Viral infections of the CNS with special emphasis on herpes simplex infections

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Introduction

Both DNA viruses and RNA viruses are able to cause neurological disease, including meningitis, encephalitis, meningoencephalitis, myelitis, cranial neuritis, radiculitis and neuritis, potentially involving the entire range of neurological anatomical sites [26, 52, 64].

Table 1 lists the families, genera and main species of DNA viruses causing human neurological disease. Table 2 comprises the RNA viruses being of relevance in human diseases.

Thanks to recent developments in recognising certain viruses as the causative agents of neurological diseases and because these are viral diseases that can be treated successfully by antiviral agents if recognised sufficiently early, this review will mainly concentrate on diseases caused by the family Herpesviridae detailing herpes simplex virus I encephalitis, neonatal infection with herpes simplex virus II, varicella zoster infection of the central nervous system, and it will offer new insights into the role of Herpesviridae in Mollaret's meningitis as well as idiopathic facial palsy (Bell's palsy).

Herpes simplex virus I encephalitis

Epidemiology

Herpes simplex virus I encephalitis (HSVE) is estimated to occur in approximately 2–4/1,000,000 individuals/year, it is the most common sporadic fatal CNS viral infection in western countries and manifests throughout the year in patients of all ages. There is a bimodal age

Abstract Within the past decade the management of acute HSV I encephalitis has been improved dramatically by the advent of the polymerase chain reaction (PCR), a method which has become the gold standard of diagnosis of HSV I encephalitis, replacing diagnostic uncertainties and, avoiding, in particular, invasive brain biopsy.

Early detection of HSV II in the neonate is mandatory; however, prevention by Caesarean section and/or prenatal therapy of the mother are for this the best option.

Very recently the causative agent of Mollaret's meningitis has proved to be, at least in part, HSV I or II. So far prospective randomized therapeutic trials are awaited for the treatment of Mollaret's meningitis using intravenous acyclovir or the more modern oral forms of virostatics (famciclovir, valaciclovir). For decades the causative agent of facial palsy (Bell’s palsy) has been sought; only with the advent of PCR has this question been answered. Although one single study indicates the superiority of a combination of acyclovir plus prednisonone, this finding has to be confirmed by a large scale prospective randomised double blind study. Nevertheless, if other causes for the clinical/neurological syndrome of peripheral facial palsy have been excluded, a combination therapy with acyclovir plus prednisonone seems to be indicated in a patient with Bell’s palsy.

Key words Viral encephalitis · Herpesviridae
distribution; more than 80% of cases develop in patients less than 20 or greater than 50 years of age. Both sexes are affected equally [26, 52, 64].

**Aetiology**

HSVE develops when herpes simplex virus I infects brain tissue in a lytic/necrotic manner [57]. Although both primary and recurrent HSV infections may lead to encephalitis, most HSVE cases in adults are due to reactivation of latent viruses [26, 52]. Primary HSVE occurs mostly in children.

**Pathogen**

Primary HSVE I infections are mainly gingivostomatitis, rarely corneal or genital lesions. The virus travels by retrograde axonal transport to the neuronal cell body and establishes a latent infection that usually persists for the life of the host. Trigeminal sensory ganglia are well-known sites of HSV I latency [52, 64]. However, viral DNA has been found within other parts of the CNS in 34% of those dying of non-neurological diseases, suggesting that the brain itself may sometimes be a site of HSV I latency [6]. Recurrent cutaneous herpetic diseases (in HSV I mostly herpes labials, also herpetic keratitis) result when HSV I is reactivated from latency to a replicative stage. Many different events are known to

