Department of Otorhinolaryngology
University of Helsinki
Finland

PERIPHERAL FACIAL PALSY

Grading, Etiology, and Melkersson-Rosenthal Syndrome

Mervi Kanerva

Academic dissertation

To be publicly discussed,
with the permission of the Medical Faculty of the University of Helsinki,
in the Lecture Room of the Department of Otorhinolaryngology,
Haartmaninkatu 4E, Helsinki, on February 29th, 2008, at 12 noon.

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Supervised by

Professor Anne Pitkäranta
Department of Otorhinolaryngology
University of Helsinki

Reviewed by

Professor Veijo Hukkanen
Department of Microbiology
University of Oulu

Docent Kalle Aitasalo
Department of Otorhinolaryngology-Head and Neck Surgery
University of Turku

Opponent

Professor Ilmari Pyykkö
University of Tampere
Medical School

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LIST OF ORIGINAL PUBLICATIONS

This study is based on the following original publications, which are referred to in the text by their Roman numerals.

I Kanerva M, Poussa T, Pitkäranta A
Sunnybrook and House-Brackmann Facial Grading Systems: Intrarater repeatability and interrater agreement
Otolaryngology-Head and Neck Surgery 135(6):865–71, 2006

II Kanerva M, Mannonen L, Piiparinen H, Peltomaa M, Vaheri A, Pitkäranta A
Search for Herpesviruses in cerebrospinal fluid of facial palsy patients by PCR
Acta Oto-Laryngologica 127(7):775–9, 2007

III Kanerva M, Jääskeläinen AJ, Suvela M, Piiparinen H, Vaheri A, Pitkäranta A
Human herpesvirus-6 and -7 DNA in cerebrospinal fluid of facial palsy patients
Acta Oto-Laryngologica, in press

IV Kanerva M, Moilanen K, Virolainen S, Vaheri A, Pitkäranta A
Melkersson-Rosenthal syndrome
Otolaryngology-Head and Neck Surgery, in press

ABSTRACT

The grading of facial appearance and function in peripheral facial palsy (FP) is inconsistent and a subject of much dispute. We assessed two grading scales to determine whether one might be superior for use in everyday clinical practice (I). Eight video-recorded FP patients were graded in two sittings by 26 doctors. Repeatability and agreement for the Sunnybrook facial grading system (SFGS) were measured by intraclass correlation coefficient and coefficient of repeatability, and for the House-Brackmann facial grading system (H-B FGS) by agreement percentage and kappa coefficients.

Repeatability for SFGS proved to be from good to excellent and for H-B FGS from fair to good depending on the statistical method used (I). Agreement between doctors for SFGS was from moderate to excellent and for H-B FGS from poor to fair. Because SFGS was at least as good in repeatability as H-B FGS and showed more reliable results in agreement between doctors, we encourage the use of SFGS over H-B FGS.

The etiology of acute peripheral FP is unverified, as is the question of whether the central nervous system is affected at some phase of the disease. Our objective was to determine whether herpesviral DNA could be found in cerebrospinal fluid (CSF) of peripheral FP patients (II, III). CSF samples from 33 peripheral FP patients (34 samples) and 36 controls were retrospectively examined for DNA of herpes simplex virus-1 (HSV-1), varicella-zoster virus (VZV), and human herpesvirus-6 (HHV-6) by polymerase chain reaction (PCR) (II) and for DNA of HSV-1 and -2, VZV, HHV-6A, -6B, and -7, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) by multiplex-PCR and oligonucleotide microarray methods (III).

Three patients and five controls had HHV-6 or -7 DNA in CSF (II, III). No DNA of HSV-1 or -2, VZV, EBV, or CMV was found. HHV-6 and-7 DNA was detectable in about 10% of the CSF samples evaluated from immunocompetent adolescents and adults without severe disease (III), an important finding that indicates caution when interpreting CSF results. Detecting HHV-7 and dual HHV-6A and -6B DNA in CSF of FP patients is intriguing, but these DNA findings in association with FP and the other diseases that they accompanied require further exploration.

Melkersson-Rosenthal syndrome (MRS) is classically defined as a triad of recurrent labial or oro-facial edema, recurrent peripheral FP, and plicated tongue. All three signs are present in the minority of patients. Edema-dominated forms are more common in the literature, while MRS with FP has received little attention. The etiology and true incidence of MRS are unknown. We investigated characteristics of MRS with FP (IV) and also compared MRS patients treated at the Departments of Otorhinolaryngology and Dermatology. We hypothesized that in MRS FP patients edema would not be the dominating feature, nor would progression with time occur, contrary to existing knowledge. Patient charts at both departments were evaluated for MRS. Patients with FP were mailed a questionnaire and clinically examined. When appropriate, a tissue biopsy was taken to search for the nonnecrotizing granulomatous infiltrations typical of MRS. Herpesviruses, among many other possibilities, have been suspected as etiologic

factors in MRS. We searched peripheral blood DNA for gene mutations leading to UNC-93B protein deficiency, which would predispose to HSV-1 infections.

Thirty-five MRS patients were found, 20 with FP and 11 with the triad form of MRS. At the Department of Otorhinolaryngology, every MRS patient had FP. Two had tissue biopsies taken during an acute edema episode, with nonnecrotizing granulomatous findings. Edema in most MRS FP patients did not dominate the clinical picture, and no progression of the disease was observed, consistent with our hypotheses. Two triad patients had recurring anterior uveitis. No UNC-93B1 gene mutations were found. At the Department of Dermatology, two patients had triad MRS and 15 had monosymptomatic granulomatous cheilitis with frequent or persistent edema and typical MRS tissue histology. The clinical picture of MRS varied according to the department where the patient was treated. More studies from otorhinolaryngology departments and on patients with FP would clarify the actual incidence and clinical picture of the syndrome.

FP is a phenomenon with many unconquered aspects (I, II, III, IV) that await future explorations.

ABBREVIATIONS

AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery
CG	cheilitis granulomatosa
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CR	coefficient of repeatability
CSF	cerebrospinal fluid
EBV	Epstein-Barr virus
ENoG	electroneuronography
FP	facial palsy
H-B FGS	House-Brackmann facial grading system
HHV	human herpesvirus
HSV	herpes simplex virus
ICC	intraclass correlation coefficient
LP	lingua plicata
MRS	Melkersson-Rosenthal syndrome
PCR	polymerase chain reaction
SD	standard deviation
SFGS	Sunnybrook facial grading system
VP	virus particle
VZV	varicella-zoster virus
σe	within-patient/doctor standard deviation

INTRODUCTION

Peripheral facial palsy (FP) is a common condition, in most cases without known cause. Being clearly visible, the cosmetic drawback for the patient is obvious, as is the inability to mimic normal communication, but the effects on vision, eating, and drinking are easily overlooked. Even though most patients recover, outcome is not predictable at palsy onset. Patients are typically under great psychological stress in addition to their physical limitations. Not knowing the cause, no effective treatments exist to offset sequelae or persistent palsy in the approximately 30% of patients who fail to recover completely (Peitersen 2002). Grading facial function is necessary for determining and reporting the spontaneous course of FP and especially the results of medical or surgical treatments. However, FP studies are hindered by the lack of an objective, standardized evaluation method. The subjective methods used vary and are prone to intra- and interrater variation.

The etiology of acute idiopathic peripheral FP (Bell's palsy) is still under debate although herpesviruses, especially herpes simplex virus-1 (HSV-1) and varicella-zoster virus (VZV), have gained support as etiologic factors (Furuta et al. 2000). HSV-1 reactivation has been reported to accompany Bell's palsy, but causality is uncertain (Murakami et al. 1996). VZV is known to cause Ramsay Hunt syndrome, a peripheral FP with herpes vesicles most commonly in the ear or mouth. In Ramsay Hunt syndrome, VZV is assumed to be able to spread widely in neural and mucocutaneous tissue and in cerebrospinal fluid (CSF) (Murakami et al. 1998). VZV infection may present without visible vesicles as zoster sine herpete, and has been suspected to be a causative agent in Bell's palsy in up to 30% of cases (Furuta et al. 2000). Human herpesvirus (HHV)-6 and -7 infections occur commonly in early childhood and the viruses persist latently after primary infection (Ward 2005). Both HHV-6 and -7 have been detected in normal brain tissue at autopsy, indicating that they are able to invade and persist asymptomatically in the central nervous system (CNS) and can be expected to reactivate occasionally (Chan et al. 2000, Ward 2005). HHV-6 and -7 have seldom been studied in association with FP, but we previously found HHV-6 DNA in the tear fluid of Bell's palsy patients more often than in controls and treated a toddler with FP following exanthem subitum, a childhood rash caused by HHV-6 or -7 (Pitkäranta et al. 2000, Pitkäranta et al. 2004). CSF studies on FP patients are scarce and especially rare for HHV-6 and -7.

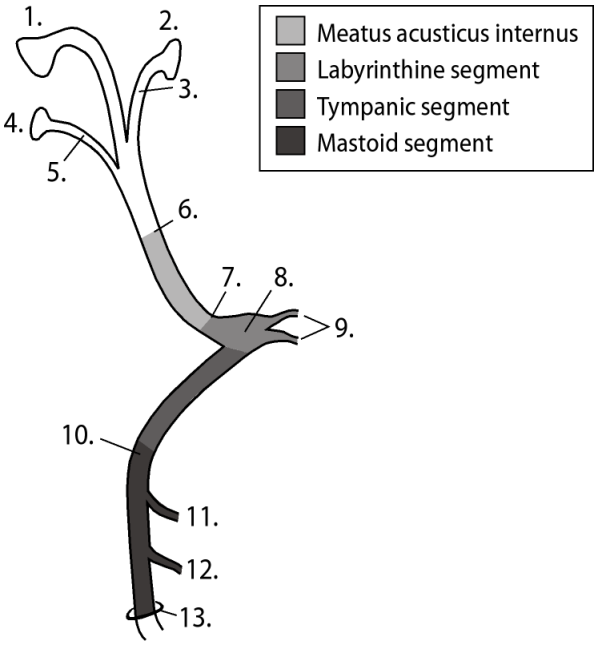
Melkersson-Rosenthal syndrome (MRS) is another entity of peripheral FP of unknown etiology. In triad form, it consists of recurrent peripheral FP, recurrent oro-facial edemas, and plicated tongue (lingua plicata, LP). All symptoms are not needed for diagnosis, and they most often occur on separate occasions (Hornstein 1997). As a rare syndrome, studies on MRS are scarce, mainly concentrating on patients with edema dominating the clinical picture, and studies from otorhinolaryngology departments and on patients with FP are few. MRS is thought to be multifactorial in origin and based on hereditary predisposition (Meisel-Stosiek et al. 1990). Many etiologic factors are considered, including herpesviruses because of the resemblance to Bell's palsy (Ziem et al. 2000).

The objective of this study was to assess the utility of two subjective facial grading systems, to evaluate the etiologic role of human herpesviruses in peripheral FP, and to explore characteristics of MRS.

REVIEW OF THE LITERATURE

Peripheral facial palsy

The facial nerve, the seventh cranial nerve, has its nuclei in the pons of the brainstem (Fig. 1) (May 2000). Nerve function disturbance at this level or distal to it, may lead to ipsilateral peripheral FP (Fig. 2), which affects voluntary and involuntary movements of all facial muscles. Muscles involved in raising and wrinkling the forehead and closing the eyes are bilaterally innervated proximal to the facial motor nucleus in the pons, and thus, function disturbances in cortical areas result in central FP, where the lower facial muscles are affected, but the forehead and eyes are spared, unlike in peripheral FP (Fig. 2) (May 2000). The facial nerve also carries parasympathetic fibers to the salivary and lacrimal glands, taste fibers to the anterior two-thirds of the tongue, other sensory fibers to mucous membranes of the pharynx, nose, and palatine, and less well-defined sensory fibers to the skin of the external auditory canal, pinna, and possibly the mastoid area (May 2000, Eshraghi et al. 2002). Variable symptoms may accompany FP resulting from dysfunctions of these nerve fibers.



1. Nucleus nervus facialis
2. Nucleus salivatorius superior
3. Nervus intermedius (fibers to lacrimal, salivary, and mucous glands)
4. Nucleus tractus solitarii
5. Nervus intermedius (taste fibers)
6. Porus acusticus internus
7. Foramen acusticus internus
8. Ganglion geniculi
9. Nn. petrosus major and minor
10. Second genu
11. Nervus stapedius
12. Chorda tympani
13. Foramen stylomastoideum

Figure 1. *Course of the facial nerve from the brainstem through internal auditory and fallopian canals (labyrinthine, tympanic, and mastoid segments) to the stylomastoid foramen (modified from Fisch and Mattox 1988, May 2000).*

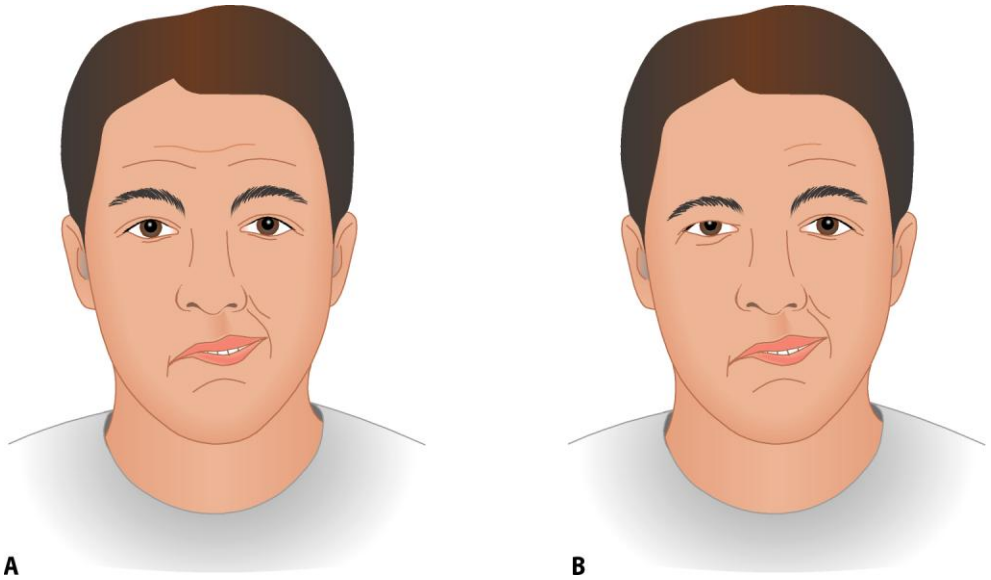


Figure 2. *A) Right-sided central facial palsy. B) Right-sided peripheral facial palsy.*
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Peripheral FP is associated with many diseases and phenomena; some causes are listed in Table 1.

