



# Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

**MEDICAL MANAGEMENT UPDATE** Editors: F. John Firriolo and Thomas Sollecito

## Syphilis: An update

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Syphilis can be spread during the practice of dentistry by direct contact with mucosal lesions of primary and secondary syphilis or blood and saliva from infected patients. The dentist also can play an important role in the control of syphilis by identification of the signs and symptoms of syphilis, patient education, and referral. The incidence of syphilis and the impact of control measures are presented with the emphasis on the past 5 years. The signs and symptoms of primary, secondary, latent, and late (tertiary) syphilis are reviewed. Current medical treatment is presented. The oral manifestations of syphilis are discussed as well as the dental management of the infected patient. (**Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:3-9**)

Syphilis is an acute and chronic sexually transmitted disease (STD) caused by *Treponema pallidum* that produces skin and mucous membrane lesions in the acute phase.<sup>1</sup> In the chronic phase, bone, viscera, cardiovascular, and neurological disease are produced. The variety of systemic manifestations associated with the later stages of syphilis resulted in its being historically designated as the "great imitator" disease. The vast majority of cases are transmitted sexually, although it may also be transmitted vertically from an infected woman to her newborn child.<sup>2-4</sup> Both genital and oral sex are implicated in the transmission of syphilis.<sup>5</sup> As with gonorrhea, humans are the only known natural host for syphilis.<sup>1</sup> The primary site of syphilitic infection is the genitalia, although primary lesions also occur extragenitally.<sup>6</sup> Syphilis remains an important infection in contemporary medicine because of the morbidity it causes and its ability to enhance the transmission of human immunodeficiency virus (HIV).<sup>7-11</sup>

The manifestations and descriptions of syphilis are classically divided into stages of occurrence, with each stage having its own peculiar signs and symptoms related to time and antigen-antibody responses. The

stages are primary, secondary, latent, tertiary, and congenital.<sup>1-4</sup>

Syphilis has important implications for dentistry.

- Syphilis has oral manifestations.
- Syphilis can be transmitted by direct contact with lesions, blood, and saliva. Because many patients may be asymptomatic, the dentist must approach all patients as though disease transmission were possible and adhere to standard precautions.
- The presence of syphilis is accompanied by additional STDs in approximately 10% of cases, and a syphilis-associated genital ulceration increases the risk for HIV infection.<sup>12,13</sup>
- Dental healthcare workers can be an important component of syphilis control through diagnosis, education, and referral.

## INCIDENCE AND PREVALENCE

In the following discussion, incidence relates to the number of new cases occurring during a year and prevalence describes the percentage of the population affected at a given time.

Until the advent of penicillin and the antibiotic era in the mid-20th century, syphilis was a prevalent disease, infecting between 8% and 14% of the population living in urban areas around the world.<sup>14</sup> Syphilis has been a reportable sexually transmitted disease in the United States since 1941.<sup>15</sup> Primary, secondary, and early late latent infections (total cases) were reported. The largest number of all types of infections was recorded in 1943.<sup>16</sup>

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Since that time the yearly incidence of total cases of reported infection has decreased until a slight increase in 1991.<sup>16</sup>

Reported total cases of primary and secondary syphilis (excluding early latent infections) in the United States have followed a similar pattern up to 1990.<sup>16</sup> However, when reported as the number of cases per 100 000 populations the pattern for the yearly incidence of primary and secondary infections showed a different pattern. In 1943 the rate of infection was 63.8 per 100 000.<sup>17</sup> By 1957 it had been reduced to 3.9 per 100 000.<sup>17</sup> From 1959 to 1990 the rate of infection tended to increase reaching a peak of 20.3 cases per 100 000 in 1990.<sup>17</sup> From 1990 to 2000 there was a 90% reduction in the number of reported cases of primary and secondary syphilis falling to 2.1 per 100 000, which is the lowest rate ever reported in the United States.<sup>17-21</sup> Unfortunately there has been a slight increase in the rate of infection each year since 2000 (2.2 in 2001, 2.4 in 2002, and 2.5 in 2003).<sup>16, 22-24</sup> The rate of reported cases of primary and secondary syphilis reported in women has been falling since 1999.<sup>16</sup> In contrast, the rate of cases reported in males has been increasing.<sup>16</sup>