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### Tab. 1 DNA-Viruses

| Family         | Genus                      | Species, relevant in human medicine                                      | Size   | nm |
|----------------|----------------------------|---------------------------------------------------------------------------|--------|----|
| Poxviridae     | Orthopoxivirus             | Varicella virus, vaccinia virus, cowpox virus                              | 200–300|    |
|                | Simplexvirus               | Herpes simplex virus, type 1                                             | 120–200|    |
|                | Varicella-zoster virus     | Cytomegalovirus, Human cytomegalovirus, Epstein-Barr virus, Roseolovirus | 70–90  |    |
|                |                            | Varicella zoster virus, type 1                                           | 45–55  |    |
|                |                            | Papovaiviridae, Human adenovirus, types 1–49                            | 40–48  |    |
|                |                            | Parvoviridae, Erythrovirus, Human parovirus B 19                        | 18–26  |    |

### Tab. 2 RNA-Viruses

| Family           | Genus                      | Species, relevant in human medicine                                      | Size   | nm |
|------------------|----------------------------|---------------------------------------------------------------------------|--------|----|
| Paramyxoviridae  | Paramyxovirus              | Human parainfluenza viruses 1 and 3                                     | 150–300|    |
|                  | Rubulavirus                | Mumps virus, Human parainfluenza viruses 2 and 4                        | 70–85  |    |
|                  | Morbillivirus              | Measles virus, Pneumovirus, Human respiratory syncytial virus            | 80–120 |    |
|                  | Orthomyxoviridae           | 80–120                                                                   |        |    |
|                  | Influenzavirus             | Influenza viruses A, B, and C                                            |        |    |
|                  | Rhadoviridae               | Lyssaviruses, Rabies virus, Vesiculovirus, Vesicular stomatitis virus    |        |    |
|                  | Filoviridae                | Ebola virus, Marburg virus, Bunyaviridae                                | 80 x 1000|    |
|                  | Bunyavirus                 | California encephalitis virus, La Crosse virus, Jamestown Canyon virus, Snowshoe hare virus, Tahyna virus, Influenza viruses, Rabies virus, Vesiculovirus, Vesicular stomatitis virus                   |
|                  |                           | 70–85                                                                   |        |    |
|                  |                           | x 180                                                                   |        |    |
|                  |                           | Rhabdovirus, Lyssavirus, Rabies virus                                    |        |    |
|                  |                           | Filovirus, Ebola virus, Marburg virus, Bunyaviridae                      | 88 x 120|    |
|                  |                           | California encephalitis virus, La Crosse virus, Jamestown Canyon virus, Snowshoe hare virus, Tahyna virus, Influenza viruses, Rabies virus, Vesiculovirus, Vesicular stomatitis virus                   |
|                  |                           | 80 x 1000                                                               |        |    |
|                  |                           | 70–85                                                                   |        |    |
|                  |                           | x 180                                                                   |        |    |
|                  |                           | Rhabdovirus, Lyssavirus, Rabies virus                                    |        |    |
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|                  |                           | California encephalitis virus, La Crosse virus, Jamestown Canyon virus, Snowshoe hare virus, Tahyna virus, Influenza viruses, Rabies virus, Vesiculovirus, Vesicular stomatitis virus                   |
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|                  |                           | x 180                                                                   |        |    |
|                  |                           | Rhabdovirus, Lyssavirus, Rabies virus                                    |        |    |
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|                  |                           | x 180                                                                   |        |    |
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|                  |                           | 80 x 1000                                                               |        |    |
|                  |                           | 70–85                                                                   |        |    |
|                  |                           | x 180                                                                   |        |    |
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|                  |                           | 80 x 1000                                                               |        |    |
|                  |                           | 70–85                                                                   |        |    |
|                  |                           | x 180                                                                   |        |    |
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|                  |                           | 80 x 1000                                                               |        |    |
|                  |                           | 70–85                                                                   |        |    |
|                  |                           | x 180                                                                   |        |    |
promote HSV I reactivation; none, however, has been epidemiologically clearly linked to the development of herpes simplex encephalitis. In most cases rami meningeales of the trigeminal ganglia or trigeminal nerve respectively lead the way of reactivated HSV I, causing temporo-polar, temporo-basal and/or fronto-basal invasion of the brain [26,52,64]. In primary infection or re-infection with HSV I, causing HSV I encephalitis, the olfactory route is usually the route of invasion, leading to an initially frontobasally accentuated encephalitis.

