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

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 prednisone, 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 prednisone seems to be indicated in a patient with Bell's palsy.

Key words Viral encephalitis · Herpesviridae

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Introduction

Both DNA viruses and RNA viruses are able to cause neurological disease, including meningitis, encephalitis, meningovasculitis, 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 detailling 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

Tab. 1 DNA-Viruses

Family *Genus* Species, relevant in human medicine	Size nm
Poxviridae	200–300
Orthopoxvirus	
Variola virus	
Vaccinia virus	
Herpesviridae	120–200
Simplexvirus	
Herpes simplex virus, type 1	
Herpes simplex virus, type 2	
Varicellovirus	
Varicella-zoster virus	
Cytomegalovirus	
Human cytomegalovirus	
Lymphocryptovirus	
Epstein-Barr virus	
Roseolovirus	
Human herpesvirus 6	
Human herpesvirus 7	
Human herpesvirus 8	
Cercopithecine herpesvirus	
(B-Virus)	
Adenoviridae	70–90
Mastadenovirus	
Human adenovirus, types 1–49	
Papovaviridae	45–55
Papillomavirus	
Wart viruses	
Polymavirus	
Simian virus 40	
JC virus	
BK virus	
Hepadnaviridae	40–48
Orthohepadnavirus	
Hepatitis B	
Parvoviridae	18–26
Erythrovirus	
Human parvovirus B 19	

Tab. 2 RNA-Viruses

Family *Genus* Species, relevant in human medicine	Size nm
Paramyxoviridae	150–300
Paramyxovirus	
Human parainfluenza viruses 1 and 3	
Rubulavirus	
Mumps virus	
Human parainfluenza viruses 2 and 4	
Morbillivirus	
Measles virus	
Pneumovirus	
Human respiratory syncytial virus	
Orthomyxoviridae	80–120
Influenzavirus	
Influenza viruses A, B, and C	
Rhabdoviridae	70–85
Lyssavirus	x 180
Rabies virus	
Vesiculovirus	
Vesicular stomatitis virus	
Filoviridae	80 x 1000
Filovirus	
Ebola virus	
Marburg virus	
Bunyaviridae	88 x 120
Bunyavirus	
California encephalitis virus	
La Crosse virus	
Jamestown Canyon virus	
Snowshoe hare virus	
Tahyna virus	
Inkoo virus	
Cache Valley virus	
Tensaw virus	
Phlebovirus	
Rift Valley fever virus	
Nairovirus	
Crimean-Congo hemorrhagic fever virus	
Hantavirus	
Hantaviruses	
Arenaviridae	50–300
Arenavirus	
Lymphocytic choriomeningitis virus	
Lassa virus	
Junin virus	
Machupo virus	
Guanarito virus	
Sabia virus	
Retroviridae	80–100
Oncovirus (HTLV-BLV)	
Human T-cell lymphotropic viruses I and II	

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

Tab. 2 *contd.*

Family *Genus* Species, relevant in human medicine	Size nm
Lentivirus	
Human immunodeficiency viruses I and II	
Spumavirus	
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 an dB human rotoviruses	
Togaviridae	70
Alphavirus	
Eastern equine encephalitis virus	
Western equine encephalitis virus	
Venezuelan equine encephalitis virus	
Rubivirus	
Rubella virus	
Flaviviridae	45–60
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	
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	

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-

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

	brain biopsy positive patients (%)	brain biopsy negative patients (%)
Prehospital signs and symptoms		
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 presentatoin		
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].

Tab. 4 Differential diagnosis of HSV I encephalitis

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
Mumpsvirus
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 30–35mm 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 occurr 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 palsies, 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, poliomyelitis 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 perineurial 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 eyball 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, meningeal 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 rehabilition 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.