In 1999, the Centers for Disease Control and Prevention (CDC) in collaboration with other federal partners initiated the National Plan to Eliminate Syphilis in the United States.<sup>23</sup> Syphilis elimination was defined to reduce the annual number of cases of primary and secondary syphilis cases to less than 1000 or a rate of 0.4 cases per 100 000 and to increase the number of syphilis-free counties to 90% by the year 2005.<sup>23</sup> In 2000 the US Department of Health and Human Services published goals for syphilis reduction (Healthy People 2010) to be achieved by 2010.<sup>25</sup> The target goal for 2010 for cases of primary and secondary syphilis was a rate of 0.20 cases per 100 000.<sup>25</sup> Due to the increases in cases of primary and secondary syphilis occurring since 2000, these national goals will be difficult to achieve.

The number of cases of congenital syphilis per year has been reported since 1963.<sup>16</sup> In 1963, there were 367 cases reported for a rate of 9.2 per 100 000 live births. From 1963 to 1987 the reported rate of congenital syphilis cases varied from 3.0 in 1978 to 11.9 in 1971.<sup>16</sup> The highest rate was reported in 1991 (107.3 per 100 000 live births). From 1991 until 2003 the rate has been dropping with a rate of 10.3 reported in 2003.<sup>16</sup>

## CLINICAL FINDINGS

The initial or first stage of infection with *T pallidum* is primary syphilis.<sup>2,4</sup> It represents a local infection at the site of inoculation of the organism. The average incubation time is 2 to 3 weeks after which a painless papule appears at the site of inoculation. Ulceration of the papule occurs producing the classic chancre of

primary syphilis. The chancre is a 1- to 2-cm ulcer with a raised, indurated margin. Chancres can be found on the genitalia, anus, lips, or in the mouth.<sup>4</sup> Regional lymphadenopathy usually is present (Table I). Chancres heal spontaneously within 3 to 6 weeks.<sup>2,4</sup> Systemic dissemination of *T pallidum* occurs during the primary stage of infection.<sup>2</sup>

About 25% of patients with untreated infection will develop secondary syphilis within 4 to 6 weeks after the primary lesion.<sup>2,4</sup> Not all of these patients will have a history of a preceding chancre because it may have gone unnoticed. Symptoms of secondary syphilis include the following: a generalized rash, fever, generalized lymphadenopathy, malaise, alopecia, aseptic meningitis, uveitis, and others (Table I). This wide array of manifestations has given syphilis the reputation as the "great imitator."<sup>2</sup> Maculopapular lesions on the palms and soles occur in about 60% to 80% of patients with secondary syphilis.<sup>4</sup> About 21% to 58% of the patients will have mucocutaneous or mucosal lesions, mucous patch, or condylomata lata (broad-based verrucal plaques) in the mouth or genital area.<sup>4</sup>

The third stage in patients with untreated syphilis is termed early latent or late latent (Table I).<sup>2</sup> Latent syphilis is the period during which patients infected with *T pallidum* have no symptoms but positive serologic testing. Early latent syphilis is infection of 1 year or less during which the patient may experience mucocutaneous relapse, otherwise they are asymptomatic.<sup>4</sup> All other cases are referred to as late latent or latent syphilis of unknown duration. Patients with late latent syphilis require a longer duration of treatment due to a slower metabolism and prolonged dividing time of the spirochete.<sup>2</sup>

The fourth stage of syphilis is referred to as late or tertiary.<sup>2</sup> It can occur after primary and secondary or latent syphilis. Tertiary syphilis can arise as early as 1 year after the initial infection or up to 25 to 30 years later.<sup>2,4</sup> It may involve the central nervous system (CNS), cardiovascular system, skin, or mucous membranes (Table I).<sup>2</sup> The gumma (nodular, ulcerative lesion) is the classic lesion found in tertiary syphilis.<sup>2-4</sup> It can involve skin, mucous membranes, skeletal system, and viscera. Cardiovascular lesions include aortitis, aneurysm, and aortic regurgitation.<sup>4</sup> CNS manifestations are tabes dorsalis, general paralysis, or insanity. Other lesions that may be found are iritis, choroidoretinitis, and leukoplakia (associated with interstitial glossitis).<sup>4,26</sup> About 33% of untreated patients with syphilis will develop signs and symptoms of late syphilis (17% gummas, 8% cardiovascular, and 8% neurosyphilis).<sup>27</sup>