The history of documented peripheral FP stems from the ancient times of Egyptians, Greeks, Romans, Incas, and other native cultures with preserved art representing deformed faces with peripheral FP (Peitersen 2002). In the medical literature, Stalpart van der Wiel described in 1686 a woman with peripheral FP in the puerperium, 14 days postpartum (van de Graaf and Nicolai 2005). In addition, an unpublished description of acute peripheral FP without known cause by Douglas in 1704 and published documentation of three patients by Friedreich in 1797 are the first references to Bell's palsy over 100 years and over 20 years before Bell's studies (Peitersen 2002, van de Graaf and Nicolai 2005). Bell demonstrated that the facial nerve controlled facial motion and the trigeminal nerve facial sensibility (Bell 1821, 1829). The facial nerve became known as "Bell's nerve". For a while, all cases of peripheral flaccid paralysis were called "Bell's palsy", but later the term narrowed to only include idiopathic palsies without known cause. Bell mentions temporary diseases of the facial nerve in his work from 1829, but the concept of acute idiopathic peripheral paralysis was not contained in these early descriptions (Bell 1821, 1829).

Table 1. *Causes of peripheral facial palsy (modified from Schaitkin et al. 2000a).*

Birth
- congenital
- acquired

Idiopathic
- Bell's palsy
- Melkersson-Rosenthal syndrome

Infections
- otitis media (acute and chronic)
- herpes zoster
- herpes simplex
- exanthem subitum, human herpesvirus-6 or -7
- mononucleosis, Epstein-Barr virus
- cytomegalovirus
- parotitis
- mycoplasma pneumoniae
- borreliosis
- influenza
- malaria
- tuberculosis
- acquired immunodeficiency syndrome
- tetanus
- diphtheria

Trauma
- fracture
- penetrating wound
- barotrauma

Neoplasms
- parotid gland
- metastases (skin, breast, lung, kidney, colon)
- cholesteatoma
- schwannoma

Familial

Metabolic and toxic reasons
- diabetes
- hyper- and hypothyreosis
- alcoholism
- carbon monoxide

Sarcoidosis

Wegener's granulomatosis

Amyloidosis

Multiple sclerosis

Guillan-Barré syndrome

Grading facial function

A reliable way of grading is needed to define the severity of facial dysfunction, to follow the progression of FP, and to compare results of interventions. An internationally accepted and implemented system has not yet been developed. To assess correctly function and dysfunction of the facial nerve, the different aspects of its physiology need to be considered. The facial nerve innervates 23 paired facial muscles and the orbicularis oris, and the functional defect can vary in different parts of the face. In addition, lacrimation, salivation, and taste may be affected to varying degrees. When overall facial nerve function is assessed, an attempt to qualify and quantify these different types of function should be made. After facial nerve injury, secondary defects such as synkinesis, contracture, and hemifacial spasms may affect facial appearance and function variably and need to be considered in the assessment.

House (1983) reviewed the existing facial grading systems and divided them into three categories: gross, regional, and specific. The general scales are called gross because they consider overall facial function, including degree of paralysis, and secondary effects simultaneously. They are descriptive, meant to categorize patients in a simple and practical way and not to give specific details about a patient's facial function. In a regional system, the assessor scores different areas of facial function independently. Regional scales can be weighted or unweighted. In a weighted regional scale, certain areas of the face are considered less important because they are less likely to have a good return of function or are cosmetically or functionally less relevant (e.g. forehead) (House 1983). Specific systems ask questions about specific areas of the face and address the presence or absence of associated symptoms and signs (House 1983, Chee and Nedzelski 2000).

The first facial grading system was introduced by Botman and Jongkees (1955). It was a simple five-category scale to judge the degree of paralysis (0 = normal, IV = total paralysis). Contractures were the only secondary defects mentioned in the grading in total paralysis. House (1983) considered this inappropriate since, according to him, in total paralysis secondary defects cannot develop. Peitersen (2002) modified the system and used that scale in his studies (Table 2). After analyzing the pre-existing grading systems, House (1983) introduced his gross scale system with six categories. Brackmann and Barrs (1984) meanwhile published a measuring system for side differences in facial movements. In 1985, the Facial Nerve Disorders Committee of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) adopted a universal standard of grading facial function based on the works of House and Brackmann (1985) (Table 3). The original House scale was modified and Brackmann's measuring scale was added to assist in placing patients in the proper group. Clinicians were encouraged to convert their existing grading system to the House-Brackmann facial grading system (H-B FGS) when reporting their results, and the use of the system was required for articles in Otolaryngology-Head and Neck Surgery, the official journal for the AAO-HNS.

Table 2. *Peitersen grading system.*

Grade	Degree of palsy	Description of palsy
0	None	Normal function
I	Slight	Only visible when patient grimaces
II	Moderate	Visible with small facial movements
III	Severe	Function just visible
IV	Complete	No function

Table 3. *House-Brackmann facial grading system.*

Grade	Description	Characteristics
I	Normal	Normal facial function in all areas
II	Mild dysfunction	*Gross*: Slight weakness noticeable on close inspection; may have very slight synkinesis *At rest*: Normal symmetry and tone *Motion*: Forehead: moderate to good function Eye: complete closure with minimal effort Mouth: slight asymmetry
III	Moderate dysfunction	*Gross*: Obvious but not disfiguring difference between two sides; noticeable but not severe synkinesis, contracture, and/or hemifacial spasm *At rest*: Normal symmetry and tone *Motion*: Forehead: slight to moderate movement Eye: complete closure with effort Mouth: slightly weak with maximum effort
IV	Moderately severe dysfunction	*Gross*: Obvious weakness and/or disfiguring asymmetry *At rest*: Normal symmetry and tone *Motion*: Forehead: none Eye: incomplete closure Mouth: asymmetric with maximum effort
V	Severe dysfunction	*Gross*: Only barely perceptible motion *At rest*: Asymmetry *Motion*: Forehead: none Eye: incomplete closure Mouth: slight movement
VI	Total paralysis	No movement

Although widely used in the United States and Europe, H-B FGS failed to reach worldwide acceptance. Originally created as a gross scale, it has been criticized as not being sufficiently sensitive to document clinically significant changes (Murty et al. 1994, Ross et al. 1996, Rickenmann et al. 1997). It is also prone to interobserver variation (Croxson et al. 1990, King et al. 1993, Murty et al. 1994, Ahrens et al. 1999, Coulson et al. 2005), and assigning only one grade may be difficult because of the different degrees of dysfunction in upper and lower parts of the face (Rickenmann et al. 1997, Scriba et al. 1999, Yen et al. 2003). The article by House and Brackmann (1985) describing the grading system has become the most cited article in otolaryngology-head and neck surgery literature (Wormald et al. 2007). Demands for validation, reliability, and reproducibility assessments of the H-B FGS and its "golden standard" status have been made (Browning 2007). In Japan, the Yanagihara grading system is generally used (Satoh et al. 2000, Ikeda et al. 2003). It is an unweighted regional scale that assesses ten areas of the face without taking secondary effects into account (Table 4). Tables have been provided to convert Yanagihara scores to H-B FGS scores (Satoh et al. 2000).

Table 4. *Yanagihara grading system.*

	Normal	Partial palsy/weak	No motion
1 At rest	4	2	0
2 Wrinkle forehead	4	2	0
3 Close eyes normally	4	2	0
4 Close eyes forcefully	4	2	0
5 Close eyes on the involved side only	4	2	0
6 Wrinkle nose	4	2	0
7 Blow out cheeks	4	2	0
8 Whistle	4	2	0
9 Grin	4	2	0
10 Depress lower lip	4	2	0

Recently, the Sunnybrook (Toronto) Facial Grading System (SFGS) (referred to also simply as the Facial Grading System) (Ross et al. 1996, Ross and Nedzelski 1998, Hu et al. 2001) has received good reviews (Ahrens et al. 1999, Kayhan et al. 2000, Schaitkin and May 2000, Coulson et al. 2004, 2005) and is considered as a leading instrument in clinical use (Rogers et al. 2007). It is a regional scale that measures also synkinesis regionally (Table 5). The regional scores are weighted for the composite score. Berg et al. (2004) considered the scale promising and suggested adding objective measurements and secondary effects other than synkinesis to the scale to make it even better.

Table 5. *Sunnybrook facial grading system (modified from Ross et al. 1996).*

Resting Symmetry Compared to normal side	**Symmetry of Voluntary Movement** Degree of muscle excursion compared to normal side					**Synkinesis** Rate the degree of involuntary muscle contraction associated with each expression			
Eye (choose one only)	**Standard expressions**	Unable to initiate movement	Initiates slight movement	Initiates movement with mild excursion	Movement almost complete	Movement complete	None*	Mild†	Moderate‡	Severe§
normal 0										
narrow 1										
wide 1	**Brow lift**	1	2	3	4	5	0	1	2	3
eyelid surgery 1										
Cheek (naso-labial fold)	**Gentle eye closure**									
normal 0		1	2	3	4	5	0	1	2	3
absent 2										
less pronounced 1	**Open mouth smile**									
more pronounced 1		1	2	3	4	5	0	1	2	3
Mouth										
normal 0	**Snarl**	1	2	3	4	5	0	1	2	3
corner drooped 1										
corner pulled up/out 1	**Lip pucker**	1	2	3	4	5	0	1	2	3
		Gross asymmetry	Severe asymmetry	Moderate asymmetry	Mild asymmetry	Normal symmetry				
Total_____						Total_____				
Resting symmetry score: Total × 5_____						Voluntary movement score: Total × 4_____	Synkinesis score: Total_____			

Voluntary movement score – (minus) Resting symmetry score – (minus) Synkinesis score = **Composite Score_____**

*no synkinesis or mass movement
† slight synkinesis of one or more muscles
‡obvious synkinesis of one or more muscles
§disfiguring synkinesis/gross mass movement of several muscles

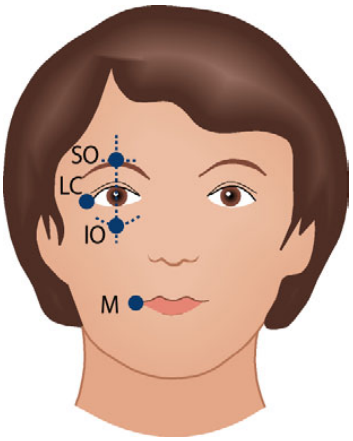
Impairment and disability experienced by the patient may differ greatly from the assessor's grading (Bagger-Sjöbäck et al. 2005). Some investigators would include subjective assessment in the composite grading of facial function (de Ru et al. 2006), and others have created separate grading instruments for subjective dysfunction measurement (VanSwearingen and Brach 1996, Kahn et al. 2001, Mehta et al. 2007).

All of the grading scales mentioned here and many others are subjective. One major problem with grading systems is finding a balance between exact descriptions of sequelae and minimizing the number of groups into which the patients are classified (Peitersen 2002). The need for an objective, simple-to-use method to measure facial dynamics is obvious, but it appears to be difficult to obtain. Significant differences exist in facial expressions from one individual to another, in sides of the face, and between genders and age groups (Giovanoli et al. 2003).

Burres and Fisch (1986) introduced an objective method to measure distances between specific facial landmarks at rest and five standard expressions comparing the affected side of the face to the normal side (Burres-Fisch Linear Measurement Index) by using photographs and still video images. However, their method is time-consuming, difficult to use, and seems to underestimate the degree of dysfunction in severe paralysis and to overestimate it in mild paralysis (Croxson et al. 1990, Murty et al. 1994). Murty et al. (1994) simplified the system to the Nottingham System (Fig. 3, Table 6) by preserving objective measurements of three facial expressions (measuring the movements of four points on the face and comparing the abnormal side with the normal side as a percentage) and specifying whether secondary effects are present or absent and whether the patient experiences crocodile tears, dry eyes, or taste disturbances. The associated sequelae do not interfere with the measurement score and are not rated by severity. The system does not take into account possible normal variance in facial expression between the halves of the face (Chee and Nedzelski 2000) and is not applicable in bilateral FP because the affected side is compared with the unaffected side (Kang et al. 2002). Some investigators have found it promising, although more systemic evaluations are needed to determine whether a widespread application is appropriate (Kang et al. 2002). Others consider all linear measurements inadequate (Meier-Gallati et al. 1998).

Many computer-aided analysis systems have been created to measure dysfunction of one part of the face (Tomat and Manktelow 2005), but to create a clinically usable and affordable method that takes into account whole-face function and secondary defects is challenging and still underway. Systems based on video-recording of facial expressions and light reflection (Neely et al. 1992, Yuen et al. 1997, Meier-Gallati et al. 1998) have been introduced, but because special equipment or techniques are required, these systems have not been taken into wide use (Chee and Nedzelski 2000). Automated facial image analysis (Cohn et al. 1999), originally created to detect, extract, and recognize emotion and paralinguistic expressions, has been used in clinical studies to distinguish subtle changes in facial movement after interventions (Rogers et al. 2007). The system requires manual marking of 40 points (with the computer mouse to video pictures), increasing the possibility for repeatability and agreement errors. Linstrom (2002) used a commercially available video-computer interactive system, The Peak Motus Motion Measurement System, to objectively measure the side-to-side displacement (asymmetry) of selected marker sites on the face during eye closure and smile, and concluded that the ideal objective system to both quantify and classify facial

motion remains to be found. Some investigators suggest that two-dimensional analyses might be inadequate and three-dimensional analyses would be more appropriate and accurate for detecting differences in facial function due to disfigurement or surgical interventions (Giovanoli et al. 2003). Some centers have three-dimensional systems in clinical use for pre- and postoperative asymmetry measurements in FP patients (Giovanoli et al. 2003). Computer-based systems to distinguish facial features and expressions are also used and developed in security systems and animation films, not only in medicine. Thus, numerous investigators work to solve this complex issue. An ideal facial grading system would be user-friendly, inexpensive, require minimal time and equipment, measure both static and dynamic components of facial function, be reliable, valid, and sensitive to changes over time or following treatments (Chee and Nedzelski 2000, Schaitkin and May 2000). Before such a method is available for clinical use, studies on FP cannot properly be compared with each other (Linstrom 2002).



SO = supraorbital
IO = infraorbital
LC = lateral canthus
M = angle of mouth

Figure 3. *Facial reference points of the Nottingham grading system.*

Table 6. *Nottingham grading system.*

Part 1: Calculations from reference points (Figure 3).