Clinical manifestation

It is accepted that HSV I encephalitis is one of the most severe human viral infections of the nervous system, although milder forms have been thought to occur. Table 3 lists the clinical signs and symptoms found in patients with a condition suggestive of HSV I encephalitis, divided into brain biopsy positive and brain biopsy negative patient groups [52,65].

Diagnosis

Since patients with HSV I encephalitis frequently show ongoing neurological deterioration and since alternative diagnoses include a number of other treatable conditions, an immediate diagnostic study is obligatory. The dramatic urgency of this is underlined by the fact that the only predictor of outcome in HSV I encephalitis which can be influenced is the level of consciousness at the time of initiation of therapy [52,64]. The first diagnostic examination is MRI (without and with i.v. contrast enhancement) mainly evaluating the temporobasal and frontobasal regions [29]. If MRI is not available CT must be done immediately. After determining the safety of lumbar puncture by imaging, CSF examination is the immediate next diagnostic step. The CSF cell count, protein, glucose and a negative Gram stain provide rapid confirmation of an inflammatory process suggesting vi-

| Family          | Size nm | Genus                         | Species, relevant in human medicine                                      |
|-----------------|---------|--------------------------------|------------------------------------------------------------------------------|
| Lentivirus      |         | Human immunodeficiency viruses I and II |
| Sputamivirus    |         | Human isolates (no known pathogens) |
| Coronaviridae   | 80–220  | Coronavirus                    | Several human serotypes                                                      |
| Reoviridae      | 60–80   | Orthoreovirus                  | Reoviruses 1–3                                                               |
|                 |         | Coltivirus                     | Clorado tick fever virus                                                     |
|                 |         | Rotavirus                      | Group A and B human rotoviruses                                              |
|                 |         |                              | Alphavirus                     | Eastern equine encephalitis virus                                            |
|                 |         |                              | Western equine encephalitis virus                                            |
|                 |         |                              | Venezuelan equine encephalitis virus                                         |
|                 |         | Rubivirus                      | Rubella virus                                                                |
|                 |         |                              | Flaviviridae                    | Flavivirus                     | St. Louis encephalitis virus                                                |
|                 |         |                              |                                 | Japanese encephalitis virus                                                 |
|                 |         |                              |                                 | Murray Valley encephalitis virus                                            |
|                 |         |                              |                                 | Tick borne encephalitis viruses                                             |
|                 |         |                              |                                 | Yellow fever virus                                                          |
|                 |         |                              |                                 | Dengue viruses                                                              |
|                 |         |                              |                                 | Pestivirus                                                                  |
|                 |         |                              |                                 | No human pathogens                                                          |
| Picornaviridae  | 28–30   | Enterovirus                    | Polioviruses 1–3                                                            |
|                 |         |                              | Coxsackie viruses A             | 1–22, A 24, B 1–6                                                          |
|                 |         |                              | Human echoviruses 1–7, 9, 11–27, 29–33                                      |
|                 |         |                              | Human enteroviruses 68–71                                                   |
| Cardiovirus     |         |                              | Encephalomyocarditis virus                                                  |
| Rhinovirus      |         |                              | Human rhinoviruses 1–100                                                    |
| Hepatovirus     |         |                              | Hepatitis A virus                                                           |
|                 |         | Flaviviridae                   | Flavivirus                     | St. Louis encephalitis virus                                                |
|                 |         |                              | Japanese encephalitis virus                                                 |
|                 |         |                              | Murray Valley encephalitis virus                                            |
|                 |         |                              | Tick borne encephalitis viruses                                             |
|                 |         |                              | Yellow fever virus                                                          |
|                 |         |                              | Dengue viruses                                                              |
|                 |         |                              | Pestivirus                                                                  |
|                 |         |                              | No human pathogens                                                          |
|                 |         |                              | Genus unnamed                                                               |
|                 |         |                              | Hepatitis C virus                                                           |

Tab. 2 contd.