Unborn children of women with untreated syphilis during pregnancy may acquire congenital syphilis in utero (Table I).<sup>28</sup> Between 40% and 70% of women with

**Table I.** Syphilis

<i>Stage</i>	<i>Incubation</i>	<i>Manifestations</i>	<i>Treatment</i>
Primary	2 to 3 weeks	Chancre Regional lymphadenopathy	Benzathine penicillin G, 2.4 million units intramuscularly in single dose*
Secondary	4 to 6 weeks after appearance of chancre	Rash, Fever, Generalized lymphadenopathy, Malaise, Alopecia, Mucous patches (mouth or genital area) Others	Benzathine penicillin G, 2.4 million units intramuscularly in single dose*
Latent			
Early	Infection of 1 year or less	Usually asymptomatic but can experience mucocutaneous relapse	Benzathine penicillin G, 2.4 million units intramuscularly in single dose*
Late	Longer than 1 year	Asymptomatic	Benzathine penicillin G, 2.4 million units intramuscularly once a week for 3 weeks*
Late (Tertiary)	Longer than 1 year; may be 25 to 30 years or longer	Gumma Aortitis Aneurysm Aortic regurgitation Tabes dorsalis General paresis Others	Gummatous or cardiovascular syphilis – intramuscular benzathine penicillin G, 2.4 million units once a week for 3 weeks <sup>†</sup> Neurosyphilis- IV aqueous penicillin G, 3 million units, every 4 hours, for 10 to 14 days <sup>‡</sup> or Daily intramuscular procaine penicillin G, 2.4 million units and oral probenecid, 500 mg, 4 times per day, both given for 10 to 14 days <sup>‡</sup>
Congenital	In utero infection if untreated can lead to latent and late syphilis	Rhinitis, Rash, Vesiculobulbous eruptions, Skin ulcers, Fever, Jaundice, Swelling of liver and spleen, Skeletal defects, Hutchinson's triad (interstitial keratitis, eighth nerve deafness, peg-shaped incisors, mulberry molars), Gummas, Mental retardation, Neurosyphilis	Infected infants - IV aqueous penicillin G (150,000 units per kg) for at least 10 days postpartum or Intramuscular procaine penicillin G, 50,000 units per day for 10 days

\*Alternate drugs for patients allergic to penicillin with primary, secondary or early latent syphilis include doxycycline (100 mg, PO bid for 14 days) or tetracycline (500 mg, PO qid for 14 days) if the patient cannot tolerate doxycycline. For patients with late latent syphilis the regimens are extended to 28 days. Pregnant patients should not be given tetracycline.

<sup>†</sup>Patients with gummatous or cardiovascular syphilis who are allergic to penicillin - doxycycline 100 mg, PO bid, for 28 days or tetracycline 500 mg, PO qid for 28 days.

<sup>‡</sup>Patients allergic to penicillin with neurosyphilis require penicillin desensitization.

active syphilis will give birth to a syphilis-infected infant.<sup>29</sup> In addition, miscarriage may occur in 25% to 50% of women acutely infected with syphilis during pregnancy.<sup>29</sup> Infected infants may have symptoms at birth with most showing symptoms within 2 weeks to 3 months following birth.<sup>29</sup> The early symptoms include rhinitis, desquamative maculopapular rash, vesiculobulbous eruptions, radial skin lesions around the mouth (rhagades), skin ulcers, fever, swollen liver and spleen, jaundice, anemia, and fetal growth retardation.<sup>28,29</sup>

Most children who survive the first 6 to 12 months of life untreated progress to latent and tertiary syphilis later in life.<sup>28</sup> The symptoms of late-stage syphilis result in damage to bones, teeth, eyes, ears, and brain.<sup>28</sup> These symptoms occur after 2 years of age.<sup>2</sup> The skeletal defects that may occur include saddle-nose, high arched palate, frontal bossing of skull, and others.<sup>2</sup>

Hutchinson's triad may be found in late congenital syphilis, which consists of interstitial keratitis, 8 nerve deafness, peg-shaped permanent incisors, and mulberry muticusped molars.<sup>2</sup> In the later stages of congenital syphilis, hydrocephalus, mental retardation, gummas, and neurosyphilis may be found.<sup>2</sup>