References

1. Adour KK, Ruboyianes JM, Von Doersten PG, Byl FM, Trent CS, Quesenberry CP, Hitchcock T (1996) Bell's palsy treatment with acyclovir and prednisone compared with prednisone alone: a double-blind, randomized, controlled trial. Ann Otol Rhinol Laryngol 105:371–378
2. Asenbauer B, McEntagart M, King MD, Gallagher P, Burke M, Farrell MA (1998) Chronic active destructive herpes simplex encephalitis with recovery of viral DNA 12 years after disease onset. Neuropediatrics 29:120–123
3. Bachmeyer C, de la Blanchardiere A, Lepercq J, et al. (1996) Recurring episodes of meningitis (Mollaret's meningitis) with one showing an association with herpes simplex virus type 2. J Infect 32:247–248
4. Baker DA (1990) Herpes and pregnancy: new management. Clin Obstet Gynecol 33:253–257
5. Balfour HH, Kelly JM, Suarez Cs, et al. (1990) Acyclovir treatment of varicella in otherwise healthy children. J Pediatr 116:633–639
6. Baringer JR, Pisani P (1994) Herpes simplex virus genomes in human nervous system tissue analyzed by polymerase chain reaction. Ann Neurol 36:823–829
7. Bauer CA, Coker NJ (1996) Update on facial nerve disorders. Otolaryngol Clin North Am 29:445–454
8. Borgo F, Sgaramella TM, Penello B, L'Erario R, Tosso V (2000) A componential analysis of visual object recognition deficits in patients with herpes simplex virus encephalitis. Brain Cogn 43:53–56
9. Bruyn GW, Straathof LJ, Raymakers GM (1962) Mollaret's meningitis. Differential diagnosis and pitfalls. Neurology 12:745–753
10. Choo PW, Donahue JG, Manson JE, Plott R (1995) The epidemiology of varicella and its complications. J Infect Dis 172:706–712
11. Croen KD, Straus SE (1991) Varicella-zoster latency. Annu Rev Microbiol 45:265–282
12. Dangood F, Engle E, Yessayan L, Sawer MH (1993) Pre-eruptive varicella cerebellitis confirmed by PCR. Pediatr Neurol 9:491–493
13. Devriese PP, Schumacher T, Scheide A, et al. (1990) Incidence, prognosis and recovery of Bell's palsy. A survey of about 1000 patients (1974–1983). Clin Otolaryngol 15:15–27
14. Donahue JG, Choo PW, Manson JE, Plat R (1995) The incidence of herpes zoster. Arch Intern Med 155:1605–1609
15. Elliot KJ (1994) Other neurological complications of herpes zoster and their management. Ann Neurol 35:557–561
16. Friedman MS, MacDonald RD (1987) Herpes zoster opththalmicus with delayed cerebral infarction and meningoencephalitis. Can J Neurol Sci 14:312–314
17. Furuta Y, Fukuda S, Chida E, Takasu T, Ohtani F, Inuyama Y, Nagashima K (1998) Reactivation of herpes simplex virus type 1 in patients with Bell's palsy. J Med Virol 54:162–166
18. Galdi AP (1996) Benign recurrent aseptic meningitis (Mollaret's meningitis): a case with increased circulating natural killer cells. Ann Neurol 20:359–361
19. Garthy DS, Spalton DJ, Hykin PG (1991) Acute retinal necrosis syndrome. Br J Opthalmol 75:292–297
20. Geiss BJ, Smith TJ, Leib DA, Morrison LA (2000) Distruption of virion host activity improves the immunogenicity and protective capacity of a replication-incompetent herpes simplex virus type 1 vaccine strain. J Virol 74:11137–11144
21. Gignoux L, Ryvling P, Najioullah F, Mauguiere F (1998) Recurrent Mollaret's meningitis of herpetic origin. Presse Med 27:1470–1472