	Right	Left
1. Raise eyebrows: measure distance SO–IO		
2. Close eyes tightly: measure distance SO–IO		
3. Smile: measure distance LC–M		
Sum	=X	=Y
X/Yx100 = %		

Part 2:

Hemifacial spasm	Absent	Present
Contractures	Absent	Present
Synkinesis	Absent	Present

Part 3:

Does your eye water when you eat?	No	Yes
Is your eye drier than before?	No	Yes
Have you noticed a change in taste?	No	Yes

Acute idiopathic peripheral facial palsy–Bell's palsy

In about 70% of adult peripheral FPs, the cause is unknown and the palsy is termed idiopathic (Bell's palsy) (Adour et al. 1978, Peitersen 2002). Bell's palsy is acute onset, usually reaching maximal intensity in a few days. The definition for the time limit within which the palsy has to reach its maximum to be Bell's palsy varies from one to two weeks (Adour and Hetzler 1984) to up to three weeks (May and Hughes 1987). Criteria for Bell's palsy have been unilateral FP without any other cranial neuropathies or neurologic deficits. The definition has been modified over the years with accumulating knowledge of the disease. Accompanying symptoms may arise from cranial nerves other than the facial nerve in acute peripheral FP without identifiable cause (Adour 2002, Benatar and Edlow 2004). Some investigators (Peitersen 2002) exclude patients with underlying conditions possibly predisposing to FP (e.g. diabetes or pregnancy) from the Bell's palsy diagnosis, but in FP studies the cause of action is not uniform. Also spontaneous recovery to some degree within six months is considered a feature of Bell's palsy by some investigators (May and Hughes 1987). In this thesis, Bell's palsy is used as a synonym for acute idiopathic peripheral FP.

Incidence of Bell's palsy is about 20–30/100 000/year worldwide (Hauser et al. 1971, Adour et al. 1978, Katusic et al. 1986, Yanagihara 1988, Peitersen 2002, Rowlands et al. 2002, Ljøstad et al. 2005). In most studies, no racial, gender, or seasonal predisposition has been noted (Adour et al. 1978, Peitersen 2002, Rowlands et al. 2002). In some studies, people with diabetes or hypertension, and pregnant women are more susceptible to peripheral FP with worse outcome, but this is not seen in all studies (Gillman et al. 2002, Peitersen 2002). Age distribution of Bell's palsy patients is variable. However, the consensus is that children under 15 years are less often affected than adults (Adour et al. 1978, Katusic et al. 1986, Peitersen 2002). Some studies report a rising frequency in patients over 60 years (Adour et al. 1978, Rowlands et al. 2002), whereas others describe the peak incidence age to be 15–45 years, with a reduced incidence in older people (Peitersen 2002). Recurrence of Bell's palsy affects 6–13% of patients (Adour et al. 1978, Katusic et al. 1986, Devriese et al. 1990, Schaitkin et al. 2000a, Peitersen 2002), and a positive family history varies between 1.5% (Katusic et al. 1986) and 17% (Schaitkin et al. 2000a).

The etiology of Bell's palsy is obscure; genetic, autoimmune, vascular, infective, and immunological causes have been speculated (McGovern et al. 1977, Fisch and Felix 1983, Schaitkin et al. 2000c). Mechanisms include primary ischemia or inflammation of the facial nerve, causing edema and entrapment of the nerve in its long course in the bony temporal canal and resulting in compression and direct damage or secondary ischemia to the nerve (Fisch and Felix 1983, Schaitkin et al. 2000c). Another proposed mechanism is viral infection directly disturbing nerve function by inflammatory immune mechanisms, possibly throughout the nerve's course and not by compression in the bony canal (Adour 2002). Herpesviruses have been suspected as etiologic factors for over 40 years, with growing evidence but still lacking the final proof (Dodge and Poskanzer 1962, McCormick 1972). The viral etiology has gained support by many associations of FP with viral diseases such as mononucleosis caused by Epstein-Barr virus (EBV), chickenpox caused by VZV, cytomegalovirus (CMV) infection, and case reports of exanthem subitum caused by HHV-6 or -7 (Traavik et al. 1983, Mori et al. 2002, Pitkäranta et al. 2004). Some investigators consider Bell's palsy to be a milder

version of Ramsay Hunt syndrome based on similar but less severe polyneuropathic symptoms, not necessarily caused by VZV (Adour 2002). Furuta et al. (2000, 2005) reported findings suggesting zoster sine herpete in about 30% of Bell's palsy patients, in both adults and children, and considered VZV to be one of the major etiologic agents in Bell's palsy. Their results were based on VZV DNA findings in saliva, VZV IgM findings in serum, or significant VZV IgG titer rise in paired serum tests. The conclusions can be challenged based on findings of VZV reactivation under nonsurgical stress (Mehta et al. 2004); VZV reactivation can be a consequence of the FP, not necessarily the cause.

The strongest evidence for HSV-1 being the major etiologic factor in Bell's palsy comes from the work of Murakami et al. (1996). Fourteen FP patients with ongoing palsies underwent decompression surgery 15–60 days after palsy onset (median 31 days). HSV-1 DNA was found by polymerase chain reaction (PCR) in facial nerve endoneurial fluid from 10 patients (13 samples) and in tissue from the posterior auricular muscle from the seven previous patients and one additional patient (14 samples). DNA of VZV or EBV was not found. Nine Ramsay Hunt syndrome patients had the same procedures done, with seven positive VZV DNA findings in endoneurial fluid (9 samples) and six (one patient other than previous patients) positive muscle tissue findings (8 samples). DNA of HSV-1 or EBV was not found. Murakami et al. (1996) concluded that HSV-1 infection of the facial nerve is directly related to the pathogenesis of Bell's palsy, to reactivation of the virus in the geniculate ganglion. Many investigators agree and consider HSV-1 a plausible etiologic factor in Bell's palsy (Furuta et al. 2001, Adour 2002, Gilden 2004, Holland and Weiner 2004, Kawaguchi et al. 2007), some with supporting animal models (Honda et al. 2002). Others think caution in conclusions is warranted. HSV-1 and VZV are assumed to reactivate during surgical stress (Shea and Ge 2001), which could explain the findings of Murakami et al. (1996), or the viruses might reactivate because of FP. The PCR method used by Murakami et al. (1996) could not distinguish active from inactive infection. Stjernquist-Desatnik et al. (2006) took tissue samples from the posterior auricular muscle of Bell's palsy patients within 72 hours of palsy onset and found one patient with HSV-1 DNA by PCR. One Ramsay Hunt patient had VZV DNA in both a tissue sample and CSF. The authors discussed the discrepancy with findings of Murakami et al. (1996), speculating that epidemiological differences may exist in the countries of origin. They also noted that in the Murakami study the palsies were total and had lasted at least two weeks before samples were taken. Rowlands et al. (2002) did not find any suggestions of an infectious etiology: no household clustering of Bell's palsy and no tendency of HSV infection preceding palsy. Linder et al. (2005) studied geniculate ganglions from 14 autopsy specimens of individuals without Bell's palsy and found HSV-1 DNA in 86% and VZV DNA in 43% of ganglions. This confirmed previous abundant HSV and VZV DNA findings in cervical ganglia (Vrabec and Payne 2001). Linder et al. (2005) question the theory of HSV reactivation inside the geniculate ganglion as the reason for Bell's palsy based on the discrepancy between the low incidence of Bell's palsy and the frequent viral genomic findings in human geniculate ganglions. They conclude that the missing link to confirm the active role of HSV in Bell's palsy is the identification of an active replicating virus, a study yet to be conducted.

Human herpesvirus-6 and -7

Studies on HHV-6 and -7 in FP patients are very few (details in Discussion). These viruses are usually acquired in childhood, persist latently for life, and reactivate occasionally (Ward 2005). Primary infections are either asymptomatic or accompanied by fever, diarrhea, rash, and roseola as the most usual symptoms (Zerr et al. 2005). So far, exanthem subitum is the only illness conclusively shown to be caused by HHV-6B or -7 (Yamanishi et al. 1988, Tanaka et al. 1994). Primary infections are sometimes accompanied by encephalitis or febrile seizures (Hall et al. 2006). The majority of documented primary infections are due to HHV-6B, and almost all children are HHV-6-seropositive by two years of age (Ward 2005, Zerr et al. 2005, Hall et al. 2006). HHV-6A has not been indisputably connected to any disease yet, and the epidemiology and clinical findings associated with acquisition of the virus remain uncertain.

HHV-6 is the only human herpesvirus occasionally known to be integrated in human chromosomes. A consequence is the finding of high viral DNA copies in whole blood or serum samples; this is assumed to affect 0.7–1.5% of the general population (Tanaka-Taya et al. 2004**,** Ward et al. 2007). No evidence of chromosomal viral integration of HHV-7 exists (Ward et al. 2007).

Epidemiological characteristics and manifestations of acute HHV-7 infections are not well known. Primary HHV-7 infection usually occurs later than HHV-6 infection and is acquired over the first 5 or 6 years of life (Ward 2005, Hall et al. 2006). This is unexplained since contact with HHV-7 during infancy is expected to be at least as frequent as with HHV-6. Saliva of infected individuals is the presumed principal source of infection for infants. Both HHV-6 and -7 are shed in saliva (Ward 2005, Hall et al. 2006).

Like all herpesviruses, HHV-6 and -7 persist for life after primary infection and are detectable in peripheral white blood cells and multiple tissues (Ward 2005). In a study of autopsy samples, HHV-6 DNA was most commonly found in salivary glands, thyroid, stomach, intestines, liver, and pancreas, and HHV-7 DNA predominated in salivary glands, tonsils, lymph nodes, and bone marrow (Chen and Hudnall 2006). HHV-6 DNA has also been detected in the bone marrow of healthy individuals (Gautheret-Dejean et al. 2000) and both HHV-6 and -7 DNA in normal brain tissue at autopsy (Chan et al. 2000, Chan et al. 2001).

The most serious clinical manifestations of infection or reactivation of these viruses occur in immunocompromised patients (Ljungman 2002). Some uncertainty remains about the clinical role of HHV-6 and -7 following organ or bone marrow transplantation (Ljungman 2002, Lehto et al. 2007). HHV-6 and -7 have been suggested to be associated with such conditions as multiple sclerosis, chronic fatigue syndrome, a variety of neoplastic disorders, infectious mononucleosis, meningitis, encephalitis, and drug hypersensitivity syndromes, and HHV-7 with pityriasis rosea (Ward 2005). Whether HHV-6 and -7 primary infections or reactivations have an etiologic role is unknown.

Treatment of Bell's palsy

Bell's palsy has been treated with various methods and medicines during its long history. Evaluation of therapy in Bell's palsy is difficult because of the high spontaneous recovery rate. In many studies, treatment suggestions are based on the opinions of investigators rather than on results (Devriese et al. 1990, Austin et al. 1993). No consensus has been reached on the treatment of acute Bell's palsy, but unanimous agreement exists on the importance of taking care of the affected eye, to protect it and prevent it from drying (May and Hughes 1987).

In the 17th and 18th centuries, the etiology of acute peripheral FP was considered rheumatic, with the nerves hollow and filled by mucous fluid after being exposed to cold, and treatments were antirheumatic ointments and medicines (Peitersen 2002, van de Graaf and Nicolai 2005). Electrotherapy emerged in the 19th century and is still controversial along with other physical therapy methods and acupuncture (Peitersen 2002, van de Graaf and Nicolai 2005, He et al. 2007, Teixeira et al. 2007).

Surgery for facial reanimation had already started at the end of the 19th century, with anastomosing of the facial nerve to the accessory nerve and later to other neighboring nerves (e.g. hypoglossal, glossopharyngeal) (Ballance et al. 1903, Ballance and Duel 1932). Decompression surgery of the facial nerve had been carried out in other indications and was introduced for Bell's palsy in 1932 (Ballance and Duel 1932). Surgery became popular as the pathophysiology of Bell's palsy was considered the entrapment and compression of the nerve in its bony temporal canal (Kettel 1947, Fisch and Esslen 1972). With the development of surgical methods and the assumed peak entrapment place of the facial nerve within the bony pathway, the area decompressed varied from the most distal part at the stylomastoid foramen to total decompression of the bony canal to the meatal foramen of the internal auditory canal (Fig. 1) (Ballance and Duel 1932, Fisch and Esslen 1972, Gantz et al. 1999, Yanagihara et al. 2001, Adour 2002). The wait for an operation varied from a few days (Fisch and Esslen 1972) to several months (Kettel 1947, Yanagihara et al. 2001) or years (Kettel 1947). Besides the clinical picture of total paralysis or persistent palsy with sequelae, decisions for decompression surgery were based on various electrical tests (Ballance and Duel 1932, Kettel 1947, Gantz et al. 1999, Yanagihara et al. 2001, Adour 2002). With the herpesviral etiology gaining support, surgical procedures have declined and attitudes towards decompression surgery are controversial (Grogan and Gronseth 2001), with many investigators opposing the procedure (May et al. 1985, Adour 2002).

Corticosteroids, cortisone initially, have been used in Bell's palsy from the 1950s onwards to reduce inflammation, degeneration, and false regeneration of the facial nerve (Taverner 1954). The use is common around the world without a generally accepted scientific proof of effectiveness. The American Academy of Neurology (Grogan and Gronseth 2001) concluded in their practice guideline meta-analysis that while the benefit of steroids has not been established, they probably are effective in improving facial functional outcomes. They called for well-designed studies to investigate the effectiveness of treatments. Several other meta-analyses have supported the use of corticosteroids (Ramsey et al. 2000, Holland and Weiner 2004). The Cochrane database concludes the following: "The available evidence from randomised controlled trials does not show significant benefit from treating Bell's palsy with

corticosteroids. More randomised controlled trials with a greater number of patients are needed to determine reliably whether there is real benefit (or harm) from the use of corticosteroid therapy in patients with Bell's palsy" (Salinas et al. 2007).

With the growing support for herpesvirus etiology in Bell's palsy, the use of antiviral agents, first acyclovir, later valaciclovir and famciclovir, has emerged. The same is true as for corticosteroids; the results of studies are controversial, even within participants of the same collaborative study, as recently reported from Japan (Hato et al. 2007, Kawaguchi et al. 2007). The American Academy of Neurology (Grogan and Gronseth 2001) stated that acyclovir (combined with prednisolone) may be effective in improving facial functional outcomes. The Cochrane database concludes: "More data are needed from a large multicentre randomised controlled and blinded study with at least 12 months' follow-up before a definitive recommendation can be made regarding the effect of aciclovir or valaciclovir on Bell's palsy" (Allen and Dunn 2007).

In 2001, a collaboration study was initiated in Finland and Sweden to assess the effectiveness of prednisolone and valaciclovir in Bell's palsy (www.clinicaltrials.gov). This is a double-blind, placebo-controlled, randomized four-arm study with 739 recruited patients and a one-year follow-up. Evidence for the benefit or ineffectiveness of these drugs in Bell's palsy will hopefully be achieved. A similar recent study from Scotland (Sullivan et al. 2007) with 496 patients and 3- to 9-month follow-up demonstrated a significant benefit from the use of prednisolone compared with placebo, whereas the use of acyclovir alone or in combination with prednisolone was not effective.