## DIAGNOSIS

The diagnosis of syphilis is made based on clinical signs and symptoms, microscopic examination (dark-field, special silver stain, or immunologic preparation of biopsy tissue), and serologic tests (Table II).<sup>26</sup> Although no single microscopic feature is specific, a diagnosis of syphilis should be considered where there is unusual epithelial hyperplasia, granulomatous or plasma cell-predominant chronic inflammation, endarteritis, and neuritis.<sup>30</sup> The definitive diagnosis of syphilis is made

**Table II.** Procedures used to establish the diagnosis of syphilis

Procedure	Source	Comments	Definitive diagnosis
Clinical findings	History Inspection Palpation	Clinical findings can be very suggestive of syphilis but final diagnosis is made by microscopic and or serologic testing	No
Microscopic			
Darkfield	Fluids/surface material from lesions	Diagnostic for chancres and mucous patches extra-orally	Yes for skin and genital lesions
Special stains	Tissue biopsy	Silver stains diagnostic for extra-oral lesions	Yes for skin and genital lesions
Antibodies	Tissue biopsy	Immunofluorescent antibodies	Yes
DNA/RNA	Tissue biopsy	Polymerase chain reaction (PCR), and reverse-transcriptase PCR	Yes
Serologic tests: Reaginic	Blood, plasma	The 2 tests most often used are the Venereal Disease Research Laboratory (VDRL) slide test and the rapid plasma regain (RPR) test	Very supportive for the diagnosis of syphilis but specific serologic tests are used to confirm the diagnosis. These tests are quantitative and are used to assess response to treatment
Serologic tests: Specific	Blood, plasma, saliva, or cerebral spinal fluid	Fluorescent treponemal antibody absorption test (FTA-ABS) The microhemagglutination assay for antibodies to <i>T pallidum</i> (TPHA) Treponemal Enzyme Immunoassay (EIA) These tests are used to confirm the diagnosis of syphilis	Yes. The most common combination of tests are the VDRL and RPR followed by the TPHA or an EIA The specific serologic tests are qualitative and are not used to assess treatment response. Once patients test positive to one of these tests they will remain positive the rest of their lives

using indirect methods due to the fact that *T pallidum* cannot be cultivated in vitro.<sup>2</sup> The chancre of primary syphilis is best diagnosed by darkfield microscopy.<sup>2,4</sup> The other stages of syphilis are usually diagnosed by serologic testing.<sup>2,28</sup> Once the diagnosis of syphilis is confirmed, quantitative nontreponemal test titers should be obtained (Table II). These titers should decline 4-fold within 6 months after treatment of primary or secondary syphilis and within 12 to 24 months after treatment of latent or late syphilis. Serial cerebrospinal fluid examinations are necessary to ensure adequate treatment of neurosyphilis.<sup>31</sup>

### Microscopic

The diagnosis of syphilis in patients with manifestations suggesting the disease is made microscopically from scrapings or exudates from lesions or lymph node aspirates by darkfield microscopic identification of *T pallidum*, direct immunofluorescent antibody testing, use of silver stains, polymerase chain reaction (PCR), or reverse-transcriptase PCR testing of biopsy tissue.<sup>3</sup>

### Serologic tests

The serologic tests for syphilis consist of 2 types.<sup>3</sup> The first are standard nontreponemal (reaginic) tests. These tests detect immunoglobulin M (IgM) and IgG antibodies to lipoidal material released from damaged host cells and to lipoidal-like antigens of *T pallidum*.

There are 4 tests available that use the Venereal Disease Research Laboratory (VDRL) antigen (cardiolipin, cholesterol, and lecithin). The tests are the VDRL slide test, unheated serum reagin (USR) test, rapid plasma regain (RPR) test, and the tuldine red unheated serum (TRUST) test.<sup>3</sup> The 2 tests that are most often used are the VDRL slide test and the RPR test. Reactivity to these tests does not develop until 1 to 4 weeks after the chancre appears in primary syphilis.<sup>3</sup> The tests may become negative in some cases of late latent and late (tertiary) syphilis.<sup>3</sup> The tests are quantitative and also are used to assess the response to treatment (Table II).<sup>3</sup>