Tab. 3 Comparison of clinical signs and symptoms in brain biopsy positive and negative HSV 1 encephalitis patients

| Prehospital signs and symptoms                      | brain biopsy positive patients (%) | brain biopsy negative patients (%) |
|------------------------------------------------------|-----------------------------------|-----------------------------------|
| Alteration of consciousness                         | 97                                | 96                                |
| CSF pleocytosis                                      | 97                                | 87                                |
| Fever                                                | 90                                | 78                                |
| Headache                                             | 81                                | 77                                |
| Personality change                                   | 71                                | 68                                |
| Seizures                                             | 67                                | 59                                |
| Vomiting                                             | 46                                | 46                                |
| Hemiparesis                                          | 33                                | 26                                |
| Memory loss                                           | 24                                | 19                                |
| Clinical findings at presentation                    |                                   |                                   |
| Fever                                                | 92                                | 81                                |
| Personality change                                   | 85                                | 74                                |
| Dysphasia                                            | 76                                | 67                                |
| Autonomic dysfunction                                | 80                                | 58                                |
| Ataxia                                               | 40                                | 40                                |
| Hemiparesis                                          | 38                                | 38                                |
| Seizures                                             | 38                                | 47                                |
| Focal                                                |                                   |                                   |
| Generalized                                          |                                   |                                   |
| Both                                                 |                                   |                                   |
| Cranial nerve defects                                | 32                                | 33                                |
| Visual field loss                                    | 14                                | 12                                |
| Papilledema                                          | 14                                | 11                                |
ral encephalitis [42]. Cultures for bacterial, fungal, mycobacterial and viral pathogens should be arranged, although viral culture is positive in less than 5% of patients with HSV I encephalitis. The identification of HSV I DNA in the CSF of patients with HSV I encephalitis by polymerase chain reaction (PCR) is the diagnostic standard technique, with a sensitivity of 98% and a specificity of at least 94%. Results of the PCR can be available within 6 to 8 hours. PCR has become the standard for diagnosing HSV I encephalitis [6, 27, 51, 68]. Brain biopsy has been replaced by the PCR, the former carrying a risk of 2–3% of serious morbidity [52, 64].

**Differential diagnosis**

Table 4 shows the most important differential diagnoses both treatable and non treatable, infectious and non infectious, diseases which can be mistaken for herpes encephalitis [65].

| Infections (treatable) | |
|-----------------------|---|
| Abscess/subdural empyema |  |
| Bacterial |  |
| Listerial |  |
| Fungal |  |
| Mycoplasmal |  |
| Tuberculosis |  |
| Cryptococcosis |  |
| Rickettsiosis |  |
| Mucormycosis |  |
| Meningococcal meningitis |  |
| Infections (nontreatable) |  |
| Viral |  |
| Togavirus infections |  |
| St. Louis encephalitis |  |
| Western equine encephalitis |  |
| Eastern equine encephalitis |  |
| California encephalitis |  |
| Other herpesviruses |  |
| Epstein-Barr virus |  |
| Others |  |
| Echoviruses |  |
| Influenza type A virus |  |
| Mumps virus |  |
| Adenoviruses |  |
| Progressive multifocal leukencephalopathy (PML) |  |
| Lymphocytic choriomeningitis |  |
| Subacute sclerosing panencephalitis (SSPE) |  |
| Non-infectious causes |  |
| Vascular disease |  |
| Toxic encephalopathy |  |
| Reye's syndrome |  |
| Tumor |  |
| Subdural haematoma |  |
| Systemic lupus erythematosus |  |
| Adrenal leukodystrophy |  |

**Management**

The management of the patient with suspected HSV I encephalitis parallels the diagnostic tests, immediate antiviral chemotherapy being mandatory. Given the appropriate, suggestive clinical setting acyclovir (Zovirax®) is promptly administered intravenously in a dose of 10–15 mg/kg bodyweight every 6–8 hours for a minimum of 10 (–14) days [26, 52, 64]. Toxicity is usually mild and not treatment-limiting; it includes thrombocytopenia, increased transaminases, creatinine, and BUN. In the rare case of acyclovir side effects or acyclovir resistance vidarabine (15 mg/kg bw/day) or foscarnet (230 mg/kg bw/day) can be given as antiviral alternatives [52, 64].