Corrective treatments for FP patients with residual palsy and associated sequelae include abundant reanimation surgical procedures to improve facial appearance and function, producing more balanced and symmetrical features (May et al. 2000a, Hadlock et al. 2006). After a spontaneous recovery period and especially after surgical corrections, physical therapy with various methods (muscle exercise, electrical stimulations, neuromuscular re-education therapies with surface electromyography biofeedback) is, albeit controversial, increasingly recognized and accepted as enhancing function and reducing discomfort and synkinesis (May et al. 2000, Targan et al. 2000, Beurskens et al. 2006, Hadlock et al. 2006, Teixeira et al. 2007). The mechanisms are thought to be CNS plasticity, resulting in better motor control of the facial muscles, and perhaps reinnervations from intact neighboring nerves or intact motor units of the facial nerve (Targan et al. 2000). Botulinum toxin is successfully used to diminish consequences caused by facial synkinesis, hemifacial spasms, hypercontracted muscles, and hyperlacrimation (May et al. 2000a, Hadlock et al. 2006).

Prognosis of Bell's palsy

Most Bell's palsy patients recover well. Total recovery is seen in 70–80% of patients overall. With incomplete palsy, the recovery rate is 95–99%, with complete palsy 50–60% (Katusic et al. 1986, Schaitkin et al. 2000c, Peitersen 2002). Roughly 30% of all patients are left with some sequelae (remaining palsy, hemifacial spasms, contracture, or synkinesis), mainly mild or moderate, but severe in 5% of cases (Devriese et al. 1990,

Peitersen 2002). In a Danish prospective 25-year study (Peitersen 2002), 70% of palsies were complete and 30% incomplete. Recovery began within three weeks for 85% and within 3–5 months for the remaining 15%. All Bell's palsy patients achieved some degree of muscular function, as was evident also in a study by Adour et al. (1978). In the Danish study (Peitersen 2002), if recovery was not total within six months, some sequelae tended to remain in the final assessment. Total recovery was seen in 71% of Bell's palsy patients, in 64% within three months (Peitersen 2002). Factors indicating unsatisfactory outcome are complete palsy, late beginning of recovery, and age over 60 years (Katusic et al. 1986, Devriese et al. 1990, Schaitkin et al. 2000c, Peitersen 2002).

There are no reliable signs or tests at palsy onset to predict outcome. Topognostic tests are unreliable because of anatomic variations, neural branching, and possible variations in the areas and components affected on the facial nerve (Karikoski 1987, Schaitkin et al. 2000b). Of the electrical tests used in prognostic evaluation, electroneuronography (ENoG), also called evoked electromyography, has been regarded as the most valuable in the acute phase of FP (Fisch 1984, Schaitkin et al. 2000b). A difference of 90% or more in the peak-to-peak amplitude of the evoked compound muscle action potential between the paretic and uninvolved sides of the face is considered to predict a 50% or greater chance of poor recovery (H-B FGS III or worse, Table 3) (Fisch 1984, Karikoski 1987, Gantz et al. 1999). The major drawback of ENoG is that the site of testing is peripheral to the stylomastoid foramen and it takes a minimum of 72 hours for denervation to reach the distal parts of the nerve to be detectable (Schaitkin et al. 2000b, Chow et al. 2002). Since the beginning of palsy is considered crucial in the attempt to diminish the amount of denervation, the results of ENoG come late in finding patients at risk of poor outcome. Other limitations include marked normal variation within tests of the sides of the face and test to retest results (Sittel et al. 1998). Patient cooperation is mandatory and variations in electrode and stimulator placement and pressure can alter results (Schaitkin et al. 2000b, Chow et al. 2002). Studies on transcranial magnetic stimulation of the labyrinthine segment of the facial nerve have been conducted to evaluate the function of the nerve without the delay of distal testing (Schaitkin et al. 2000b, Nowak et al. 2005), but this method has not reached clinical significance. Magnetic resonance imaging has its place in differential diagnostics of Bell's palsy, but studies on predictive value of contrast enhancement findings in Bell's palsy are contradictory (Kress et al. 2004).

Peripheral facial palsy in children

In Peitersen's Danish study (Peitersen 2002), neonates formed the largest group of children's palsies (congenital and acquired). If neonatal age is excluded, Bell's palsy comprised 77% of cases, which is in accordance with other studies (Ogita et al. 2006). Some studies have revealed the proportion of Bell's palsy to be lower, 26–40% (Cook et al. 1997, Peltomaa et al. 1998, May et al. 2000b). In Peitersen's study (2002), the overall incidence of peripheral FP in children under 15 years (excluding neonates) is 3.4/100 000/year and of Bell's palsy 2.6/100 000/year. Higher incidences have also been reported: for peripheral FP 21/100 000/year (under 14 years) (Tveitnes et al. 2007) and 7/100 000/year (Christen et al. 1993), and for Bell's palsy 5–8/100 000/year (Adour et al. 1978, Katusic et al. 1986). Many studies conclude prognosis of FP in children to

be excellent; 90% recovered completely in Peitersen's study (2002), but full recovery rates of 70–80% are also common (Peltomaa et al. 1998, Skogman et al. 2003).

In adult populations, borreliosis as a causative agent for peripheral FP accounts for 0–20% of cases (Roberg et al. 1991, Peitersen 2002, Ljøstad et al. 2005) mostly manifesting with additional symptoms besides FP (Ljøstad et al. 2005). In studies from endemic areas, borreliosis explains 30–65% of children's FPs (Christen et al. 1993, Peltomaa et al. 1998, Tveitnes et al. 2007). Many of these children have no other neurological signs besides FP (Christen et al. 1993, Tveitnes et al. 2007). The Danish study (Peitersen 2002) did not have any children with diagnosed borreliosis. The same was true with 30 children in Japan (Furuta et al. 2005); instead VZV was suspected as the causative agent in 30% of cases. False-positive findings of IgM antibodies to *Borrelia burgdorferi* in CSF can be caused by VZV or EBV, and it is important to rule out these infections before confirming borreliosis as the causative factor for FP (Christen et al. 1993).

Melkersson-Rosenthal syndrome

In 1928, Swedish neurologist Ernst Melkersson published a case study of a 35-year-old man whose FP had reoccurred four times and who had had attacks of edema in the upper and lower lip since age 14 (Melkersson 1928). The swelling in the lower lip gradually became persistent. In 1931, a German neurologist Curt Rosenthal published a family study in which four women from three unrelated families had at least one episode of FP, recurrent episodes of edema, and LP (Rosenthal 1931). Two of these four women were sisters and their mother had had reoccurring facial edema. The third woman had a sister with FP and LP, and a mother with LP. The fourth woman was the only one in her family with these symptoms. In one additional family, edema and LP were seen in two generations without FP (Rosenthal 1931). Recurrent labial or oro-facial edema, recurrent FP, and associated LP (also referred as fissured or furrowed tongue) occurring without recognizable cause became known as the classical triad of MRS. Swiss dermatologist Alfred Guido Miescher studied histology of reoccurring labial edema and found peri- and paravascular tuberculoid character granulations in edematous tissue samples (Miescher 1945). He regarded the finding as cheilitis granulomatosa (CG). Later, German dermatologists (Richter and Johne 1950, Gahlen and Brückner 1951) made similar findings in edematous tissue samples from MRS patients: nonnecrotizing (-caseating) lymphoepiteloid granulomas. Miescher's CG has since been considered by many investigators as a monosymptomatic form of MRS (Hornstein 1973, Worsaae et al. 1982, Greene and Rogers 1989). When two of the possible three symptoms are present, the form is called oligosymptomatic MRS (Greene and Rogers 1989, Hornstein 1997). Some investigators demand that edema be one of the two symptoms for the diagnosis of MRS (Mair and de Graaf 1974), most, however, also include patients with FP and LP without edema (Ekbom 1950, Greene and Rogers 1989, Hornstein 1997). Some investigators still question the supposed mutual etiology of monosymptomatic form of MRS with oligosymptomatic or triad form of MRS, because most CG patients never develop other symptoms of MRS (van der Waal et al. 2002).

Edema is considered the most frequent and dominating clinical feature in MRS eventually affecting virtually all patients (Hornstein et al. 1987, Greene and Rogers 1989). The upper lip (skin and mucosa) is the most common site, but any oro-facial area (outer or inner sides of cheeks, eyelids, forehead, nose, gingiva, oral cavity, floor of mouth, tongue, pharynx, and larynx) may be involved (Zimmer et al. 1992, Hornstein 1997). Extrafacial edemas have been described in the chest, dorsum of hands and feet, buttocks, and genitals (Hornstein 1973, Tsuboi et al. 2005). The edema is nonpitting, painless, and thought to eventually become persistent (Greene and Rogers 1989). The triad form of MRS is estimated to occur in up to 20% of all cases and FP in 20–50% (Vistnes and Kernahan 1971, Hornstein 1973, Worsaae et al. 1982, Hornstein et al. 1987, Greene and Rogers 1989, van der Waal et al. 2002). LP is found in about 6% of the general population, with an increasing prevalence with age (children 0.5%–elderly people 15%) (Axell 1976). LP is considered the least important clinical feature of MRS and is found in about 50% of patients (Rintala et al. 1973, Worsaae et al. 1982, Greene and Rogers 1989). Most MRS studies, usually from departments of dermatology or oral or plastic surgery, have many CG patients and patients with FP are the minority (Worsaae et al. 1982, Hornstein et al. 1987, van der Waal et al. 2002).

Besides the triad of classical symptoms, additional symptoms frequently accompany MRS. Hornstein (1997) considers palsies or dysfunctions of other cranial nerves besides the facial nerve to be “major signs” of MRS in addition to edema and FP. In the complete form of MRS, Hornstein (1997) emphasizes recurrent facial edemas and histopathological findings of nonnecrotizing granulomatous infiltarations in edematous tissue samples. He also lists numerous “minor signs” of uni- or bilateral sensory, motor neuron, or autonomous disturbances that can accompany MRS and support the diagnosis of MRS in oligosymptomatic forms. These include facial dysesthesia, headaches, tinnitus, relapsing hearing loss, dizziness, recurrent pharyngeal neuralgias and spasms, dysphagia, recurrent dysfunctions of salivary and tear secretion, excessive facial sweating or anhidrosis, and recurrent dry eye or dry mouth sensations. When FP and LP are the presenting symptoms without edema, Hornstein (1997) demands the presence of two or more minor signs for a diagnosis of MRS. Hornstein et al. (1987) found migraine in 41% of MRS patients.

The etiology of MRS is unknown. Family occurrence has been documented starting with Rosenthal in the 1930s (Rosenthal 1931, Carr 1966, Lygidakis et al. 1979, Levenson et al. 1984). Whether the familiar pattern is a result of a genetic predisposition, immunodeficiency, or transmission of an infectious agent remains to be elucidated (Levenson et al. 1984). To exclude a pure infectious origin, Meisel-Stosiek et al. (1990) examined spouses of MRS patients alongside family members. They found an increased risk for MRS of 24% in first-degree relatives of MRS patients. The risk dropped to 5% in second-degree relatives. Based on their study and a review of previous reports on family occurrence of MRS, they concluded that MRS is most likely multifactorial in origin, with a hereditary component. Besides heredity, a disturbed autonomous nervous or immune system, obstructive microcirculation, allergies, sarcoidosis, Crohn’s disease, inflammatory agents (toxoplasmosis, tuberculosis, viral infection) have been suggested as causative agents (Hornstein 1973, Greene and Rogers 1989, Sussman et al. 1992, van der Waal et al. 2002). Hornstein (1997) speculated that one common causative denominator of the disease is very unlikely in view of the variety of clinical forms and accompanying symptoms in MRS patients.

The incidence of MRS remains obscure. Hornstein (1973) reported an incidence of 80/100 000 (120 MRS patients in 18 years, most patients with monosymptomatic CG). About 25% of his MRS patients had FP, corresponding to an incidence of 20/100 000. It is not defined, whether the incidence is for a year or for all 18 years. For an annual incidence this seems high since the incidence of Bell's palsy is the same: 20–30/100 000/year worldwide (Devriese et al. 1990, Peitersen 2002). The Danish study (Peitersen 2002) collecting information on FP etiology and incidence had 19 MRS patients (only the number given, no further information). This equals an incidence of 0.36/100 000/year for MRS with FP and a total incidence of 0.7–1.8/100 000/year for MRS if FP is present in 20–50% of all cases.

MRS has been found in children as well as in the elderly, but the most common age at onset is 25–40 years (Worsaae et al. 1982, Hornstein et al. 1987, Zimmer et al. 1992). Whether both genders are affected equally is difficult to determine due to the small number of patients: the female–male ratio has been reported to be 2:1 in some studies (Hornstein et al. 1987, Zimmer et al. 1992), but equal distribution or male predominance have also been described (Rintala et al. 1973, Worsaae et al. 1982).

Treatment of MRS has been unsatisfactory. For edema, the most common treatment is corticosteroids: systemically, topically, or as intralesional injections, with inconsistent results (Worsaae et al. 1982, Zimmer et al. 1992, Hornstein 1997, van der Waal et al. 2002, Mignogna et al. 2004). Allergy medications and antibiotics have mostly been ineffective (Worsaae et al. 1982, Zimmer et al. 1992). Medications used for tuberculosis, or autoimmune diseases, and skin and connective tissue diseases, such as dapsone, azathioprine, sulfasalazine, chloroquine, clofazimine, and tumor necrosis factor alpha inhibitors (thalidomide and infliximab), have been tried without definite results (Sussman et al. 1992, Zimmer et al. 1992, Hornstein 1997, Barry et al. 2005). Eradication of underlying odontogenic infections has proved successful in some patients with edema (Worsaae et al. 1982). Reduction cheiloplasty has produced some good results in permanent lip swellings with nonactive disease, but recurrence is common (Kruse-Lösler et al. 2005). For relapsing FP, total nerve decompression has been suggested (Dutt et al. 2000), but the limited number of patients treated and followed up and the varying natural cause of the disease make it difficult to draw conclusions. Whether the syndrome sometimes completely resolves is uncertain (Worsaae et al. 1982).

AIMS OF THE STUDY

The general aim of this study was to assess grading and etiology of peripheral FP and characteristics of MRS.

Specific aims were as follows:

1. To assess intrarater repeatability and interrater agreement of H-B FGS and SFGS.

2. To evaluate the etiologic role of human herpesviruses in peripheral FP by searching for HSV-1 and -2, VZV, HHV-6A, -6B, and -7, EBV, and CMV DNA in CSF of FP patients.

3. To investigate differences in MRS patient characteristics in the two specialty departments of Otorhinolaryngology and Dermatology, and special characteristics of MRS in patients with FP.

SUBJECTS AND METHODS

All study protocols (I, II, III, IV) were approved by the ethics committee of Helsinki University Central Hospital.