Specific treponemal antibody tests are used for confirmation (Table II).<sup>3</sup> They are qualitative tests and are not used in assessing treatment responses.<sup>3</sup> Once a patient tests positive to any one of these tests he or she will remain positive for life even after treatment. The specific treponemal antibody tests are also used to differentiate true-positive from false-positive results in patients tested with the standard nontreponemal antibody tests.<sup>3</sup> The tests used are the fluorescent treponemal antibody absorption test (FTA-ABS) and fluorescent treponemal antibody absorption double-staining test (FTA-ABS DS), both of which are indirect immunofluorescent tests; the microhemagglutination assay for antibodies to *T pallidum* (TPHA); *T pallidum* particle agglutination test (TPPA); and commercial treponemal enzyme immunoassay (EIA) tests.<sup>3</sup> Acon

Laboratories (San Diego, Calif) sell 2 ultrarapid tests (1SY-U401 [test strips], 1SY-U402 [device]) that can be used on whole blood, serum, or plasma. Immuno Science Inc (Las Vegas, Nev) sells a system (Salivax-41287) using saliva to test for syphilis. Studies have suggested that a treponemal EIA test is an appropriate alternative to the combined VDRL-RPR and TPHA screen.<sup>3</sup> Screening can be done using either EIA or the combined VDRL-TPHA. Positive results are confirmed by using a treponemal test of a different type on a second patient specimen.<sup>3</sup>

## PREVENTION

Primary prevention depends on reducing the number of sexual partners and consistent use of condoms in genital and oral sex with men.<sup>3,32</sup> Community outreach activities should target education at those who are at high risk. Single-dose intramuscular benzathine penicillin G and oral azithromycin have been used as treatment for incubating syphilis. Administration of treponemidal antibiotics to treat other STDs, such as gonorrhea and chancroid, may also abort incubating concurrent syphilis. The development of a vaccine against syphilis has long been inhibited by the inability to grow the organism on artificial media, although the recent sequencing of the *T pallidum* genome should advance new research efforts.<sup>3</sup> Secondary prevention by early diagnosis, treatment, partner notification, education, and counseling remain the mainstay of prevention efforts.<sup>3</sup>

## TREATMENT

The current treatment of primary, secondary, or early latent syphilis includes the use of a single dose of parenteral long-acting benzathine penicillin G (Table I).<sup>1,4</sup> Patients with late latent, gummatous, or cardiovascular syphilis should be given 1 injection intramuscularly (IM) once a week for 3 weeks.<sup>29</sup> Alternate drugs for patients allergic to penicillin with primary, secondary, early latent, late latent, gummatous, or cardiovascular syphilis include oral doxycycline or tetracycline if the patient cannot tolerate doxycycline.<sup>29</sup> For patients with late latent, gummatous, or cardiovascular syphilis the 14-day regimens of doxycycline or tetracycline are extended to 28 days.<sup>29</sup> Pregnant patients should not be given tetracycline. Penicillin-allergic pregnant patients who cannot tolerate doxycycline will require penicillin desensitization.<sup>4,29</sup>

The first choice of treatment for patients with neurosyphilis is IV aqueous penicillin.<sup>4,29</sup> For patients unable to follow this regimen, daily IM procaine penicillin G and oral probenecid are recommended (Table I).<sup>4,29</sup> Patients with neurosyphilis who are allergic to penicillin require penicillin desensitization.



Fig 1. Chancre of the hard palate (Mandell,<sup>27</sup> Vol. V, p. 9.5).

Testing for HIV status also is recommended.<sup>1</sup> After treatment, patients periodically should be retested serologically to monitor their conversion to negative.<sup>1,4</sup> This conversion usually will occur within a year. A low failure rate exists in the treatment of syphilis. Noteworthy in the management of syphilis is that infectiousness is reversed rapidly, probably within a matter of hours on initiation of medical treatment.<sup>6</sup> The Jarisch-Herxheimer reaction, manifested by fever, chills, myalgias, and headache, occurs in more than 50% of patients after treatment for syphilis is initiated.<sup>1</sup> The symptoms of the reaction occur within 24 hours following the initiation of any antibiotic therapy for syphilis.<sup>33</sup>