22. Haanpaa M, Dastidar P, Weinberg A, LevinM, Miettenen A, Lapinlampi A, Laippala P, Nurmikko T (1998) CSF and MRI findings in patients with acute herpes zoster. Neurology 51:1405–1411
23. Hokkanen L, Launes J (2000) Cognitive outcome in acute sporadic encephalitis Neuropsychol Rev 10:151–167
24. Imarhiagbe D, Prodinger W, Schmutzhard E (1993) Infektionserreger als mögliche Ursache der idiopathischen Facialisparese. Wr Klin Wschr 105:611–613
25. Jensenius M, Myrvang B, Storvold G, Bucher A, Hellum KB, Brun AL (1998) Herpes simplex virus type 2 DNA detected in cerebrospinal fluid of 9 patients with Mollaret's meningitis. Acta Neurol Scand 98:209–212
26. Johnson RT (1998) Viral Infections of the Nervous System. 2nd ed. Lippincott-Raven, Philadelphia, New York
27. Lakeman FD, Whitley RJ, NIAID Collaborative Antiviral Study Group (1995) Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain biopsied patients and correlation with disease. J Infect Dis 171:857–863
28. Launes J, Siren J, Valanne L, Salonen O, Nikkinen P, Seppalainen AM, Liewendahl K (1997) Unilateral hyperfusion in brain-perfusion SPECT predicts poor prognosis in acute encephalitis. Neurology 48:1347–1351
29. Leonard JR, Moran CJ, Cross DT, Wippold FJ, Schlesinger Y, Storch GA (2000). MR imaging of herpes simplex type 1 encephalitis in infants and young children: a separate pattern of findings. Am J Roentgenol 174:1651–1655
30. Levin MJ, Murray M, Zerbe GO, White CJ, Hayward AR (1994) Immune responses of elderly persons four years after receiving a live attenuated varicella vaccine. J Infect Dis 170:522–526
31 Levinson RD, Reidy R, Chiu MT (1999) Acute retinal necrosis after neonatal herpes encephalitis. Br J Ophthalmol 83:123–124
32. Liu G, Urion DK (1992) Pre-eruptive varicella encephalitis and cerebellar ataxia. Pediatr Neurol 8:69–70
33. Malm G, Forsgren M (1999) Neonatal herpes simplex virus infections: HSV DNA in cerebrospinal fluid and serum. Arch Dis Child Fetal Neonatal Ed 81:24–29
34. Malouf DJ, Oates RK (1995) Herpes simplex virus infections in the neonate. J Paediatr Child Health 31:332–335
35. Marra CM (1999) Bell's palsy and HSV-1 infection. Muscle Nerve 22:1476–1478
36. May M, Klein SR (1991) Differential diagnosis of facial nerve palsy. Otolaryngol Clin North Am 24:613–645
37. Mc Cormick DP, Spruance RB (2000) Herpes simplex virus as a cause of Bell's palsy. Rev Med Virol 10:285–289
38. Meyding-Lamade UK, Lamade WR, Wildemann DT, Sartor K, Hacke W. (1999) Herpes simplex virus encephalitis: chronic progressive cerebral magnetic resonance imaging abnormalities in patients despite good clinical recovery. Clin Inf Dis 28:148–150
39. Mizock BA, Bartt R, Agbemazdo B (2000) Herpes zoster oticus with pontine lesion: segmental brain-stem encephalitis. Clin Infect Dis 30:229–230
40. Morgella S, Block GA, Price RW, Petito CK (1988) Varicella-zoster virus leukoenzephalitis and cerebral vasculopathy. Arch Pathol Lab Med 112:173–177
41. Murakami S, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N (1996) Bell's palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. Ann Intern Med 124:27–30