Supportive measures in the management of a patient with suspected HSV I encephalitis are extremely important, including early intubation for airway protection, mechanical ventilation and, if necessary, mild hyperventilation to a PCO2 of 30–35 mm Hg. If necessary osmodiuresis with 20% mannitol (0.25 g/kg i.v.) can be instituted. The administration of phenytoin is, even in the presence of seizures, in most cases not necessary, since patients undergoing intensive care therapy are treated with the appropriate, equally anticonvulsive sedation with benzodiazepines (e.g. midazolam or lorazepam). If intracranial pressure (ICP) continues to rise, evident either clinically (anisocoria, decortication- or decerebration pattern etc.) or by neuroimaging, ICP monitoring is mandatory; occasionally decompressive craniectomy can be life saving.

**Complications and prognosis**

After a full course of antiviral therapy, relapse of the infection has been documented in a few cases. Ongoing and deteriorating MRI findings have been reported, despite appropriate therapy [2, 38].

Although acyclovir therapy has led to a dramatically decreased mortality in HSV I encephalitis, it has resulted in survivors with varying degrees of neurological impairment. Both cognitive and behavioural disorders as well as seizure disorders are encountered [8, 23, 53].

Patient's age and level of consciousness at the onset of treatment are the primary determinants of outcome; improved survival is seen in patients younger than 30 years and with initial Glasgow coma score greater than 6 [52, 64]. Focal hyperperfusion of the involved brain regions evidenced by SPECT scanning seems to be another independent predictor of poor outcome in acute HSV I encephalitis patients [28].

Animal studies suggest a possible role of virion proteins for human vaccination [20]; their applicability in human medicine still awaits confirmation.
## Neonatal herpes simplex virus infection

Herpes simplex infection of the newborn is acquired in utero, intra partum or postnatally [4, 34, 60, 67]. The most common time of transmission of herpes simplex virus II (HSV II) infection from mother to the fetus occurs intra partum when the infant comes into contact with infected maternal genital secretions at delivery. This accounts for more than 80% of cases of neonatal HSV II infection [54, 67].

Children with disseminated infection present to medical attention after 8 to 11 days of life. However, signs of infections are usually present 4 to 5 days earlier. The principal organs involved in this disseminated HSV II infection are the liver, brain and adrenals. However, infection can involve the lungs, oesophagus, stomach, gastrointestinal tract, kidneys, heart, spleen and pancreas [31]. The clinical signs and symptoms include irritability, seizures, respiratory distress, jaundice, bleeding diathesis and shock in addition to a characteristic vesicular exanthema, which is considered pathognomonic for neonatal HSV II infection [26, 34, 52, 60]. Mortality in the absence of therapy exceeds 80%, the survivors being usually severely handicapped. Encephalitis is a common component of disseminated HSV II infection, occurring in about 60 to 70% of the infected newborns. It manifests as focal and/or generalised seizures, lethargy, irritability, poor feeding, tremors, temperature instability, bulging fontanel and pyramidal tract signs [34, 60]. CSF cultures yield the virus in up to 40% [45]; the CSF shows a pleocytosis and a high protein content. EEG, CT or MRI are useful adjunctive diagnostic techniques in the presence of CSF abnormalities. HSV II-DNA detection in CSF and serum is highly sensitive for the diagnosis of neonatal HSV infections but does not replace virus isolation and antigen detection in other locations [33]. Mortality rate is 50%; up to 50% of the surviving children have some degree of psychomotor retardation, often associated with microcephaly, hydrocephaly, porencephalic cysts, spasticity, blindness, learning disabilities etc. [26, 52].

