E, Pekkafali Z, Baykal KV, Karsli AF. Mumps epididymo-orchitis: sonography and color Doppler sonographic findings. *Abdom Imaging*. 2000;25:322–325.
13. Beard CM, Benson RC Jr, Kelalis PP, Elveback LR, Kurland LT. The incidence and outcome of mumps orchitis in Rochester, Minnesota, 1935 to 1974. *Mayo Clin Proc*. 1977;52:3–7.
14. The Benevento and Compobasso Pediatricians Network for the Control of Vaccine-Preventable Diseases. Field evaluation of the clinical effectiveness of vaccines against pertussis, measles, rubella and mumps. *Vaccine*. 1998;16:818–822.

15. Bergh A. Treatment with human chorionic gonadotropin induces inflammation-like changes in the testicular microcirculation in adult unilaterally cryptorchid rats. *Horm Res*. 1988;30:207–209.
16. Bergh A, Damber JE. Treatment with an LHRH agonist or hCG increases interstitial fluid volume and permeability to Evans blue in the mouse testis. *Int J Androl*. 1988;11:449–456.
17. Bergh A, Widmark A, Damber JE, Cajander S. Are leukocytes involved in the human chorionic gonadotropin-induced increase in testicular vascular permeability? *Endocrinology*. 1986;119:586–590.
18. Bertschat FL, Alexander M. Infertility after mumps orchitis (author's transl). *MMW Munch Med Wochenschr*. 1981;123:606–608.
19. Bjorvatn B. Mumps virus recovered from testicles by fine-needle aspiration biopsy in cases of mumps orchitis. *Scand J Infect Dis*. 1973;5:3–5.
20. Bjorvatn B, Skoldenberg B. Meningitis in mumps and orchitis in Stockholm during 1955-1976—an epidemiological background for a vaccination policy. *Lakartidningen*. 1978;75:2295–2298.
21. Bjorvatn B, Skoldenberg B. Mumps and its complications in Stockholm. *Br Med J*. 1978;1:788.
22. Bloom S, Wharton M. Mumps outbreak among young adults in UK. *BMJ*. 2005;331:E363–E364.
23. Brown-Woodman PD, Post EJ, Gass GC, White IG. The effect of a single sauna exposure on spermatozoa. *Arch Androl*. 1984;12:9–15.
24. Candel S. Epididymitis in mumps, including orchitis: further clinical studies and comments. *Ann Intern Med*. 1951;34:20–36.
25. Cardenosa N, Dominguez A, Camps N, Martinez A, Torner N, Navas E, Salleras L. Non-preventable mumps outbreaks in schoolchildren in Catalonia. *Scand J Infect Dis*. 2006;38:671–674.
26. Carlsen E, Andersson AM, Petersen JH, Skakkebaek NE. History of febrile illness and variation in semen quality. *Hum Reprod*. 2003;18:2089–2092.
27. Casella R, Leibundgut B, Lehmann K, Gasser TC. Mumps orchitis: report of a mini-epidemic. *J Urol*. 1997;158:2158–2161.
28. Castilla J, Garcia Cenoz M, Barricarte A, Irisarri F, Nunez-Cordoba JM, Barricarte A. Mumps outbreak in Navarre region, Spain, 2006–2007. *Euro Surveill*. 2007;12:E070215 070211.
29. CDC. Brief report: update: mumps activity—United States, January 1–October 7, 2006. *MMWR Morb Mortal Wkly Rep*. 2006;55:1152–1153.
30. CDC. Mumps epidemic—United kingdom, 2004–2005. *MMWR Morb Mortal Wkly Rep*. 2006;55:173–175.
31. CDC. Mumps outbreak at a summer camp—New York, 2005. *MMWR Morb Mortal Wkly Rep*. 2006;55:175–177.
32. CDC. Mumps outbreaks on university campuses—Illinois, Wisconsin, South Dakota. *MMWR Morb Mortal Wkly Rep*. 1987;36:496–498, 503–495.
33. CDC. Notice to readers: updated recommendations of the Advisory Committee on Immunization Practices (ACIP) for the control and elimination of mumps. *MMWR Morb Mortal Wkly Rep*. 2006;55: 629–630.
34. CDC. Update: multistate outbreak of mumps—United States, January 1–May 2, 2006. *MMWR Morb Mortal Wkly Rep*. 2006;55:559–563.
35. Chamot E, Toscani L, Egger P, Germann D, Bourquin C. [Estimation of the efficacy of three strains of mumps vaccines during an epidemic of mumps in the Geneva canton (Switzerland)]. *Rev Epidemiol Sante Publique*. 1998;46:100–107.
