Neuroradiological and clinical features in ophthalmoplegia

Stefan Weidauer 1 · Christian Hofmann 2 · Marlies Wagner 3 · Elke Hattingen 3

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Abstract
Purpose Especially in acute onset of ophthalmoplegia, efficient neuroradiological evaluation is necessary to assist differential diagnosis, clinical course, and treatment options.
Methods Different manifestations of ophthalmoplegia are explained and illustrated by characteristic neuroradiological and clinical findings.
Results To present those ophthalmoplegic disorders in a clear manner, this review refers to different neuroanatomical structures and compartments. From neuroophthalmological point of view, diseases going ahead with ophthalmoplegia can be divided into (1) efferent infranuclear/peripheral disturbances involving oculomotor cranial nerves, (2) conjugate gaze abnormalities due to internuclear or supranuclear lesions, and (3) diseases of the extraocular eye muscles or their impairment due to intraorbital pathologies.
Conclusion The knowledge of the relationship between neurological findings in ophthalmoplegia and involved neuroanatomical structures is crucial, and neuroradiology can be focused on circumscribed anatomical regions, using optimized investigation protocols.

Keywords Ophthalmoplegia · MRI · Cranial nerve palsy · Conjugate gaze abnormality · Horner syndrome

Introduction
One of the cardinal clinical symptoms in ophthalmology is diplopia. Since the perception of double vision (DV) is a subjective sensation, it is the main task for the neuroophthalmologist to objectify the symptoms [1]. The more precise the clinical description and findings, the better the diagnostic clarification can be, which is a consequent step-by-step procedure. The first step is to differentiate between monocular and binocular DV, the former often due to an optical problem or macular diseases. Binocular DV, however, is caused by an imbalance of position or motility of both eyes. Almost any case of binocular DV is accompanied by strabismus. As a second step, the neuroophthalmologist should examine the motility of the eyes in order to differentiate between non-paretic (concomitant) and paretic (inconmitant) strabismus which can roughly be summarized as ophthalmoplegia (OP). OP can be provoked by harmless and self-limiting causes, but it can also be the overture to a severe neurological disease.

Neuroimaging plays a central role in the diagnostic clarification of OP and planning of treatment options, particularly in the case of acute onset [1–6]. For optimized imaging, it is essential to provide the neuroradiologist with precise information on the neuroophthalmologically involved structures [4, 6]. Consecutive, neuroimaging can be focused on circumscribed anatomical regions, using specialized investigation protocols, e.g., additional thin slice sequences to obtain most appropriate neuroanatomical information [1, 2]. At this point, however, it must be mentioned that some causes of OP, such as neuromuscular junction disorders, cannot be identified by imaging [1].

From neuroophthalmological point of view, diseases being accompanied by OP can be divided into (1) efferent infranuclear/peripheral neuroophthalmic disorders involving oculomotor cranial nerves (CN), i.e., oculomotor nerve (CN...
III), trochlear nerve (CN IV), and abducens nerve (CN VI) (see Table 1, Fig. 1) [1, 7, 8]; (2) conjugate gaze abnormalities due to internuclear or supranuclear disorders (see Table 2) [1–4]; and (3) diseases of the extraocular eye muscles (EOM) and orbital diseases affecting the EOM (see Table 3) [1, 9–13]. In this review, characteristic neurological and