Mothers with active herpetic genital lesions should deliver their children by Caesarean section if delivery is within 4 hours of membrane rupture. Caesarean section is of unproven benefit if the membranes have been ruptured for more than 4 hours.

## Neurological manifestations of varicella zoster infection

### Neurological complications of varicella

The incidence of CNS complications with varicella is reported to be 1 to 3/10,000 cases, a figure that seems to overestimate the frequency of neurological varicella complications, since many uncomplicated varicella cases do not come to medical attention [10, 14].

The CNS manifestations most frequently associated which chickenpox are cerebellar ataxia and encephalitis, rare neurological complications include transverse myelitis, aseptic meningitis and Guillain-Barré-syndrome. Reye’s syndrome (encephalopathy with fatty infiltration and degeneration of the liver) is a known complication of varicella, but is now attributed to concomitant Salizylate therapy [10, 12, 32, 49, 55, 58].

### Neurological complications of herpes zoster

These can occur during the acute eruption (e.g. segmental motor-paresis, radiculitis leading to sensory and motor radicular dysfunction) or appear weeks (even months) after the herpes zoster rash has resolved.

Neurological complications appear more frequently in immunocompromised patients [54]; they are seen, however, also in immunocompetent individuals after even prolonged intervals of latency [11, 15]. The following distinct clinical syndromes have been described [16, 19, 39, 40, 43, 62, 63]: encephalitis, myelitis, multifocal leukoencephalitis, ophthalmic zoster with contralateral hemiparesis, brainstem vascular syndrome (locked in syndrome) with herpes zoster in the upper cervical segments, cranial and peripheral nerve palsy, acute retinal necrosis, post herpetic neuralgia.

Subclinical extension of viral inflammation into the CNS occurs commonly in acute herpes zoster which can be visualized by magnetic resonance [22]. In CSF Varicella zoster viral DNA can be detected by PCR in case of neurological disease [44, 56].

### Treatment

Oral acyclovir therapy is optional in otherwise healthy children with varicella, but it should definitely be used in adolescents and adults with varicella because of their increased risk of more severe illness. In immunocompromised individuals with varicella acyclovir therapy must be initiated as quickly as possible.

Few data exist to help address the question of antiviral therapy for neurological complications of varicella. The most frequently seen complication, the cerebellar ataxia syndrome, is benign and self limiting and there is no evidence that antiviral therapy or corticosteroid therapy alters the natural course of this syndrome. Varicella encephalitis is associated with a substantial degree of morbidity and – although there has been no randomised prospective trial – therapy with acyclovir in patients with varicella encephalitis is warranted. Aggressive supportive care and nursing are necessary for critically ill children with varicella encephalitis. Appropriate supportive care for patients with herpes zoster includes: keeping the skin lesions clean and try-
ing to reduce the risk of bacterial superinfection and generous analgesic therapy.

Three oral antiviral drugs are in use for treatment of herpes zoster in the immunocompetent host: oral acyclovir (800 mg 5 times daily), valacyclovir (1000 mg 3 times daily) and famciclovir (500 mg 3 times daily). The antiviral therapy reduces the duration of viral shedding, limits the duration of new lesion-formation, accelerates the cutaneous healing and is superior to placebo in reducing the duration of postherpetic neuralgia [62, 63]. All these 3 drugs are safe and well tolerated for short term administration. Patients most likely to benefit from antiviral therapy of herpes zoster are those who present for medical attention within 72 hours after onset of lesions and elderly patients who are at high risk for long term complications [52].

Herpes zoster ophthalmicus is a special situation in which antiviral therapy is clearly beneficial; it reduces significantly the risk of ocular complications in such patients and, possibly, also the risk of delayed contralateral hemiparesis (caused by granulomatous arteritis of the intracranial basal arteries, e.g. ACM).