36. Cohen C, White JM, Savage EJ, Glynn JR, Choi Y, Andrews N, Brown D, Ramsay ME. Vaccine effectiveness estimates, 2004–2005 mumps outbreak, England. *Emerg Infect Dis*. 2007;13:12–17.
37. Copelovici Y, Strulovici D, Cristea AL, Tudor V, Armasu V. Data on the efficiency of specific antimumps immunoglobulins in the prevention of mumps and of its complications. *Virologie*. 1979;30:171–177.
38. Damber JE, Bergh A, Daehlin L. Testicular blood flow, vascular permeability, and testosterone production after stimulation of unilaterally cryptorchid adult rats with human chorionic gonadotropin. *Endocrinology*. 1985;117:1906–1913.
39. de Kretser DM, Meinhardt A, Meehan T, Phillips DJ, O'Bryan MK, Loveland KA. The roles of inhibin and related peptides in gonadal function. *Mol Cell Endocrinol*. 2000;161:43–46.
40. Diehl K. Treatment results and andrological follow-up in orchitis due to mumps. *Wien Klin Wochenschr*. 1990;102:647–650.
41. Diehl K, Hondl H. Mumps orchitis—symptoms and treatment possibilities. *Z Urol Nephrol*. 1990;83:243–247.
42. Echevarria JM, de Ory F, Echevarria C, Lozano A, Tenorio A. [Re-emergence of acute lymphocytic meningitis caused by mumps virus in Spain]. *Enferm Infecc Microbiol Clin*. 1999;17:373–374.
43. Emerson C, Dinsmore WW, Quah SP. Are we missing mumps epididymo-orchitis? *Int J STD AIDS*. 2007;18:341–342.
44. Erpenbach K, Derschum W. Systemic alpha-interferon therapy: a possible method for prevention of testicular atrophy and permanent sterility in patients with bilateral mumps orchitis. *Urologe A*. 1991;30:244–248.
45. Erpenbach K, Miller K. Prospective randomized multicenter phase IIB study in patients with mumps orchitis. *Urologe A*. 1992;31:317–318.
46. Erpenbach KH. Systemic treatment with interferon-alpha 2B: an effective method to prevent sterility after bilateral mumps orchitis. *J Urol*. 1991;146:54–56.
47. Falk WA, Buchan K, Dow M, Garson JZ, Hill E, Nosal M, Tarrant M, Westbury RC, White FM. The epidemiology of mumps in southern Alberta 1980-1982. *Am J Epidemiol*. 1989;130:736–749.
48. French DJ, Leeb CS, Jecht EW. Reduction in sperm output by febrile attacks of familial Mediterranean fever: a case report. *Fertil Steril*. 1973;24:490–493.
49. Germann D, Strohle A, Eggenberger K, Steiner CA, Matter L. An outbreak of mumps in a population partially vaccinated with the Rubini strain. *Scand J Infect Dis*. 1996;28:235–238.
50. Gerstel L, Lenglet A, Garcia Cenoz M. Mumps outbreak in young adults following a village festival in the Navarra region, Spain, August 2006. *Euro Surveill*. 2006;11:E061109 061104.
51. Gillis D, Shulman A, Slepon R, Zeida Y, Green M. Mumps vaccination of young adults is unwarranted. *Scand J Infect Dis*. 1991;23:271–272.
52. Goncalves G, De Araujo A, Monteiro Cardoso ML. Outbreak of mumps associated with poor vaccine efficacy—Oporto Portugal 1996. *Euro Surveill*. 1998;3:119–121.
53. Gupta RK, Best J, MacMahon E. Mumps and the UK epidemic 2005. *BMJ*. 2005;330:1132–1135.
54. Hall WT, Killeen RN. Diethylstilbestrol in mumps orchitis. *U S Armed Forces Med J*. 1954;5:332–344.
55. Harling R, White JM, Ramsay ME, Macsween KF, van den Bosch C. The effectiveness of the mumps component of the MMR vaccine: a case control study. *Vaccine*. 2005;23:4070–4074.
56. Health Protection Agency. General information on mumps. [Health Protection Agency Web site]. May 28, 2008. Available at: http://www.hpa.org.uk/webw. Accessed December 10, 2008.
57. Hersh BS, Fine PE, Kent WK, Cochi SL, Kahn LH, Zell ER, Hays PL, Wood CL. Mumps outbreak in a highly vaccinated population. *J Pediatr*. 1991;119:187–193.
58. Hilleman MR, Weibel RE, Buynak EB, Stokes J Jr, Whitman JE Jr. Live attenuated mumps-virus vaccine. IV. Protective efficacy as measured in a field evaluation. *N Engl J Med*. 1967;276:252–258.