Subjects

Study I

Eight patients with unilateral peripheral FP were video-recorded showing five standard facial expressions. One of the patients had FP after vestibular schwannoma operation 12 years earlier and had had an eyelid operation. The other seven patients had Bell's palsy, which had lasted one year in five patients, two months in one patient, and two weeks in one patient. Five patients had synkinesis and two had contracture.

Thirty doctors at the Department of Otorhinolaryngology, Helsinki University Central Hospital, volunteered to be assessors of the videos. There were two assessment rounds and 28 doctors (15 residents and 13 specialists) returned their gradings for the first round and 26 (13 residents and 13 specialists) for both two rounds.

Studies II and III

The study group comprised 33 peripheral FP patients with 34 CSF samples. Of these patients, 26 had Bell's palsy, 5 had simultaneous herpesvirus infection, one had MRS, and one had puerperal FP two weeks after delivery. These patients were selected because herpesviruses are suspected etiologic factors in Bell's palsy and in FP cases with concomitant herpesvirus infection, and an association may also exist in MRS. Puerperal FP is not considered Bell's palsy by some investigators, whereas others include it in the definition.

There were 19 females and 14 males. Their median age was 19 (range 4–78) years, and 16 patients were 15 years or younger (median 13 years). The median time for the CSF sample to be taken after palsy onset was 21 days (range 0–148, 0 being the day palsy started). One of the patients had three episodes of Bell's palsy and her CSF sample was taken twice. Three other patients had a second occurrence of Bell's palsy. For the MRS patient, this was her fourth FP episode. Among the five patients with concurrent herpesvirus infection, one had bilateral FP and EBV infection, two had varicella/chickenpox preceding FP, one had Ramsay Hunt syndrome with blisters in her mouth a week before FP, and one had simultaneous eruption of herpes blisters on her lower lip on the palsy-affected side.

The 36 control subjects were unmatched and their CSF samples were taken during the same time interval as those of the study group. Six controls had FP with borreliosis. Possible borreliosis with elevated serum antibodies to *Borrelia burgdorferi* but normal CSF samples was evident in 13 control subjects: nine with FP, two with sudden

deafness, one with hearing loss and tinnitus, and one with vertigo. No borreliosis was suspected in the remaining control subjects. Four had sudden deafness, five had vertigo, and four had headache and arthralgia. Of the last four controls, one had headache, one had vocal cord paralysis, one had facial erysipelas with sepsis and simultaneous cavernous sinus thrombosis and peripheral FP, and one had ear symptoms, atypical papillitis, headache, and vertigo. The control group comprised 19 females and 17 males. Their median age was 47.5 (range 5–75) years, with three controls being 15 years or younger.

No diabetic or immunocompromised patients or controls were included in the study.

Study IV

There were 35 patients with MRS or suspicion of the syndrome: 23 females and 12 males. Median age at study onset was 47 (range 19–75) years. Median age at symptom onset was 24 (range 5–71) years. Twenty of the 35 patients had history of FP: 13 females and 7 males. Median age for MRS FP patients was 45.5 (range 34–74) years when the study started and 21.5 (range 10–67) years at symptom onset. The remaining 15 patients, 10 females and 5 males, had CG, monosymptomatic MRS. Their median age at study onset was 47 (range 19–75) years and at symptom onset 34 (range 5–71) years.

Methods

Study I

Video-recording of the FP patient was started with the face at rest, followed by five standard facial expressions: lifting the eyebrows/wrinkling the forehead, closing eyes gently and then more powerfully, wrinkling the nose, smiling mouth open, and puckering the lips. Each movement was repeated three times. After doing all five expressions three times each, the patient again repeated each three times. By doing this, we tried to minimize the need to pause the videotape while assessing.

Doctors graded the facial appearance and movements from the videotapes by H-B FGS and SFGS. Before the first-round videos were delivered to the assessors, a session with an opportunity to view an SFGS teaching video was held. A brief memo highlighting both grading scales and synkinesis accompanied the grading booklet together with patient information on FP duration and palsy side. Assessments by doctors were done twice, with a three-week interval. For the second round, the order of the patients in the video was changed from the first round. The grading was done anonymously and privately, independently from the other assessors.

Study II

PCRs for HSV-1, VZV, and HHV-6 were performed as described in detail by Pitkäranta et al. (2000). Briefly, DNA was isolated from CSF by proteinase K digestion, followed by phenol extraction and ethanol precipitation. Ten microliters of the template was

added to the PCR reaction representing 100 µl of the CSF sample. The primers used in PCR reactions were chosen from the polymerase genes for HSV-1 according to Piiparinen and Vaheri (1991) (5′-biotin-AAGGAGGCGCCCAAGCGTCCG-3′ and 5′-TGGGGTACAGGCTGGCAAAGT-3′) and for VZV according to Echevarria et al. (1994) (5′-AGGTACC GAAAAGCGT-3′ and 5′-biotin-GGCATGTCCCGATGTGGA AA-3′), and from the U67 gene for HHV-6 according to Gopal et al. (1990) (5′-AAGCTTGCACAATGCCAAAAAAC G-3′ and 5′-biotin-CTCGAGTATGCCGAGA CCCCTAATC-3′). Positive and negative controls were included in each run. The amplified products were detected by microplate hybridization. Hybridization was carried out as described previously by Vesanen et al. (1996) and Pitkäranta et al. (2000). Specific oligonucleotide probes were used (5′-CCC TCC TCG CGT TCG TCC TCG-3′ for HSV-1, 5′-ATA ACT CGC TAC CGG AAC GTA TGC CAC AAG-3′ for VZV, 5′-AAC TGT CTG ACT GGC AAA AAC TTT T-3′ for HHV-6) to demonstrate different amplified products.

Study III

The controls of the multiplex-PCRs and microarrays were viral DNA of HSV-1 strain MacIntyre, HSV-2 strain G, CMV strain AD169, EBV strain B95-8, HHV-7 strain H7-4, HHV-6A strain U1102, HHV-6B strain Z-29, and VZV Rod strain (Autogen Bioclear, Wiltshire, UK).

DNA was extracted using a High Pure Viral Nucleic Acid Extraction Kit (Roche Diagnostics, Basel, Switzerland). The CSF (200 µl) was extracted and eluted to 50 µl of elution buffer. Two multiplex-PCRs were used for amplification of herpesvirus genomes, as described in detail by Jääskeläinen et al. (2006). Multiplex-PCR1 (5 µl of extraction) was used to identify HSV-1 and -2. Multiplex-PCR2 (10 µl of extraction) contained primer pairs for amplification of CMV, EBV, VZV, HHV-6A, -6B, and -7. Both multiplex-PCRs were carried out for each sample. The T3 RNA polymerase promoter sequence (AATTAACCCTCACTAAAGGGAGA) was included in the reverse primers of the multiplex-PCRs. The oligonucleotides, oligonucleotide positions, GenBank accession numbers, and gene names are provided in the Appendix.

Microarrays were prepared at the National Public Health Institute (Finland), as described by Jääskeläinen et al. (2006) with a minor modification. Instead of spotting solution containing 0.3 M sodium carbonate buffer (pH 9), the commercial 1× microarray spotting solution (ArrayIt, Telechem International, Sunnyvale, CA, USA) was used. The array consisted of a 5 × 12 matrix that included 14 oligonucleotides (Proligo, Paris, France); 8 were specific and 6 unspecific for herpesviruses. Microarrays contained 44 subarrays, and the herpesvirus-specific oligonucleotides were spotted in 2× triplicate and unspecific oligonucleotides twice per subarray. The spotting was performed at room temperature and 50% humidity. Microarrays were stored overnight at room temperature before use.

First, two multiplex-PCR products of each sample were pooled, and the product solution was transcribed into single-stranded RNA using a AmpliScribe™ T3 High Yield Transcription Kit (Epicentre, Madison, WI, USA) following the manufacturer's instructions. Second, the hybridization of single-stranded RNA to specific oligonucleotides on microarrays was performed**.** Finally, primer extension reactions

were performed, and microarrays were washed with array washing buffer and dried before scanning (Jääskeläinen et al. 2006).

The microarrays were analyzed using a ScanArray Express scanner (PerkinElmer, Wellesley, MA, USA). Images were generated with the ScanArray^{TM} software and quantified using the QuantArray^{TM} software provided by PerkinElmer. A cut-off value was determined for each array separately using QuantArray^{TM} software and signals of unspecific oligonucleotides and background (Jääskeläinen et al. 2006). Microarray detection and genotyping were carried out in duplicate for each sample. The detection limits of the microarray, using commercial viral DNA controls, were as follows: HSV-1 9.1 virus particles (VPs), HSV-2 8.0 VPs, VZV 4.5 VPs, HHV-6A 7.0 copies, HHV-6B 2.5 VPs, HHV-7 3.0 copies, EBV 3.0 copies, and CMV 1.0 copies (Jääskeläinen et al. 2006).

Study IV

A computer search of patient records from January 1st, 1996 to June 30th, 2007 was done for MRS at the Departments of Otorhinolaryngology and Dermatology (Skin and Allergy Hospital), Helsinki University Central Hospital.

LP was defined according to Axell (1976): the dorsum or margins of the tongue are crossed by one or several grooves estimated to be at least 2 mm deep over a minimum total length of 15 mm. If there was any question in patient charts about the LP, severity was considered moderate and not recorded as actual LP.

All patient records were studied and a questionnaire was sent to patients with FP. They were asked about the time, side, and number of their FPs; about the location, duration, frequency, and persistence of facial edema; and about the existence of edemas in other body parts. We inquired whether any relatives had FP, edemas, or fissured tongue. Patients were also questioned about additional symptoms (IV, Table 1). They were asked about allergies, any other diseases, medications, or gastrointestinal symptoms. Finally they were requested to attend a clinical examination.

If the patient had LP, the tongue was photographed. Facial function was determined by H-B FGS (Table 3) and SFGS (Table 5).

A tissue sample from the edematous area (lip, cheek, tongue) was taken with a 4-mm biopsy punch (in cheek and lip edema from inside the mouth deep to the underlying muscle) for possible granulomatous infiltration diagnosis. The samples were stored in formalin overnight. Paraffin-embedded samples were then cut and stained with hematoxylin-eosin and periodic acid-Schiff. The slides were examined by a dermatopathologist.

A blood sample was drawn for genetic testing from 13 patients. The samples were stored at -20°C until further use. Genomic DNA was isolated using a QiaAmp DNA blood mini kit according to the manufacturer's instructions (Qiagen, Hilden, Germany). DNA was eluted into 100 µl of water. Mutation locations in chromosome 11q13 for gene UNC-93B1 were amplified in two independent reactions using 2.5 µl of extracted DNA. The specific primers used for 1034del4 were forward 5'-GGAGGGGGATATTT

GGGATA-3' and reverse 5'-CAAGTAATGGGTTCGCAGGT-3', and for 781G>A forward 5'-GGCTGGGTCAGATGTCCTAA-3' and reverse 5'-CCAGCTGCCCATGAT TTATT-3'. PCR was performed by using 2.5 units of AmpliTaq Gold polymerase enzyme (Applied Biosystems, Foster City, CA, USA), 1× buffer, 2 mM $MgCl_2$, 0.25 mM dNTP mix (Finnzymes, Espoo, Finland), 0.6 μM each of primers (purchased from Sigma-Proligo, Paris, France), and 5% DMSO. PCR-products were purified by QIAquick Gel Extraction Kit (Qiagen) and sequenced.

Statistical analysis

In **Study I**, statistical analyses were performed using SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA).

Repeatability for SFGS was assessed by calculating coefficient of repeatability (CR) and intraclass correlation coefficient (ICC) with 95% confidence intervals (CIs) for each doctor and for the composite score and each component (resting symmetry, voluntary movement, and synkinesis) separately. The within-patient standard deviation (σe) was estimated from the standard deviation (SD) of the difference between the second- and first-round scores (S2-S1): $\sigma e = SD/\sqrt{2}$. CR was then estimated as $CR = 2.83 \times \sigma e$. The ICC values were interpreted as follows: <0.40 poor, 0.40–0.75 fair to good, and >0.75 excellent repeatability (Fleiss 1986).

To indicate the degree of repeatability for H-B FGS, exact agreement percentage and weighted kappa coefficients were calculated for each doctor (Altman 1991). In weighted kappa, different weights were assigned to disagreements since a discrepancy of one category was considered to indicate less disagreement than a discrepancy of two categories, and a discrepancy of three categories to indicate even more disagreement. The kappa values were interpreted as follows: <0.20 poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1.00 very good agreement (Altman 1991).

Agreement between doctors for SFGS was assessed by calculating CR and ICC for the composite score and for each individual component. The first and second assessments were analyzed separately. The within-doctor SD (σe) was estimated by using the square root of the mean square error from one-way analysis of variance, with patient as the grouping factor (and doctor as the repeated factor). CR was then estimated as $CR = 2.83 \times \sigma e$. For H-B FGS, agreement was estimated by calculating overall agreement percentage and generalized kappa coefficients.

Student´s *t*-test was applied to compare repeatability and agreement estimates between the two observer groups.

In **Study IV**, Mann-Whitney *U*-test was used to calculate the significance of the median age difference.

RESULTS

Study I

Repeatability results (intrarater reliability) for composite score and the individual components of SFGS by CR are presented in Table 7. The mean composite score CR with observer groups combined was 16.97, indicating that with 95% probability 17 points would be the upper limit of a score difference between two random assessments for one patient. CR results have to be interpreted case by case; no available standard exists. On a scale from 0 to 100, 17 points is a good outcome (1/6 of the scale range), although not excellent. The mean CR for repeatability of resting symmetry was 1.62 points (~1/3 of scale range 0–4), a moderate or fair outcome; for voluntary movement 3.13 (~1/7 of scale range 5–25), an excellent outcome; and for synkinesis 3.47 (~1/5 of scale range 0–15), a good outcome. No statistical difference was present between the two groups of assessors, residents and specialists in any of the measurements: composite score (*t*-test, $P = 0.159$), resting symmetry ($P = 0.370$), voluntary movement ($P = 0.143$), and synkinesis ($P = 0.112$). The mean ICC representing the repeatability for composite score and the individual components of SFGS varied from 0.819 to 0.983, meaning excellent repeatability. Differences between assessor groups again were not significant: composite score (*t*-test, $P = 0.234$), resting symmetry ($P = 0.289$), voluntary movement ($P = 0.203$), and synkinesis ($P = 0.078$). In conclusion, the SFGS composite score repeatability varied from good to excellent and the individual components repeatability from moderate or fair to excellent depending on the statistical method used.