Immunocompromised patients who develop herpes zoster are at significant risk for morbidity and mortality related to disseminated infection. Intravenous acyclovir substantially reduces the risk for cutaneous and visceral dissemination and is, therefore, currently the treatment of choice [54, 55, 63].

Mollaret’s meningitis

Mollaret’s meningitis is a rare syndrome with recurrent signs and symptoms of meningeal irritation, with fever, accompanied by CSF pleocytosis without readily identifiable cause [9, 18]. The clinical criteria [52] are:

- recurrent attacks of fever, associated with signs and symptoms of meningeal irritation
- the attacks last usually days and may be accompanied by generalized myalgia and are separated by symptom-free intervals lasting for weeks or months,
- during the attacks a CSF pleocytosis of a mixed type, including endothelial cells, leucocytes and lymphocytes is found. Endothelial cells (Mollaret cells) are rather typical but not pathognomonic,
- the disease remits spontaneously without residual signs,
- approximately 5% of the patients will have transitory neurological symptoms and signs in addition to meningeal irritation
- there may be an increased gamma globulin fraction in the CSF.

Until recently an integral part of the clinical criteria was that no causative micro-organism could be found. Recently, a highly likely link with herpes simplex virus has been established. HSV II (in few instances also HSV I) DNA has been detected in the CSF using PCR in patients with Mollaret’s meningitis. Even HSV II DNA has been seen in the “classic” endothelial (Mollaret) cells [3, 21, 25, 59, 70]. CSF from patients between episodes or from control patients without a recurrent meningitis syndrome did not have the viral DNA. The association of Mollaret’s meningitis with HSV II has potential therapeutic importance, since acyclovir therapy might prevent further recurrence. Further studies of this are needed.

Idiopathic peripheral facial nerve palsy (Bell’s palsy)

Epidemiology and Aetiology

Although the biological basis of Bell’s palsy is so far not completely clear [48], various studies report an association of acute facial palsy with a variety of viruses including herpes simplex virus I, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, Coxsackie viruses, influenza viruses, poliomielitis viruses and mumps virus; furthermore bacteria, e.g. *Mycoplasma pneumoniae*, *Bartonella henselae*, *Borrelia burgdorferi* spp. etc. have been incriminated in the pathogenesis of Bell’s palsy [7, 13, 24, 36, 50].

However, most recent studies have shown that Herpes simplex virus I may be the most likely candidate virus and by polymerase chain reaction (PCR) of endoneurial fluid Herpes simplex virus I genome has been identified in more than three quarters of Bell’s palsy cases, whereas varicella zoster virus or Epstein-Barr virus have not been found therein [17, 35, 37, 41]. Reactivation of herpes simplex virus I probably results in the initial facial weakness and the virus will become indetectable with recovery [17]. Histological studies of the facial nerve during the acute stage of Bell’s palsy, either at autopsy or during surgery, have shown signs of oedema, perivascular perineural lymphocytic and macrophage infiltration of the nerve, an increase in the axon:myelin surface ratio (thinning of myelin) and a decrease in the total fibre count.

The incidence of Bell’s palsy is 20 to 30/100,000 persons/year. The rate increases with age up to the fourth decade and then remains steady until the 8th decade when it again increases. Bell’s palsy is equally frequent in man and women (ratio 46:54). The disease occurs on either side of the face and approximately 5% of patients will have a recurrent palsy affecting the same or opposite side. Pregnancy, diabetes mellitus and arterial hypertension have all been associated with an increased incidence of Bell’s palsy [13, 46, 48].
Signs and symptoms

Bell’s palsy usually has an acute onset, is unilateral and there is no evidence of disease of the central nervous system, ear or posterior fossa. Approximately 60% of patients have a preceding viral illness. Numbness or pain in front or behind the ear is present in about 50% of patients. Up to 90% have a decreased ipsilateral stapes reflex, approximately 25% have impaired taste perception on direct questioning and 10% of patients suffer from loss or significant decrease of ipsilateral tearing or submandibular salivary flow.