59. Hjertkvist M, Bergh A, Damber JE. HCG treatment increases intratesticular pressure in the abdominal testis of unilaterally cryptorchid rats. *J Androl*. 1988;9:116–120.
60. Horiguchi A, Uchida A. Mumps vaccine-associated acute orchitis with accompanying idiopathic thrombocytopenic purpura. *BJU Int*. 2002;90:970.
61. Hoyne AL, Diamond JH, Christian JR. Diethylstilbestrol in mumps orchitis; prophylactic and therapeutic use. *J Am Med Assoc*. 1949;140:662–665.
62. Hviid A, Rubin S, Muhlemann K. Mumps. *Lancet*. 2008;371:932–944.
63. Instituto de Salud Carlos III Centro Nacional de Epidemiologia. Enfermedades de declaracion obligatoria. [ISCIII Web site]. Dec 2007. Available at: http://www.isciii.es/. Accessed January 21, 2009.
64. Instituto Nacional de Estadistica. Cifras de poblacion y censos demograficos. [INE Web site]. Available at: http://www.ine.es/. Accessed January 21, 2009.
65. Jalal H, Bahadur G, Knowles W, Jin L, Brink N. Mumps epididymo-orchitis with prolonged detection of virus in semen and the development of anti-sperm antibodies. *J Med Virol*. 2004;73:147–150.
66. Jarow JP. Serum sperm antibodies are not elevated after mumps orchitis. *J Urol*. 2002;168:860–861.
67. Jimenez-Caballero PE, Servia M, Mondejar-Marin B, Navarro S, Perez-Martinez I, Marsal-Alonso C, Alvarez-Tejerina A. Meningitis urliana: casuistica en un servicio de Neurologia. *Rev Neurol*. 2005;40:420–422.
68. Kalaydjiev S, Dimitrova D, Nenova M, Peneva S, Dikov I, Nakov L. Serum sperm antibodies are not elevated after mumps orchitis. *Fertil Steril*. 2002;77:76–82.
69. Kalaydjiev S, Dimitrova D, Tsvetkova P, Tsvetkov D. Serum sperm antibodies unrelated to mumps orchitis. *Andrologia*. 2001;33:69–70.
70. Kaljalovic R. Hormones in the treatment of mumps-virus orchitis. *Vojnosanit Pregl*. 1964;21:393–396.
71. Kaplan KM, Marder DC, Cochi SL, Preblud SR. Mumps in the workplace. Further evidence of the changing epidemiology of a childhood vaccine-preventable disease. *JAMA*. 1988;260:1434–1438.
72. Karagiannis A, Harsoulis F. Gonadal dysfunction in systemic diseases. *Eur J Endocrinol*. 2005;152:501–513.
73. Klemola E. Stilbestrol prophylaxis and treatment of mumps orchitis. *Sotilaslaak Aikak*. 1951;26:190–197.
74. Konig MP. Findings: small testicles. *Schweiz Med Wochenschr*. 1987;117:731–735.
75. Krieger JN. Epididymitis, orchitis, and related conditions. *Sex Transm Dis*. 1984;11:173–181.
76. Ku JH, Kim YH, Jeon YS, Lee NK. The preventive effect of systemic treatment with interferon-alpha2B for infertility from mumps orchitis. *BJU Int*. 1999;84:839–842.
77. Kuczyk MA, Denil J, Thon WF, Djamilian M, Truss M, Schlick R, Jonas U. Orchitis following mumps vaccination in an adult. *Urol Int*. 1994;53:179–180.
78. Lambert B. The frequency of mumps and of mumps orchitis and the consequences for sexuality and fertility. *Acta Genet Stat Med*. 1951;2:1–166.
79. Lane TM, Hines J. The management of mumps orchitis. *BJU Int*. 2006;97:1–2.
80. Lapides J, Herwig KR, Anderson EC, Lovegrove RH, Correa RJ Jr, Sloan JB. Oxyphenbutazone therapy for mumps orchitis, acute epididymitis and osteitis pubis. *J Urol*. 1967;98:528–530.