Table 7. *Repeatability results for Sunnybrook facial grading system composite score and individual components (scale range in parentheses) by coefficient of repeatability.*

Assessor		**Composite score** (0–100)	**Resting symmetry** (0–4)	**Voluntary movement** (5–25)	**Synkinesis** (0–15)
Residents	Mean	**15.01**	**1.53**	**2.81**	**2.96**
	Min	8.62	0.71	1.07	1.67
	Max	26.61	2.82	5.21	7.49
Specialists	Mean	**18.92**	**1.70**	**3.45**	**3.98**
	Min	10.30	1.28	2.33	1.04
	Max	36.59	2.38	6.32	7.29
Total	Mean	**16.97**	**1.62**	**3.13**	**3.47**

Residents (n=13) and specialists (n=13) graded eight patients twice.

To define repeatability for H-B FGS, the mean agreement percentage for identical assessments was 63% (Table 8). The difference between the two observer groups was not significant (P = 0.835). We consider this result fair. The weighted kappa coefficient was calculated for each doctor separately. Residents (n = 13) had a good weighted kappa in nine cases (69%) and a very good weighted kappa in four cases (31%). Specialists (n = 13) had a moderate weighted kappa in two cases (15%), a good weighted kappa in seven cases (54%), and a very good weighted kappa in four cases (31%). The mean weighted kappa for residents was 0.75 (good) and for specialists 0.71 (good) (Table 8). The difference between the observer groups was not statistically significant (P = 0.349). In conclusion, H-B FGS repeatability varied from fair to good depending on the statistical method used.

Table 8. *Repeatability results for House-Brackmann facial grading system by percentage of identical assessments for each doctor (Agreement %) and weighted kappa coefficient.*

Assessor		Agreement %	Weighted kappa
Residents	Mean	**63.46**	**0.75**
	Min	50.0	0.64
	Max	87.5	0.91
Specialists	Mean	**62.50**	**0.71**
	Min	50.0	0.49
	Max	75.0	0.85
Total	Mean	**63.0**	**0.73**

Residents (n=13) and specialists (n=13) graded eight patients twice.

To assess agreement between doctors (interrater reliability) for SFGS, the composite score CR was 23.90 in the first round and 22.90 in the second round. The agreement between doctors was slightly but not significantly better in the second round. The mean of 23.40 is about 1/4 of the scale range of 0–100, a moderate result. The composite scores are presented in Fig. 4. The agreement result for resting symmetry by CR was 1.88/1.94 (assessment round 1/round 2). The mean of 1.91 is more than 1/3 of the scale range of 0–4, a moderate or fair outcome. For voluntary movement, CR was 4.74/4.16; the mean of 4.45 is 1/5 of the scale range of 5–25, a good outcome. For synkinesis, CR was 5.32/4.96; the mean of 5.14 is approximately 1/3 of the scale range of 0–15, a moderate or fair outcome. The assessment round with a better outcome varied, but the results did not differ significantly. The ICC for the composite score was 0.997 (95% CI 0.992–1.000) in the first round and 0.997 (95% CI 0.993–1.000) in the second round. The agreement results for SFGS components by ICC varied from 0.980 to 0.997. All ICC results indicated excellent agreement. In conclusion, SFGS agreement for composite score varied from moderate to excellent and the individual components agreement from moderate or fair to excellent depending on the statistical method used.

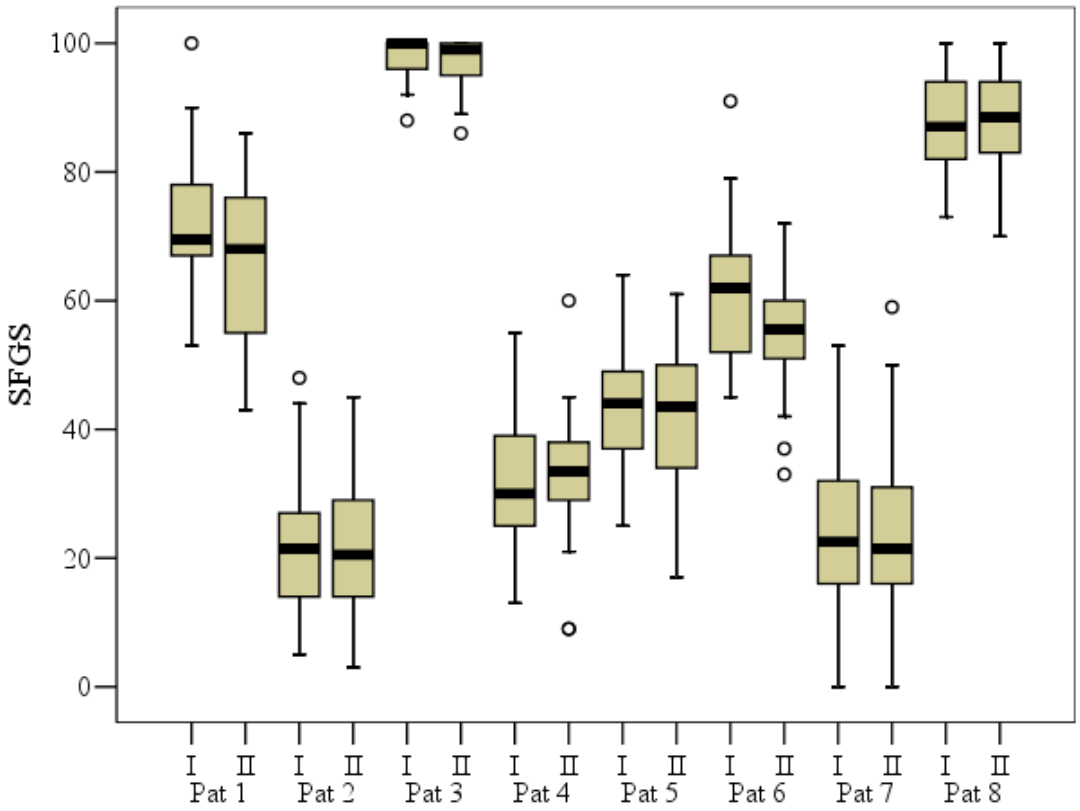


Figure 4. *Sunnybrook facial grading system (SFGS) composite scores for eight patients (Pat 1–8) assessed twice (I, II) by 26 doctors. The boxes indicate the lower and upper quartiles, and the central line is the median. The upper end of the bar is the maximum value, and the lower end the minimum value. Outliers are presented as open circles (o).* *(Reprinted with permission from Elsevier.)*

The distribution of H-B FGS grades in assessing agreement between doctors is shown in Table 9. The overall agreement percentage between doctors was 48% in the first round and 51% in the second round. We consider the mean overall agreement percentage of 50% a poor outcome. The generalized kappa coefficient of 0.34 (95% CI 0.32–0.36) in the first round and 0.37 (95% CI 0.34–0.40) in the second round of assessment indicated only fair agreement among the 28 and 26 doctors, respectively. Agreement was slightly but not significantly better in the second round. In conclusion, H-B FGS agreement varied from poor to fair depending on the statistical method used.

Table 9. *Distribution of House-Brackmann facial grading system (H-B FGS) grades (I–VI) for each of the eight patients by 28 assessors in the first assessment round and 26 assessors in the second assessment round.*

Patient	1st assessment H-B FGS grades							2nd assessment H-B FGS grades						
	I	II	III	IV	V	VI	Total	I	II	III	IV	V	VI	Total
1	1	18	9	0	0	0	28	0	12	14	0	0	0	26
2	0	0	8	14	6	0	28	0	0	3	11	12	0	26
3	23	5	0	0	0	0	28	23	3	0	0	0	0	26
4	0	1	8	9	10	0	28	0	0	3	15	8	0	26
5	0	0	6	19	3	0	28	0	0	2	18	6	0	26
6	0	11	16	1	0	0	28	0	4	16	6	0	0	26
7	0	0	4	8	16	0	28	0	0	0	8	17	1	26
8	7	21	0	0	0	0	28	7	18	1	0	0	0	26
Total	31	56	51	51	35	0	224	30	37	39	58	43	1	208

Studies II and III

Three patients and five controls revealed HHV-6 or -7 DNA in CSF (Table 10). HSV-1 or -2, VZV, or CMV DNA was not detected in CSF of any patient or control. Of the positive patient findings, one HHV-6 DNA was in Study II from a 58-year-old man who had FP with arthralgia (Table 10, patient 1). He had suffered poliomyelitis and tuberculosis as a child and his CSF albumin ratio and protein levels were slightly elevated. The CSF sample was taken 45 days from FP onset. The patient recovered totally in six months. In Study II, distinction between HHV-6 variants A and B was not possible. In Study III, a 13-year-old girl (Table 10, patient 2) with FP and no additional symptoms had HHV-7 DNA, and a woman (Table 10, patient 3) who had given birth two weeks prior to FP onset had simultaneous findings of HHV-6A and -6B DNA in CSF. In addition, four patients had results just under the true positive microarray cut-off level: one simultaneous HHV-6A and -6B DNA (Table 10, patient 4), two HHV-6B DNA (Table 10, patients 5 and 6), and one EBV DNA (Table 10, patient 7). One of the five control subjects with a positive DNA finding was a previously healthy 28-year-old woman with papillitis in one eye, mild vertigo, headache, and emesis (Table 10, control 1). Neuritis of the optic nerve was excluded. She was thoroughly examined without definite diagnosis. Her CSF revealed HHV-7 DNA. She recovered completely. Another control subject with sudden deafness had HHV-6A DNA detected in CSF (Table 10, control 2). She had elevated serum antibodies to *Borrelia burgdorferi* without CSF findings supporting the diagnosis of borreliosis. Her CSF albumin ratio was slightly elevated. One control subject with HHV-6B DNA finding was a seriously ill man with sepsis, cavernous sinus thrombosis, and FP (Table 10, control 3). His CSF albumin ratio was also elevated, indicating a possible blood-CSF barrier defect. The other two control subjects with HHV-6B DNA findings had vertigo and ear symptoms without borreliosis (Table 10, controls 4 and 5).

Table 10. *Characteristics and cerebrospinal fluid (CSF) findings of subjects with viral DNA in CSF (normal values in parentheses).*

Subject Age, years	**Symptoms, signs**	**DNA**	**Protein** mg/l	**WBC**[*] (0–3)	**RBC**[†] (0)	**Albumin ratio**[‡] (1.8–6.9)	**IgG index**[§] (≤0.6)
Patient 1 58	Facial palsy (FP)	HHV-6	**626** (150–450)	2	0	**9.09**	0.53
Patient 2 13	FP	HHV-7	285 (150–300)	**5**	**310**	Not available	0.49
Patient 3 33	FP, puerperium	HHV-6A & -6B	**748** (150–460)	**4**	1	**7.05**	0.40
Patient 4 32	FP	Faint HHV-6A & -6B	312 (150–450)	0	0	4.97	0.43
Patient 5 41	Ramsay Hunt syndrome	Faint HHV-6B	209 (150–450)	1	0	2.82	0.31
Patient 6 11	FP, herpes labialis	Faint HHV-6B	171 (150–300)	1	0	1.98	0.37
Patient 7 9	FP	Faint EBV	205 (150–300)	2	0	2.00	0.33
Control 1 28	Vertigo, headache, papillitis	HHV-7	307 (150–450)	1	0	4.74	0.38
Control 2 54	Sudden deafness, possible borreliosis	HHV-6A	**460** (150–450)	0	0	**8.96**	0.41
Control 3 41	Sinus cavernous thrombosis, FP, sepsis	HHV-6B	442 (150–450)	**95**	**17**	**9.72**	**0.61**
Control 4 8	Vertigo, ear symptoms	HHV-6B	237 (150–300)	0	0	2.96	0.34
Control 5 55	Vertigo, ear symptoms	HHV-6B	176 (150–450)	2	0	2.60	0.40

[*]Leukocyte count E6/l
[†]Erythrocyte count E6/l
[‡]Albumin ratio = CSF albumin/serum albumin
[§]IgG index = (CSF/serum IgG ratio)/(CSF/serum albumin ratio)

Study IV

The search for MRS revealed 35 patients; 29 with MRS, four with probable MRS, and two with possible MRS (Table 11). Patients at the Department of Dermatology all had labial or facial edema as a frequent or persistent symptom (Table 12). Samples of edematous tissues had revealed typical findings of MRS. Two of these patients also had FP and LP, thus, a complete form of MRS (Table 11, patients 1 and 2), all of the rest were monosymptomatic CG patients.

All 18 patients at the Department of Otorhinolaryngology had FP and 11 had LP (Tables 11 and 12, Fig. 5). The full triad of symptoms was found in nine patients (Table 11, patients 3, 5–12). MRS FP patient characteristics are shown in Table 11. Median age at symptom onset was 21.5 years in the FP group and 34 years in the CG group. The difference was not statistically significant (Mann-Whitney *U*-test, $P = 0.26$).

Of the 20 patients with FP, 17 answered the questionnaire and 14 were able to attend the clinical examination. Two of the FP patients at the Department of Dermatology with persistent labial edema had previously had a tissue biopsy taken showing typical nonnecrotizing granulomatous infiltrations (Table 11, patients 1 and 2). For several years, patient 3 (Table 11) had had in the upper lip short episodes of edema, which gradually became more persistent. He had visited the Department of Dermatology and tissue biopsies were taken without specific findings. The patient was sent to an otorhinolaryngologist who noted LP, discovered FP, and diagnosed MRS. New tissue biopsies were taken during an acute edema episode, revealing nonnecrotizing granulomatous infiltration. Another patient (Table 11, patient 4) had had edemas recurring in the right cheek for a year, resolving in 5–7 days. She was also seen with an acute edema episode, and a tissue sample was taken with edema clinically almost resolved. After sample-taking, the edema worsened for few days, but then subsided. The tissue sample revealed nonnecrotizing granulomas consisting of histiocytic cells and small lymphocytes. A sample taken from six other patients (Table 11) revealed no specific findings. A blood sample to search for UNC-93B1 gene mutations predisposing to HSV-1 infection was obtained from 13 patients (Table 11); no gene mutations were found.

In the FP group, three triad patients had constant facial edema and patient 1 (Table 11) had had cheiloplasty of the upper and lower lip. Even though most of the other FP patients had edema recorded in patient history (Table 12), it was not the dominating feature of the syndrome; it appeared seldom and was mostly moderate in nature. The first symptom of the syndrome in FP patients was FP in most cases. In the CG group, 12 of the 15 patients had persistent edema, which had developed over the years. The most common site of edema in both groups was the upper lip, but both lips and cheeks were also common, as was the tongue. Other sites included the neck, eyelids, and larynx, and one patient (Table 11, patient 1) had biopsy-proven vulvitis granulomatosa.