The clinical features of Bell’s palsy include the impairment of the entire voluntary movement of facial and platysmal muscles; on attempting to close the eye, the eyeball is diverted upward and inward (Bell’s phenomenon). If the lesion is proximal to the geniculate ganglion there may be decreased tearing in the affected eye; if the chorda tympani is affected, salivation and taste in the anterior two thirds of the tongue is decreased. Every patient with Bell’s palsy should be examined for masses in the head or neck, signs of ear vesicles and facial twitching.

Diagnosis

Electroneurography of the direct facial response and the blink reflex are helpful in confirming the presence of a peripheral facial neuropathy. Transcranial magnetic stimulation allows the study of the intracranial part of the facial nerve and has proved useful in differentiating a “classical Bell’s palsy” from a mononeuritis cranialis as part of other diseases. The radiographic imaging includes MRI with and without gadolinium or cerebral CT (with and without i.v. contrast medium) of the brain stem, cerebello-pontine angle, temporal bone and skull base; both have not proved to be of prognostic value. A full blood count including differential count should help to detect infectious mononucleosis, a blood glucose estimation, erythrocyte sedimentation rate, perhaps also antinuclear antibody test, rheumatoid factor test, Lyme serology, HIV titre and serum angiotensin converting enzyme (for sarcoidosis) may be indicated in certain patients with Bell’s palsy. If by transcranial magnetic stimulation an intracranial affection is suspected, every such patient with an isolated facial palsy must undergo lumbar puncture in order to look for an acute inflammatory demyelinating polyradiculoneuropathy, oligosymptomatic polyneuritis cranialis, meningitis, meningeval carcinomatosis and lymphoma, postinfectious or autoimmune disease [24, 36].

Differential diagnosis

The differential diagnosis of acute facial weakness that may mimic Bell’s palsy is large and includes – as the most important – the following diagnoses [7, 46, 50]:

- trauma
- Ramsay-Hunt-syndrome (varicella zoster virus infection of the geniculate ganglion)
- neoplasms of the facial nerve
- infections of the middle ear or mastoid
- demyelinating disorders including acute inflammatory demyelinating polyneuropathy
- space occupying lesion in the cerebello-pontine angle (tumour, aneurysms, etc.)
- Lyme borreliosis
- neurosarcoidosis
- syphilis
- tuberculosis
- Melkersson-Rosenthal-syndrome
- diabetes mellitus.

The combination of acyclovir (500 mg four times daily) and prednisone has been shown in a single, small, double blinded, controlled study to be superior to prednisone alone. Metaanalysis of four randomised controlled studies suggest only a marginal benefit of steroids alone concerning eventual complete recovery. Patients who had undergone a combination therapy of acyclovir with prednisone showed a more rapid improvement in facial strength and less nerve degeneration. However, another study using similar outcome measures found that single dose prednisone was more useful than acyclovir alone. Thus, although early use of prednisone seems to be indicated, and the combination of acyclovir plus prednisone may prove superior to prednisone or acyclovir alone, at this time further combination studies are warranted and urgently awaited [1, 48, 50, 52].

Eye care, eye lid surgery, facial rehabilitation and surgical decompression of the facial nerve as well as botulinum toxin injections in symptomatic synkineses are beyond the scope of this article to discuss.

Prognosis and complications

Full recovery occurs in up to 90% of patients; up to 10% may have recurrence of Bell’s palsy [13, 46]. Recovery is usually complete by 4 to 6 months and is finished at the most by 12 months. A facial motor potential amplitude of less than 10% of normal is an indicator of poor prognosis; however, even in this group up to 50% of patients will have at least partial recovery. Other indicators of a poor recovery include age over 60 years, untreated arterial hypertension, pains and abnormal electrogustometry at onset.