81. Levitt LP, Mahoney DH Jr, Casey HL, Bond JO. Mumps in a general population. A sero-epidemiologic study. *Am J Dis Child*. 1970;120:134–138.
82. Lin YM, Hsu CC, Lin JS. Successful testicular sperm extraction and fertilisation in an azoospermic man with postpubertal mumps orchitis. *BJU Int*. 1999;83:526–527.
83. Lopez Pacios JC, Parra Muntaner L, Pineiro Fernandez MC, Gomez Cisneros SC, Sanchez Sanchez E, Rivas Escudero JA, Madrid Garcia FJ, Garcia Alonso J. Mumps orchitis; review of 8 casesa. *Arch Esp Urol*. 1998;51:331–333.
84. MacLeod J. Effect of chickenpox and of pneumonia on semen quality. *Fertil Steril*. 1951;2:523–533.
85. Manson AL. Mumps orchitis. *Urology*. 1990;36:355–358.
86. Marin M, Quinlisk P, Shimabukuro T, Sawhney C, Brown C, Lebaron CW. Mumps vaccination coverage and vaccine effectiveness in a large outbreak among college students—Iowa, 2006. *Vaccine*. 2008;26:3601–3607.
87. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child*. 1970;45:13–23.
88. Masarani M, Wazait H, Dinneen M. Mumps orchitis. *J R Soc Med*. 2006;99:573–575.
89. Matter HC, Cloetta J, Zimmermann H. Measles, mumps, and rubella: monitoring in Switzerland through a sentinel network, 1986–94. Sentinella Arbeitsgemeinschaft. *J Epidemiol Community Health*. 1995;49 Suppl 1:4–8.
90. McAnally T. Parotitis: clinical presentations and management. *Postgrad Med*. 1982;71:87–93, 97–89.
91. McKendrick GD, Nishtar T. Mumps orchitis and sterility. *Public Health*. 1966;80:277–278.
92. McLean DM, Bach RD, Larke RP, McNaughton GA. Mumps meningoencephalitis, Toronto, 1963. *Can Med Assoc J*. 1964;90:458–462.
93. Meachem SJ, Nieschlag E, Simoni M. Inhibin B in male reproduction: pathophysiology and clinical relevance. *Eur J Endocrinol*. 2001;145:561–571.
94. Miller DL. The prophylactic and therapeutic uses of immunoglobulin in virus infections. *Mod Trends Med Virol*. 1970;2:284–309.
95. Niermann H. Male infertility after mumps infection without mumps orchitis?. *Med Welt*. 1980;31:794–797.
96. Niizuma T, Terada K, Kosaka Y, Daimon Y, Inoue M, Ogita S, Kataoka N, Tanaka K. Elevated serum C-reactive protein in mumps orchitis. *Pediatr Infect Dis J*. 2004;23:971.
97. Nordlander E. Diethylstilboestrol in mumps orchitis. *Acta Obstet Gynecol Scand*. 1959;38:586–598.
98. Paccaud MF, Hazeghi P, Bourquin M, Maurer AM, Steiner CA, Seiler AJ, Helbling P, Zimmermann H. A look back at 2 mumps outbreaks. *Soz Praventivmed*. 1995;40:72–79.
99. Peltola H, Davidkin I, Paunio M, Valle M, Leinikki P, Heinonen OP. Mumps and rubella eliminated from Finland. *JAMA*. 2000;284:2643–2647.
100. Peltola H, Heinonen OP, Valle M, Paunio M, Virtanen M, Karanko V, Cantell K. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. *N Engl J Med*. 1994;331:1397–1402.
101. Peltola H, Kulkarni PS, Kapre SV, Paunio M, Jadhav SS, Dhere RM. Mumps outbreaks in Canada and the United States: time for new thinking on mumps vaccines. *Clin Infect Dis*. 2007;45:459–466.
102. Penttinen K, Cantell K, Somer P, Poikolainen A. Mumps vaccination in the Finnish defense forces. *Am J Epidemiol*. 1968;88:234–244.
103. Philip J, Selvan D, Desmond AD. Mumps orchitis in the non-immune postpubertal male: a resurgent threat to male fertility? *BJU Int*. 2006;97:138–141.