Two triad MRS patients were siblings (Table 11, patients 8 and 9), but other members in their family showed no signs of the syndrome. One triad MRS patient (Table 11, patient 7) had a father with FP, a mother with facial edemas, and siblings with LP. She was also a symptomless carrier of a gene mutation in chromosome 10q24 for an autosomal recessively inherited severe neurodegenerative disorder called infantile onset

spinocerebellar ataxia. One triad patient had a brother with FP (Table 11, patient 3), another triad patient had a sister and a grandfather with LP (Table 11, patient 2), and one patient had an uncle with FP (Table 11, patient 16). Two triad MRS patients had recurring anterior uveitis (Table 11, patients 1 and 5). Examinations did not reveal sarcoidosis or diseases other than MRS. Both patients were HLA-B27-negative. Migraine was found in 47% of the MRS FP patients answering the questionnaire.

Table 11. *Melkersson-Rosenthal syndrome (MRS) patients (n = 20) with facial palsy (FP).*

	Patients																			
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
MRS	Proven														Probable				Possible	
Gender	F	F	M	F	M	M	F	M	F	F	F	F	F	F	M	F	M	M	F	F
Age	50	37	59	47	36	39	60	41	40	36	74	34	48	54	36	47	72	44	59	67
Age at onset	22	10	39	12	24	21	23	31	21	21	48	15	13	47	20	43	20	44	12	67
Number of FP	1	2	1	1	2	2	3	1	2	2	3	4	4	2	3	2	3	1	4	1
Lingua plicata	●	●	●	–	●	●	●	●	●	●	●	●	–	–	–	◘	●	●	–	–
Facial edema	●	●	●	●	●	●	●	●	●	●	●	●	●	●	x1	x1	–	–	◘	●
Questionnaire	●	●	●	●	●	●	●	●	●	●			●	●	●	●	●		●	●
Examination	●	●	●	●	●	●	●	●	●				●		●	●			●	●
Mutations*	–	–		–	–	–	–	–	–				–		–	–			–	–
Histology +/–	+	+	+	+	–	–	–	–							–					–

F = female, M = male
● = yes, ◘ = mild symptom, – = no
*Leading to UNC-93B protein deficiency: – = mutations not found
Histology: + = nonnecrotizing granulomas, – = atypical finding

Table 12. *Frequency of symptoms in 35 Melkersson-Rosenthal syndrome patients in two specialty departments.*

Symptom	**Otorhinolaryngology** (n = 18) **Number of patients** (%)	**Dermatology** (n = 17) **Number of patients** (%)
Facial palsy	18 (100)	2 (12)
Triad of symptoms*	9 (50)	2 (12)
Edema	16 (89)	17 (100)
Lingua plicata (LP)	11 (61)	2 (12)
LP or moderately plicated tongue	12 (67)	5 (29)

*Facial palsy, lingua plicata, and edema

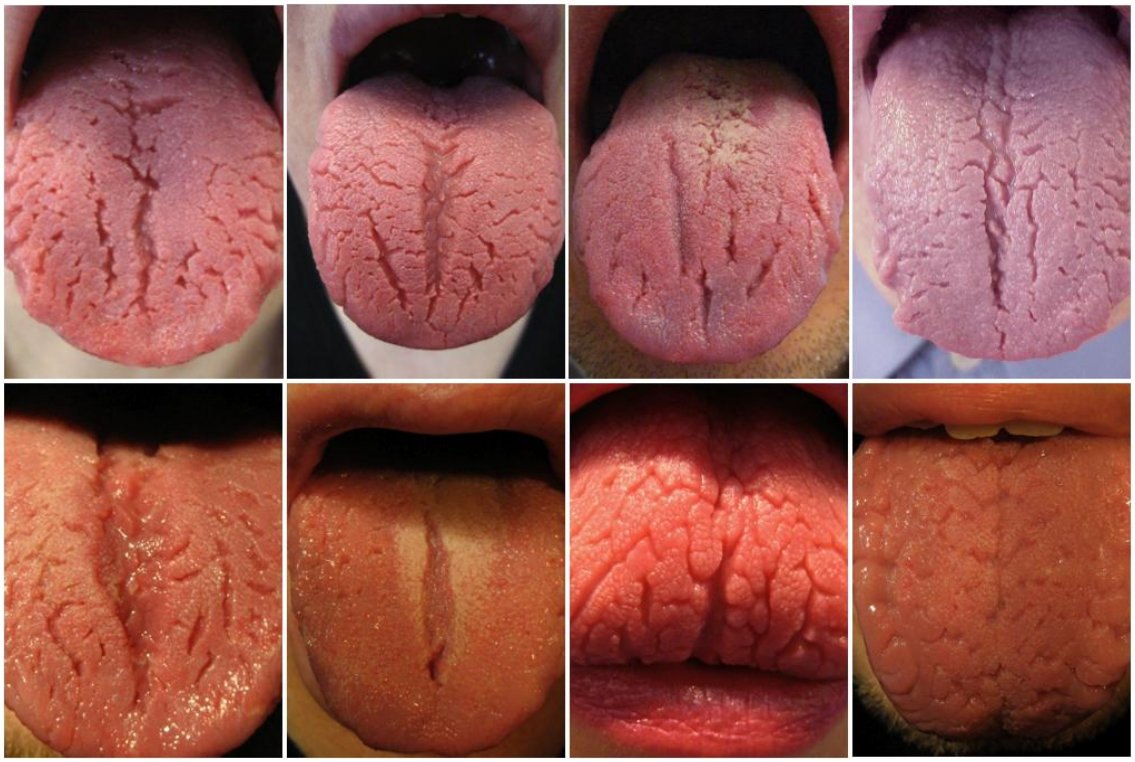


Figure 5. *Tongues of eight Melkersson-Rosenthal syndrome patients with lingua plicata.*

DISCUSSION

Grading

An objective evaluation method for everyday clinical use to grade facial function has not yet been developed or at least agreed upon. We assessed two subjective methods in Study I: H-B FGS because it is the method suggested for standard reporting of facial function by the Facial Nerve Disorders Committee of the AAO-HNS and SFGS because of its gaining popularity and the good reviews it has recently received. We discovered that the statistical method used to evaluate SFGS repeatability and agreement had a marked effect on study outcome; ICC, previously almost exclusively used to assess SFGS, gave excellent results in every measurement, whereas CR, suggested to be more reliable by Altman and Bland (1983), was not as flattering. Still our results showed that SFGS reliability was at least as good as H-B FGS reliability, and agreement for SFGS was better than that for H-B FGS. We concluded that while waiting for an ideal facial grading method, the usage of SFGS over H-B FGS should be encouraged.

Although H-B FGS has a standard grading scale status, studies on its repeatability are few. Repeatability of H-B FGS was previously found to be moderate (Ahrens et al. 1999), with unweighted kappa (considered a more appropriate statistical method than weighted kappa based on the material studied). Our results varied according to the statistical method used and were from fair (agreement %) to good (weighted kappa). Since weighted kappa usually gives better results than unweighted kappa, our results are in accordance with the earlier finding. Studies estimating agreement for H-B FGS have been more frequent although the number of studies is still rather low and the results vary. Our findings were in accordance with the poor or fair agreement results described in several studies (Croxson et al. 1990, Murty et al. 1994, Ahrens et al. 1999) and supported the view that H-B FGS is prone to interobserver variation. Others report reasonably good agreement results, but have reservations about H-B FGS as an international standard scale because of wide variations among expert assessors (Smith et al. 1992, Rickenmann et al. 1997, Coulson et al. 2005). One study (Evans et al. 1989) found agreement of H-B FGS to be very good, presenting no drawbacks in their discussion.

Previous studies on SFGS repeatability have used ICC, and their results for composite score are excellent (Ross and Nedzelski 1997, Ahrens et al. 1999, Hu et al. 2001), as was our result by ICC. When we used CR, the result was still good, but not near-perfect as with ICC. Agreement between doctors for SFGS composite score in earlier studies has also been found to be excellent (Ross and Nedzelski 1997, Ahrens et al. 1999, Kayhan et al. 2000, Hu et al. 2001), consistent with our result by ICC. However, with CR, our result was only moderate. No previous studies using CR were found.

When testing SFGS individual components, Kayhan et al. (2000) reported voluntary movement agreement to be very good, and resting symmetry and synkinesis agreement to be good (method used was kappa statistics, which is described as being equivalent to ICC, kappa statistics interpretation used). Coulson et al. (2005) reported agreement for voluntary movement to be from fair to good, but agreement for synkinesis as only poor by ICC. In our study, with ICC, all agreement results for individual components were

excellent. With CR, the voluntary movement result was good, but resting symmetry and synkinesis results were only moderate or fair. These findings indicate that individual components of resting symmetry and synkinesis are difficult for assessors to define. This is further supported by our repeatability CR result for individual components, where voluntary movement and synkinesis received good results, but resting symmetry only moderate results; thus, it was difficult for the assessor to even agree with him/herself in resting symmetry grading. No other study defining repeatability of SFGS individual components was found. Doctors may be more prone to define the severity of FP from voluntary movements, while synkinesis and resting symmetry are paid less attention. Using H-B FGS, this is possible. With SFGS, the severity of synkinesis and the resting symmetry appearance must be described in detail. Most of our resident assessors had used SFGS for about 1.5 years before this study, whereas most of our specialists were unfamiliar with SFGS, having more experience with FP patients and H-B FGS. With beforehand preparations (SFGS teaching video, booklet outlining grading scales and synkinesis), however, no statistical difference was present between our assessor groups. SFGS has previously been reported to be used as reliably by both experts and novice users (Hu et al. 2001). Our novice users were the specialists. Our agreement results of the individual SFGS components were probably better than in the two forementioned studies (Kayhan et al. 2000, Coulson et al. 2005) because ICC was excellent and only CR showed a less than perfect outcome. This could be a result of the beforehand preparations, indicating that even a brief introduction is helpful in achieving more reliable findings.

Our patient number was small (n = 8), which is a weakness of the study, but this was a deliberate choice to obtain as many assessors as possible. It took about 30 minutes in each round to assess these eight patients, and we thought that increasing the assessment time would diminish the number of voluntary assessors. We had 28 assessors, which is more than in any previous study (maximum eight). We tried to simulate a clinical setting; in our hospital, all doctors come into contact with FP patients and need to define the grade of FP, not only the doctors primarily involved with these patients. A good grading scale should work reliably whether the user needs it once or twice a year (general practitioners) or daily (FP investigators).

In the current situation with no unambiguous way of expressing the facial appearance and function with one standard method worldwide, comparing one study with another or one method of treatment with another gives only approximate results, the accuracy of which remains uncertain. Because normal facial function is already quite variable within individuals, a reliable grading system is hard to develop. The first clinically affordable and usable objective methods will likely have cameras and computers at a fixed location and clinicians can order a “facial grading test”, similar to the current request for audiometry. While this would be a giant step from today’s clinical reality, it would not solve the everyday, ubiquitous need to grade facial appearance and function. SFGS is an easy-to-use scale with good reviews and suggestions for improvements, as discussed earlier; it is a promising tool, while waiting for a simple, affordable, and portable objective system.

Etiology

While herpesviruses are suspected etiologic factors in Bell' palsy, confirmation remains elusive. With the decreasing popularity of decompression surgery as a treatment method, there are less studies trying to find signs of viruses directly in the facial nerve. Bell's palsy is peripheral in nature, but some studies have raised suspicion of CNS involvement, at least in some cases (Roberg et al. 1991, Adour 2002). Some investigators perform decompression surgeries proximal to the geniculate ganglion in selected Bell's palsy cases and simultaneously acknowledge reactivation of herpesviruses in the geniculate ganglion as the etiologic factor (Gantz et al. 1999). This supports the view of concurrent retrograde affision of the facial nerve towards CNS. We found no signs of DNA of HSV-1 or VZV, the two most suspected etiologic factors for Bell's palsy. Instead HHV-6 and -7 DNA were observed in CSF of both FP patients and controls.

Studies on CSF findings of peripheral FP patients are scarce. In most studies preceding the use of PCR, the outcome was inconclusive and abnormalities included pleocytosis and previously undiagnosed borreliosis (Jonsson et al. 1990, Hydén et al. 1993, Inci et al. 1999, Kohler et al. 1999, Birkmann et al. 2001). Later with PCR, VZV DNA has been found in CSF of Ramsay Hunt syndrome patients (Murakami et al. 1998, Stjernquist-Desatnik et al. 2006). Because all patients did not show VZV DNA, the hypothesis was tendered that VZV genomes disappear during the early stages of the disease (Murakami et al. 1998). Studies searching for HSV-1 and -2, VZV, EBV, and CMV DNA in CSF of Bell's palsy patients have not succeeded in finding any DNA of these viruses, even when samples have been taken soon after palsy onset (Larsson et al. 1998, Stjernquist-Desatnik et al. 2006). Many of the CSF samples had elevated white blood cell counts or protein levels as an indicator of inflammatory activity (Stjernquist-Desatnik et al. 2006) and intrathecal antibodies showing a longer duration of the infection than indicated by symptoms (Larsson et al. 1998). In FP, the infection was concluded to be transient and essentially terminated by the onset of symptoms (Larsson et al. 1998).

Most CSF studies on HHV-6 and -7 involve immunocompromised patients or small children. CSF studies on other patients, particularly FP patients, are scarce. These viruses have rarely been found in the CSF of immunocompetent and noncritically ill patients, especially adults. Previously, HHV-6 DNA was searched for and found in CSF of three multiple sclerosis patients, but specimens from FP patients (n = 19), Guillain-Barré syndrome patients, and controls were negative (Wilborn et al. 1994). In Study II, we identified one FP patient with HHV-6 DNA. His CSF albumin ratio and protein level were increased, thus whether the virus DNA originated from the CNS is uncertain. If he had a blood-CSF barrier defect, it could have been a constant feature because of the poliomyelitis he had suffered as a child. This patient was later tested again by microarray (III), and the sample no longer yielded a positive HHV-6 DNA result. The reason for this discrepancy can only be speculated, but it may arise from a technical failure: the sample had already gone through several freezing and thawing cycles when tested in Study III. HHV-7 DNA has previously been found in CSF of one Bell's palsy patient, a 6-year-old girl without any additional symptoms (Pohl-Koppe et al. 2001). Our patient with HHV-7 DNA finding was a teenager, beyond the age at which primary infection generally occurs. Whether she was undergoing an exceptionally late primary

infection or a reactivation of HHV-7 is unknown. One of our patients had a dual detection of HHV-6A and -6B DNA in CSF. We found no other reports of dual detection of these viruses in CSF.

Previously, HHV-7 DNA has been found in adult CSF in three cases, none of them FP (Sgarabotto et al. 2000, Ward et al. 2002, Mihara et al. 2005). These patients had severe CNS symptoms, whereas our control subject with HHV-7 DNA had only mild symptoms. She showed no indication of a blood-CSF barrier defect, so HHV-7 presumably came from the CNS. Whether the virus was an etiologic factor in her symptoms remains unknown.