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical characteristics</th>
<th>Lesion site</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN III palsy</td>
<td>Ophthalmological</td>
<td>Peripheral/subarachnoid space</td>
<td>Vasculopathic, inflammation, uncal herniation, intracranial hypotension (ICH), other (e.g., ophthalmoplegic migraine, congenital)</td>
</tr>
<tr>
<td>Additional neurological symptoms</td>
<td>Contralateral ptosis</td>
<td>Nuclear (midbrain)</td>
<td>Ischemia (microangiopathy), other</td>
</tr>
<tr>
<td></td>
<td>“Crossed brainstem syndromes”</td>
<td>Fascicular (midbrain and cerebral peduncle)</td>
<td>Ischemia, tumor, inflammation, other</td>
</tr>
<tr>
<td></td>
<td>Contralateral: sensation deficits, tremor, hyperkinesia, pyramidal tract signs (Benedikt syndrome)</td>
<td>Fascicular (midbrain, red nucleus)</td>
<td>Ischemia, tumor, inflammation, other</td>
</tr>
<tr>
<td></td>
<td>Contralateral: ataxia (Claude-/Nothnagel syndrome)</td>
<td>Fascicular (midbrain, tegmentum/tegmentum), superior cerebellar peduncle</td>
<td>Ischemia, tumor (pinealis), other</td>
</tr>
<tr>
<td>CN IV palsy</td>
<td>Ophthalmological</td>
<td>Peripheral/subarachnoid space</td>
<td>Inflammation, tumor (e.g., schwannoma), intracranial hypotension, other</td>
</tr>
<tr>
<td>Additional neurological symptoms</td>
<td>Contralateral: dysmetria, ataxia</td>
<td>Nuclear/fascicular (dorsal midbrain, superior cerebellar peduncle)</td>
<td>Ischemia, hemorrhage, tumor, inflammation, other</td>
</tr>
<tr>
<td></td>
<td>Contralateral: relative afferent pupillary defect and/or Horner syndrome</td>
<td>Nuclear/fascicular (dorsal pontomesencephal junction, brachium of the superior colliculus)</td>
<td>Ischemia, hemorrhage, tumor, inflammation, other</td>
</tr>
<tr>
<td>CN VI palsy</td>
<td>Ophthalmological</td>
<td>Peripheral/subarachnoid space</td>
<td>Inflammation, ICH, ischemia, other</td>
</tr>
<tr>
<td>Additional neurological symptoms</td>
<td>Ipsilateral facial pain, facial numbness CN V/supraorbital nerve (Gradenigo syndrome)</td>
<td>Cavernous sinus</td>
<td>ICA aneurysm</td>
</tr>
<tr>
<td></td>
<td>Horner syndrome (possible)</td>
<td>Caudal pontine bulb</td>
<td>Ischemia, inflammation, other</td>
</tr>
<tr>
<td></td>
<td>Contralateral: hemiparesis, sensation deficits Ipsilateral: nuclear CN VII paresis (caudal pontine bulb syndrome; Millard-Gubler syndrome/Foville syndrome)</td>
<td>Caudal pontine tegmentum</td>
<td>Ischemia, inflammation, other</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nuclear</td>
<td>Ischemia, inflammation, other</td>
</tr>
<tr>
<td>Combined CN III, IV, VI palsies</td>
<td></td>
<td>Cavernous sinus/skullbase</td>
<td>Thrombosis</td>
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<td></td>
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<td></td>
<td>Carotid-cavernous sinus fistula</td>
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<td></td>
<td></td>
<td></td>
<td>Tolosa Hunt syndrome</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Inflammation, neoplasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICA aneurysm, fungal infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Congenital fibrosis syndromes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nuclear/fascicular</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inflammation, e.g., multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bickerstaff’s brainstem encephalitis (anti-GQ1b-antibody syndrome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Metabolic (e.g., Wernicke encephalopathy, Leigh syndrome), other</td>
</tr>
</tbody>
</table>

BA basilar artery, CN cranial nerve, ICA internal carotid artery, PcomA posterior communicating artery, SCA superior cerebellar artery
neuroimaging findings and also differential diagnostic aspects are presented for the individual groups. Taking clinical relevance into account, additionally the oculosympathetic paresis (Horner syndrome) is discussed (see Table 4) [1, 7, 8]. However, description and analysis of the different forms of pathological nystagmus forms, impairment of saccades, as well as pathologies of the optic nerve go beyond the scope of this review and will not be discussed.

**Neuroimaging protocol**

Neuroimaging of small structures requires high-resolution MR sequences with thin slices, e.g., slice thickness of 0.75 up to 3 mm [14–17]. For example, the trochlear nerve (CN IV) has a diameter of 0.75 to 1.00 mm [18] and sequences with a slice thickness of 1.00 mm in maximum without gap are necessary for clear anatomical detection [14, 15]. Therefore, strongly T2-weighted 3D sequences as well as isovolumetric high-resolution high contrast T1-weighted 3D sequences after administration of gadolinium contrast agent are recommended [14–17]. These sequences allow the reconstruction of the CN courses in the subarachnoid space, the skull base, the cavernous sinus, and the orbit. Due to the often small size of mesencephalic and other brainstem lesions with a diameter between 2 and 4 mm, neuroimaging of the posterior fossa structures also requires thin slice sequences [18–20]. Because fluid-attenuated inversion recovery (FLAIR) sequences are prone to artifacts in this region, one should prefer spin-echo T2-weighted images (WI) with thin slices. Depending on the neurologically suspected etiology of the lesion, e.g., ischemic brainstem disorders, additional diffusion-weighted imaging (DWI) [21] in axial and coronal acquisition may be necessary. MR studies focusing on suspected lesions in the orbits and the cavernous sinus should include axial and coronal spin-echo T1 WI with a slice thickness of 3 mm at most and fat saturation (FS) after intravenous administration of gadolinium (pc T1 WI FS) [12, 22].