104. Philip RN, Reinhard KR, Lackman DB. Observations on a mumps epidemic in a "virgin" population. 1958. *Am J Epidemiol*. 1995; 142:233–253; discussion 231–232.

105. Philip RN, Reinhard KR, Lackman DB. Observations on a mumps epidemic in a virgin population. *Am J Hyg*. 1959;69:91–111.

106. Pons C, Pelayo T, Pachon I, Galmes A, Gonzalez L, Sanchez C, Martinez F. Two outbreaks of mumps in children vaccinated with the Rubini strain in Spain indicate low vaccine efficacy. *Euro Surveill*. 2000;5:80–84.

107. Radl H. Significance of mumps meningitis. *Dtsch Med Wochenschr*. 1969;94:1599–1603.

108. Richard JL, Zwahlen M, Feuz M, Matter HC. Comparison of the effectiveness of two mumps vaccines during an outbreak in Switzerland in 1999 and 2000: a case-cohort study. *Eur J Epidemiol*. 2003;18:569–577.

109. Robinson D, Rock J. Intrascrotal hyperthermia induced by scrotal insulation: effect on spermatogenesis. *Obstet Gynecol*. 1967;29: 217–223.

110. Russell RR, Donald JC. The neurological complications of mumps. *Br Med J*. 1958;2:27–30.

111. Ruther U, Stilz S, Rohl E, Nunnensiek C, Rassweiler J, Dorr U, Jipp P. Successful interferon-alpha 2 a therapy for a patient with acute mumps orchitis. *Eur Urol*. 1995;27:174–176.

112. Sandler B. Recovery from sterility after mumps orchitis. *Br Med J*. 1954;2:795.

113. Sartorius B, Penttinen P, Nilsson J, Johansen K, Jonsson K, Arneborn M, Lofdahl M, Giesecke J. An outbreak of mumps in Sweden, February–April 2004. *Euro Surveill*. 2005;10:191–193.

114. Schirren C. Oligospermia due to mumps orchitis?. *Dtsch Med Wochenschr*. 1971;96:766.

115. Scully C, Eckersall PD, Emond RT, Boyle P, Beeley JA. Serum alpha-amylase isozymes in mumps: estimation of salivary and pancreatic isozymes by isoelectric focusing. *Clin Chim Acta*. 1981;113:281–291.

116. Shulman A, Shohat B, Gillis D, Yavetz H, Homonnai ZT, Paz G. Mumps orchitis among soldiers: frequency, effect on sperm quality, and sperm antibodies. *Fertil Steril*. 1992;57:1344–1346.