HHV-6 reactivation has been detected in critically ill but otherwise immunocompetent patients and during infections with other viruses (Ward 2005). One of our controls had severe infections, and possibly a reactivation of HHV-6B. Our control subject with sudden deafness could have had reactivation of HHV-6A because of underlying suspected borreliosis. Rising antibody titers to HHV-6 in some sudden deafness patients have been reported previously (Takasaki et al. 1998), and thus, an association is possible. Two of our control subjects with vertigo and ear symptoms had HHV-6B DNA in CSF, but no similar literature reports were found. The youngest subject with HHV-6 DNA in CSF was 8 years old, the others were adults. Therefore, the results are not explained by transient CSF DNA findings associated with primary infections (Ward et al. 2007).

Our positive HHV-6 DNA results may be argued to arise from chromosomal viral integration. Because the studies were retrospective, we could not test whole blood or serum for viral DNA to compare the results. However, our positive findings for HHV-6 DNA exceeded considerably the assumed integration prevalence in the general population (7% vs. ~1%) (Ward et al. 2007). Furthermore, we found DNA of HHV-7, which is not known to be able to integrate in chromosomes. A total of 10% of the tested samples contained HHV-6 or -7 DNA.

In addition to the retrospective nature of our etiology studies (II, III), they were limited by the late timing of part of the CSF samples, and the young age of many of our study group patients. Limitations of our methods included an inability to differentiate active disease from inactive disease and our PCR method was not able to measure the DNA load. Strengths included the numerous CSF samples of FP patients and the very sensitive microarray method: the detection limit was less than 10 copies or virus particles. Although we could not determine the significance of HHV-6 and -7 DNA in CSF of FP patients or controls, we showed more frequent appearance of the DNAs in immunocompetent patients than could be expected. Most FP patients in our study had no herpesviral DNA in CSF, and this could be interpreted to speak against CNS involvement in peripheral FP. However, finding HHV-7 and dual HHV-6A and -6B DNA in CSF of FP patients is intriguing because DNA of these viruses is seldom found in CSF.

In our clinical practice, CSF samples to exclude CNS infections are taken from all children with FP. Blood samples to search for signs of infections are also frequently tested in children. This accelerates the possibility of finding associations of FP with other diseases, especially viral infections, among pediatric FP patients. Adults with

classical monosymptomatic Bell's palsy rarely get tested beyond exclusion of borreliosis by serology. Prospective CSF studies are difficult to arrange in uncomplicated adult FP patients. More thorough testing of adults, both serum and CSF, would probably yield associations with other diseases, perhaps shedding light on the path to solving the mystery of FP etiology and, in doing so, also the proper management for the disease.

Melkersson-Rosenthal syndrome

As a rare disorder of unknown etiology, undefined incidence, and inconsistent definition and classification, the diagnosis of MRS is based on the alertness of the physician. We studied 35 patients with MRS or suspicion of it at the Departments of Dermatology and Otorhinolaryngology and found that the clinical picture of the disease varied greatly according to the department specialty where the patient was treated. All patients at the Department of Otorhinolaryngology (n = 18) had FP in patient history, whereas only two at the Department of Dermatology did, with the remaining 15 patients having monosymptomatic CG. These results support our hypothesis that the existing knowledge on MRS might be influenced by most published studies being from the departments of dermatology and oral and plastic surgery dealing with MRS patients troubled by edemas. Studies from departments of otorhinolaryngology are rare, and patients with FP the clear minority. Monosymptomatic CG patients have received the most attention in the literature.

MRS affects all age groups, but the most common time of onset is often stated to be the second decade of life or young adulthood. From studies with more than a few patients, the (median or mean) onset age is higher, 25–40 years (Rintala et al. 1973, Worsaae et al. 1982, Hornstein et al. 1987, Greene and Rogers 1989, Zimmer et al. 1992), consistent with our age median of 24 years. We had twice the number of females compared with males in our study; the gender ratio has varied markedly in previous studies (Rintala et al. 1973, Worsaae et al. 1982, Hornstein et al. 1987, Zimmer et al. 1992).

In the literature, the most common initial symptom is edema (Rintala et al. 1973, Worsaae et al. 1982, Hornstein et al. 1987, Zimmer et al. 1992), and the same was true in our study when considering patients from both departments. Among patients with FP, the most common initial symptom was FP, which has also been reported previously (Greene and Rogers 1989). The most common site for edema is the upper lip both in the literature (Rintala et al. 1973, Worsaae et al. 1982, Hornstein et al. 1987, Zimmer et al. 1992) and in our study. Edema is considered to be the most frequent and dominating feature, eventually affecting almost all MRS patients and gradually becoming persistent (Hornstein et al. 1987, Greene and Rogers 1989). This was the case with our patients at the Department of Dermatology, but even though most of the patients at the Department of Otorhinolaryngology had edema in patient history, it tended to be moderate in severity, appeared seldom, and no signs of progression were seen. FP episodes in MRS have also been postulated to gradually last longer or become permanent (Zimmer et al. 1992). In our patients, the palsies did not last longer, nor did they come permanent, although more then half of the examined patients had residual symptoms from FP.

FP is estimated to appear in 20–30(–50)% of all MRS cases, and the triad form in up to 20% of cases (Hornstein 1973, Rintala et al. 1973, Worsaae et al. 1982, Hornstein et al. 1987, Zimmer et al. 1992, van der Waal et al. 2002). In our study, with both departments combined, FP was present in over half of the patients and the triad form in one-third of all cases, which is higher than in previous reports. If we consider only the patients treated at the Department of Otorhinolaryngology, every patient had FP and half had the triad form. This supports our hypothesis that the existing knowledge on the clinical picture of MRS may be influenced by most published studies being from departments treating patients with edemas. In our study, with both departments combined, one-third of patients had LP. This is less than the reported average of about half of MRS patients having LP (Rintala et al. 1973, Worsaae et al. 1982, Hornstein et al. 1987, Zimmer et al. 1992). Most patients at the Department of Dermatology being monosymptomatic CG patients and mildly fissured tongues not being included in the count explains our low LP incidence.

MRS is sometimes associated with herpes infection type blisters at the beginning of edema (Hornstein 1973, Worsaae et al. 1982, Ziem et al. 2000), and two of our patients reported reappearing blisters on the tongue. Herpesvirus etiology has been suggested in MRS as well as in Bell's palsy (Ziem et al. 2000). We searched for single-gene mutations that would lead to UNC-93B protein deficiency and susceptibility to HSV-1 infection, but detected no signs of this. These mutations have been described in otherwise healthy children with HSV-1 encephalitis (Casrouge et al. 2006). None of our patients had serious infections recorded in their patient histories.

Typical MRS histology shows nonnecrotizing lymphoepitheloid granulomatous infiltrations, which may also be replaced by small lymphoplasmocytic clusters or mononuclear infiltrates surrounding small vessels (Hornstein 1997). In our study, patients at the Department of Dermatology all had histology-proven CG (n = 15) or MRS (n = 2). One MRS FP patient with slight persistent upper lip edema had unspecific previous biopsy results, but a new sample taken during an acute edema episode revealed nonnecrotizing granulomas. If edema is already persistent, repeated biopsies are recommended because negative histology findings in typical clinical MRS are common (Zimmer et al. 1992). It has been speculated that granulomatous infiltrations can only develop in advanced disease with persistent edema (Greene and Rogers 1989). Another MRS FP patient had recurring edemas, not persistent, of the cheek for only one year, but revealed nonnecrotizing granulomas in a tissue sample taken during an acute edema episode. Typically, edema periods had lasted 5–7 days and edema was almost resolved on the sixth day when the biopsy was taken. New activation of the edema was observed following the biopsy for three days, but resolved again. Tissue samples taken from six other patients without persistent edema were unspecific. These results encourage timing biopsies to acute edema periods. Most of the MRS patients at the Department of Otorhinolaryngology had mild edema symptoms, attacks were far apart, and the patients had never visited a doctor because of their edema. Emphasizing the importance of edema in MRS diagnosis (Hornstein 1997) might underestimate the number and forms of MRS patients treated at otorhinolaryngology departments.

Two of our patients had reappearing acute anterior uveitis, and one earlier report was found of the association (Ates and Yoruk 2006). This could be due to immunologic or

autoimmune disturbances considered among possible etiologic factors in MRS (Hornstein 1997). In our study, migraine was common among MRS FP patients, as also demonstrated previously (Hornstein et al. 1987), but incidences comparable with those of the general population exist as well (Vistnes and Kernahan 1971, Greene and Rogers 1989). Two of our triad patients were siblings and four other FP MRS patients had a relative with FP or LP. This is in accordance with the knowledge of a somewhat increased risk of MRS in relatives, especially first-degree relatives (Meisel-Stosiek et al. 1990). One of our patients was a gene mutation carrier (chromosome 10q24) for infantile onset spinocerebellar ataxia. One previous publication with an MRS patient as a carrier of balanced de novo 9p/21p translocation and her child with unbalanced 9p trisomy (without MRS symptoms) has been published with the conclusion that MRS has autosomal dominant inheritance with variable expression and gene 9p11 could be the location (Smeets et al. 1994). We consider these mutations coincidental.

In our study, we probably missed some MRS patients. At the Department of Dermatology, only histology-proven cases were coded under MRS and were found by computer search. At the Department of Otorhinolaryngology, MRS diagnosis is not easy because symptoms most often appear at different times and far apart from each other. If an FP patient presents with a deeply grooved LP, the connection to MRS is made easier. Since only half of the MRS patients have LP, many MRS patients probably have not been diagnosed, especially if their edemas are mild and appear seldom. Every FP patient should be asked about oro-facial edemas, especially if FP has reoccurred. Although treatments of MRS are often unsatisfactory, patients are usually relieved to get a diagnosis, tying the odd separate symptoms together. A broader view of the clinical picture, the true incidence, and perhaps data enabling the etiology of MRS to be solved could potentially emerge from the accumulation of information from different specialties. At otorhinolaryngology departments, probably more MRS patients with FP are met than in other specialties treating MRS patients. Studies on this patient group are scarce.

CONCLUSIONS

1. SFGS proved to be at least as good as, if not better than, H-B FGS in repeatability and was more reliable in agreement. The usage of SFGS can thus be recommended over H-B FGS.

2. HHV-7 and dual HHV-6A and -6B DNA, rare findings in any patient, were found in CSF of FP patients. Since DNA of HHV-6A, -6B, and -7 was also found in CSF of control subjects, the significance of the results in association with the diseases they accompany was not established. The abundant finding of HHV-6 or -7 DNA in the CSF of about 10% of evaluated immunocompetent adolescents and adults without severe diseases was markedly higher than expected, suggesting caution when interpreting CSF findings. No CSF of patients or controls had DNA of HSV-1 or VZV, the most suspected etiologic factors for Bell's palsy.

3. The clinical picture of MRS varied according to department specialty; every MRS patient at the Department of Otorhinolaryngology had FP, and edema was mostly not progressive and did not dominate the clinical picture, contrary to existing knowledge and to those patients treated at the Department of Dermatology. Among MRS patients with FP, the triad form of MRS was very common. Our findings support taking tissue biopsies during acute edema episodes to reveal nonnecrotizing granulomatous infiltrations. We found no UNC-93B1 gene mutations predisposing to HSV-1 infections. Two triad MRS patients had recurring acute anterior uveitis; an association warranting further investigations.

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Appendix. Primers used for multiplex-PCR1, multiplex-PCR2, and oligonucleotides on microarray (Study III).

Genus,GenBank accession No.	Oligonucleotides	Gene name	Sequences (5'→ 3')	Position
HSV-1, X14112	HSV-FW	DNA pol.	AAGGAGGCGCCCAAGCGCCCG	64750–64768
	HSV-RV		AATTAACCCTCACTAAAGGGAGA TGGGGTACAGGCTGGCAAAGT	64976–64956
	HSV-1-T3		Am-TTTTTTTTTGTCCTTGACCCCACTT	64907–64922
HSV-2, Z86099	HSV-FW	DNA pol., UL30	AAGGAGGCGCCCAAGCGCCCG	65209–65229
	HSV-RV		AATTAACCCTCACTAAAGGGAGA TGGGGTACAGGCTGGCAAAGT	65449–65429
	HSV-2-T3		Am-TTTTTTTTTAGGATAAGGACGACGAC	65279–65295
VZV, AY548171	VZV-FW	DNA pol., ORF28	CCATTTTCTCGCCGATTTTA	48508–48527
	VZV-RV		AATTAACCCTCACTAAAGGGAGA GCCGCATTTGAACGTTTTAT	48670–48651
	VZV-T3		Am-TTTTTTTTTACCTCGTACGCTTTTTG	48597–48613
CMV, AY446894	CMV-FW	DNA pol., UL44	GTACAACAGCGTGTCGTGCT	57044–57063
	CMV-RV		AATTAACCCTCACTAAAGGGAGA CACCGGCCATCAAGTTTATC	57240–57221
	CMV-T3		Am-TTTTTTTTTGTAGAAGTTCTTCAGCTGC	57122–57140
EBV, AJ507799	EBV-FW	DNA pol., BALF5	CGTAGATGACTCGAAGCTG	154029–154047
	EBV-RV		AATTAACCCTCACTAAAGGGAGA ACCATCCTCGACAAGCAG	154278–154261
	EBV-T3		Am-TTTTTTTTTGAGAGGCAGGGAAAGAGG	154184–154201
HHV-6A, X83413	HHV-6-FW	DNA pol., U38	CTCGATCGAATCCGTAAACA	59289–59308
	HHV-6-RV		AATTAACCCTCACTAAAGGGAGA CCGCGTATGTTTTATCGAGAC	59444–59424
	HHV-6A-T3		Am-TTTTTTTTTATCCTTGGACCGAGCTA	59361–59377
HHV-6B, AF157706	HHV-6-FW	DNA pol., U38	CTCGATCGAATCCGTAAACA	60409–60428
	HHV-6-RV		AATTAACCCTCACTAAAGGGAGA CCGCGTATGTTTTATCGAGAC	60564–60544
	HHV-6B-T3		Am-TTTTTTTTTATCCTTGGACCGAACTC	60481–60497
HHV-7, AF037218	HHV-7-FW	DNA pol., U38	AGGTCCAACATGCACAGTGA	56787–56806
	HHV-7-RV		AATTAACCCTCACTAAAGGGAGA GGCAAAGAAAATGTGGGCTA	56993–56974
	HHV-7-T3		Am-TTTTTTTTTGGATACAAACTTTGGAA	56893–56909

FW, forward primer (sense); RV, reverse primer (anti-sense, T3 RNA polymerase promoter sequence AATTAACCCTCACTAAAGGGAGA before virus sequence); T3, oligonucleotide (sense, 9×T spacer arm before sequence); Am, amino-link.