Congenital syphilis is managed best by implementation of preventive measures. This requires that all pregnant women be tested for syphilis by serology.<sup>34</sup> If positive, the expectant mother should be treated with penicillin and retested at the 28th week and again at delivery.<sup>34</sup> Infants born to seroreactive mothers should be evaluated with a nontreponemal serologic test and if positive treated with intravenous aqueous penicillin G or procaine penicillin G for 10 days postpartum (Table I).<sup>4,29</sup> Although treatment is recommended for congenital and tertiary stage of syphilis, response is limited by the extent of damage already incurred.<sup>1</sup>

## DENTAL MANAGEMENT

The dental management of patients with an STD begins with identification. The obvious goal is to identify all individuals who have active disease because many are potentially infectious. Unfortunately, this is not possible in every case because some persons will not provide a history or may not demonstrate significant signs or symptoms suggestive of their disease.<sup>1</sup> The inability to identify potentially infectious patients applies to other diseases, such as HIV infection and viral hepatitis. Therefore, all patients must be managed as though they were infectious.<sup>1</sup> The US Public Health Service, through the CDC, has published recommendations for standard



Fig 2. Mucous patch of secondary syphilis (lower lip) (Neville,<sup>41</sup> p. 169).

precautions to be followed in controlling the transmission of infectious agents in dentistry.<sup>35,36</sup> Strict adherence to these recommendations will, for all practical purposes, eliminate the danger of disease transmission between dentist and patient.<sup>1</sup>

The lesions of untreated primary and secondary syphilis are infectious, as are the patient's blood and saliva. Even after treatment is begun, absolute effectiveness of therapy cannot be determined except by conversion of the positive serologic test to negative; however, early reversal of infectiousness following the institution of antibiotics is to be expected. The time required for this conversion varies from a few months to more than a year.<sup>1</sup> Therefore, patients who are being treated or have a positive result on the serologic test for syphilis following treatment should be viewed as potentially infectious. Necessary dental care may be provided unless oral lesions are present. Dental treatment can commence once oral lesions successfully have been treated.<sup>1</sup>

No modifications in the technical treatment plan are required for a patient with syphilis. No adverse interactions exist between the usual antibiotics or drugs used to treat syphilis and drugs commonly used in dentistry. Patients with Hutchinson's incisors caused by congenital syphilis may request esthetic repair of their anterior teeth.<sup>1</sup>

Dentists should be aware of local statutory requirements regarding reporting STDs to state health officials. Syphilis, gonorrhea, and AIDS are reportable diseases in every state. Local health departments or state STD programs are sources of information regarding this matter.<sup>1</sup>

## ORAL MANIFESTATIONS

Syphilitic chancres and mucous patches are usually painless unless they become secondarily infected. Both



Fig 3. Atrophic glossitis (interstitial glossitis) of tertiary syphilis (Neville,<sup>41</sup> p. 170).

lesions are highly infectious. The chancre begins as a papule that erodes into a painless ulcer with a smooth, grayish surface. The size can vary from a few millimeters to 2 to 3 centimeters (Fig 1). A key feature is lymphadenopathy that may be unilateral.<sup>1</sup> The intraoral mucous patch often appears as a slightly raised asymptomatic papule with an ulcerated surface. The lips, tongue, buccal, and labial mucosa may be affected (Fig 2). Both the chancre and mucous patch regress spontaneously regardless of whether antibiotic therapy is used, although chemotherapy is required to eradicate the systemic infection. Other oral lesions associated with secondary syphilis have been reported to appear like those of hairy leukoplakia, erythema multiforme, and lichen planus.<sup>37-40</sup> The gumma is a painless lesion that may become secondarily infected. It is noninfectious and frequently occurs on and destroys the hard palate. Interstitial glossitis (Fig 3), the result of contracture of the tongue musculature after healing of a gumma, is viewed as a premalignant lesion.<sup>1</sup> There is about a 4-fold increase in squamous cell carcinoma reported in these lesions. This may be due to carcinogenic agents formerly used to treat syphilis (arsenicals and heavy metals) rather than the infectious agent.<sup>26</sup> Oral manifestations of congenital syphilis include peg-shaped permanent central incisors with notching of the incisal edge (Hutchinson's incisors); defective molars with multiple

supernumerary cusps (mulberry molars); atrophic glossitis; a high, narrow palate; and perioral rhagades (skin fissures).<sup>1</sup>

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