42. Nahimas AJ, Whitley RJ, Visintine AN, Takei Y, Alford CA, NIAID Collaborative Antiviral Study Group (1982) Herpes simplex virus encephalitis: laboratory evaluations and their diagnostic significance. J Infect Dis 145:829–836
43. Nau R, Lantsch M, Stiefel M, Polak T, Reiber H (1998) Varicella zoster virus-associated focal vasculitis without herpes zoster: recovery after treatment with acyclovir. Neurology 51:914–915
44. Puchhammer-Stöckl E, Popow-Kraupp T, Heinz FX, Mandi CW, Kunz C. (1991) Detection of varicella-zoster virus DNA by polymerase chain reaction in the cerebrospinal fluid of patients suffering from neurological complications associated with chickenpox or herpes zoster. J Clin Microbiol 29:1513–1516
45. Prober CG, Hensleigh PA, Boucher FD, Yasukawa LL, Au DS, Arvin AM (1988) Use of routine viral cultures at delivery to identify neonates exposed to herpes simplex virus. N. Engl J Med 318:887–891
46. Qui WW, Yin SS, Stucker FJ, et al. (1996) Time courses of Bell's palsy. Arch Otolaryngol Head Neck Surg 122:967–972
47. Roob G, Fazekas F, Hartung HP (1999) Peripheral facial palsy: etiology, diagnosis and treatment. Eur Neurol 41:3–9
48. Roggenkamper P, Laskawi R, Damenz W, et al (1994) Orbicular synkinesis after facial paralysis: treatment with botulinum toxin. Doc Ophthalmol 86:395–402
49. Rosenfeld J, Taylor CL, Atlas SW (1993) Myelitis following chikenpox: a case report. Neurology 43:1834–1836
50. Saito O, Aoyagi M, Tojima H, Koike Y (1994) Diagnosis and treatment of Bell's palsy associated with diabetes mellitus. Acta Otolaryngol (Stockh) 511:153–155
51. Sauerbrei A, Eichhorn U, Hottenrott G, Wutzler P (2000) Virological diagnosis of herpes simplex encephalitis. J Clin Virol 17: 31–36
52. Schmutzhard E (2000) Entzündliche Erkrankungen des Nervensystems. Thieme Verlag, Stuttgart
53. Sgaramella TM, Borgo F, Fenzo F, Garofalo P, Toso V (2000) Memory for/and execution of future intentions: evidence from patients with Herpes Simplex Encephalitis. Brain Cogn 43:388–392
54. Srugo I, Israela V, Wittek AE, et al. (1993) Clinical manifestations of varicella zoster infections in human immunodeficiency virus-infected children. Am J Dis Child 147:742–745
55. Straus SE, Ostrove JM, Inchauspe G, Felser JM, Freifeld A, Croen KD, Sawyer MH (1988) Varicella-zoster virus infections. Ann Intern Med 108:221–237
56. Straus SE, Reinhold W, Smith HA, Ruyechan WT, Henderson DK, Blaese RM, Hay J (1984) Endonuclease analysis of viral DNA from varicella and subsequent zoster infection in the same patient. N Engl J Med 311:1362–1364
57. Studahl M, Rosengren L, Gunter G, Hagber L (2000) Difference in pathogenesis between herpes simplex virus type 1 encephalitis and tick-borne encephalitis demonstrated by means of cerebrospinal fluid markers of glial and neuronal destruction. J Neurol 247:636–642
58. Tagawa Y, Yuki N (2000) Bickerstaff's brainstem encephalitis associated with shingles. J Neurol 247:218–219
59. Tang YW, Cleavinger PJ, Li H, Mitchell PS, Smith TF, Persing DH (2000) Analysis of candidate-host immunogenetic determinants in Herpes simplex virus-associated Mollaret's meningitis. Clin Infect Dis 30:176–178
60. Tookey P, Peckham CS (1996) Neonatal herpes simplex virus infection in the British Isles. Paediatr Perinat Epidemol 10:432–442
61. Troendle-Atkins J, Demmler GJ, Buffone GJ (1993) Rapid diagnosis of herpes simplex virus encephalitis by using the polymerase chain reaction. J Pediatr 123:376–380
62. Watson CPN, Evand RJ, Walt VR, Birkett N (1988) Postherpetic neuralgia: 208 cases. Pain 35:289–297
63. Weller TH (1992) Varicella and herpes zoster: a perspective and overview. J Infect Dis 166:1–6
64. Whitley RJ (1997) Herpes Simplex Virus. In: Scheld WM, Whitley RJ, Durack DT (eds). Infections of the Central Nervous System. Philadelphia, New York Lippincott-Raven, pp 73–89
65. Whitley RJ, Cobbs CG, Alford CA, et al. (1989) Diseases which mimic herpes simplex encephalitis: diagnosis, presentation, and outcome. JAMA 262:234–239
66. Whitley RJ, Nahmias AJ (1985) Therapeutic challenges of neontatal herpes simplex virus infection. Scand J Infect Dis 47:97–106
67. Whitley RJ, Nahmias AJ, Visintine AM, Fleming CL, Alford CA (1980) The natural history of herpes simplex virus infection of mother and newborn. Pediatrics 66:489–494
68. Wildemann B, Ehrhart K, Storch-Hagenlocher B, Meyding-Lamade U, Steinworth S, Hacke W, Haas J (1997) Quantitation of herpes simplex virus type 1 DNA in cells of cerebrospinal fluid of patients with herpes simplex virus encephalitis. Neurology 48:1341–1346
69. Willeit, Schmutzhard E (1991) Cervical Herpes zoster and delayed brainstem infarction. Clin Neurol Neurosurg 93:245–247
70. Yamoto LJ, Tedder DG, Ashley R, Levin MJ (1991) Herpes simplex virus type I DNA in cerebrospinal fluid of a patient with Mollaret's meningiits. N Engl J Med 325:1082–1085