117. Siemer SW, Uder M, Scholz M, Steffens J, Jeanelle JP, Humke U. Increased incidence of mumps orchitis in adolescence and adulthood—sequelae of low vaccination rate?. *Urologe A*. 1997;36:456–459.

118. Singh R, Mostafid H, Hindley RG. Measles, mumps and rubella—the urologist's perspective. *Int J Clin Pract*. 2006;60:335–339.

119. Spanaki A, Hajiioannou J, Varkarakis G, Antonakis T, Kyrmizakis DE. Mumps epidemic among young British citizens on the island of Crete. *Infection*. 2007;35:104–106.

120. Steinberger E. The etiology and pathophysiology of testicular dysfunction in man. *Fertil Steril*. 1978;29:481–491.

121. Strati I, Copelovici Y, Cajal N, Marinescu G, Vulcan V. Presence of C-reactive protein in the development of acute mumps infection. Preliminary report. *Virologie*. 1987;38:121–125.

122. Strati I, Copelovici Y, Selim G. [C-reactive protein (CRP) in different clinical forms of mumps infection]. *Rev Roum Virol*. 1993;44:305–306.

123. Tarantino L, Giorgio A, de Stefano G, Farella N. Echo color Doppler findings in postpubertal mumps epididymo-orchitis. *J Ultrasound Med*. 2001;20:1189–1195.

124. Tecle T, Mickiene A, Johansson B, Lindquist L, Orvell C. Molecular characterization of two mumps virus genotypes circulating during an epidemic in Lithuania from 1998 to 2000. *Arch Virol*. 2002;147: 243–253.

125. Toscani L, Batou M, Bouvier P, Schlaepfer A. Comparison of the efficacy of various strains of mumps vaccine: a school survey. *Soz Praventivmed*. 1996;41:341–347.

126. Tsvetkov D. Spermatological disorders in patients with postmumps orchitis. *Akush Ginekol (Sofiia)*. 1990;29:46–49.

127. Vicari E, Mongioi A. Effectiveness of long-acting gonadotrophin-releasing hormone agonist treatment in combination with conventional therapy on testicular outcome in human orchitis/ epididymo-orchitis. *Hum Reprod*. 1995;10:2072–2078.

128. Visser LE, Gonzalez Perez KC, Ramos Tejera J, Berjon Barrientos AC, Vergara Guerrero Y, Martinez Navarro JF. An outbreak of mumps in the Province of Leon Spain 1995–1996. *Euro Surveill*. 1998;3:14–18.

129. von Eckardstein S, Simoni M, Bergmann M, Weinbauer GF, Gassner P, Schepers AG, Nieschlag E. Serum inhibin B in combination with serum follicle-stimulating hormone (FSH) is a more sensitive marker than serum FSH alone for impaired spermatogenesis in men, but cannot predict the presence of sperm in testicular tissue samples. *J Clin Endocrinol Metab*. 1999;84:2496–2501.

130. Waxman MA, Abrahamian FM, Talan DA, Moran GJ, Pinner R. Update on emerging infections from the Centers for Disease Control and Prevention. Multistate outbreak of mumps—United States, January 1-May 2, 2006. *Ann Emerg Med*. 2006;48:332–335; discussion 335–336.

131. Werner CA. Mumps orchitis and testicular atrophy; a factor in male sterility. *Ann Intern Med*. 1950;32:1075–1086.

132. Wharton M, Cochi SL, Hutcheson RH, Bistowish JM, Schaffner W. A large outbreak of mumps in the postvaccine era. *J Infect Dis*. 1988;158:1253–1260.

133. World Health Organization. Mumps virus vaccines. *Wkly Epidemiol Rec*. 2001;76:346–355.

134. World Health Organization. *Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction*. 4th ed. Cambridge, UK: Cambridge University Press; 1999.

135. Yeniyol CO, Sorguc S, Minareci S, Ayder AR. Role of interferon-alpha-2B in prevention of testicular atrophy with unilateral mumps orchitis. *Urology*. 2000;55:931–933.