**Efferent infranuclear/peripheral neuroophthalmic disorders**

**Isolated CN paresis**

Isolated paresis of the CN III, IV, and VI are often caused by ischemia, and typical vascular risk factors are diabetes and hypertension [1, 7]. From neurological point of view, clinical examination cannot reliably differentiate between peripheral (infranuclear) and nuclear CN palsy [5, 7, 20]. In contrast, while neuroimaging in peripheral CN palsies is often negative—apart from inflammatory etiologies, pathologies involving CN nuclei often have a neuroradiological correlate [20].

Painless diabetic-induced CN III palsy often spares the parasympathetic fibers (i.e., external OP) and may be caused by impaired microcirculation within the CN as well as by circumscribed paramedian mesencephalic infarcts (Fig. 2) [21–24]. However, ischemic involvement of the Edinger-Westphal nucleus in the neighborhood causes additional parasympathetic neurological features with mydriasis and ptosis (Fig. 2).

An important differential diagnosis is the acute painful paresis of CN III due to a so called ophthalmoplegic
aneurysm with consecutive CN compression (Fig. 3) [25]. Aneurysm-related CN III palsy typically leads to mydriasis with unequal size of pupils (anisocoria; Fig. 3b) due to compromised parasympathetic fibers in the external layers of the nerve (internal OP) besides variable palsies of the EOM innervated by the CN III (external OP). This represents an emergency situation and acute neuroimaging followed by prompt aneurysm treatment is necessary [26–29]. Most often, aneurysm arises from the terminal segment of the internal carotid artery (ICA) at the origin of the posterior communicating artery (PcomA; Fig. 3e). Rarer aneurysms of the superior cerebellar artery (SCA) or the tip of the basilar artery might also cause affection of the third CN [1, 2, 7, 30].

### Table 2 Conjugate gaze abnormalities (internuclear and supranuclear disorders), additional neurological symptoms depending upon lesion site

<table>
<thead>
<tr>
<th>Conjugate gaze abnormality</th>
<th>Ophthalmological and clinical characteristics</th>
<th>Lesion site</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horizontal gaze deficits</td>
<td>Internuclear ophthalmoplegia (INO): ipsilateral limitation of adduction, preserved convergence, contralateral abducting nystagmus</td>
<td>Pons/mesencephalon</td>
<td>Inflammation, e.g., multiple sclerosis; ischemia, other</td>
</tr>
<tr>
<td></td>
<td>One-and-a-half syndrome: bilateral limitation of adduction and monocular abduction paresis</td>
<td>MLF (lower) pontine tegmentum</td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td>Eight-and-a-half syndrome: additional CN VII palsy</td>
<td>MLF (upper) pontine tegmentum and CN VI nucleus (PPRF)</td>
<td>Ischemia, other</td>
</tr>
<tr>
<td></td>
<td>Foville syndrome: ipsilateral horizontal gaze palsy, CN VII palsy; contralateral hemiparesis</td>
<td>Additional CN VII fascicle</td>
<td>Ischemia, other</td>
</tr>
<tr>
<td></td>
<td>Locked-in syndrome: horizontal gaze palsy, partially sparing of upward gaze and blinking; quadriplegia, anarthria</td>
<td>Caudal tegmental pons</td>
<td>Ischemia</td>
</tr>
<tr>
<td></td>
<td>Bilateral abduction deficit (CN VI palsy), nystagmus; additional: disturbance of consciousness (“global state of confusion”), ataxia</td>
<td>Ventral and central pons</td>
<td>Hemorrhage</td>
</tr>
</tbody>
</table>

**Abnormal horizontal conjugate gaze deviations**

- The patient looks at the lesion; “right way eyes” sign (contralateral hemiparesis)
- The patients looks away from the lesion, “wrong way eyes” sign

**Vertical gaze deficits**

- Parinaud syndrome (pretectal syndrome): upgaze palsy, convergence-retraction nystagmus, light-near pupillary dissociation, lid lag
- Top-of-the-basilar-artery syndrome (variable paramedian mesencephalic and thalamic symptoms)
- Progressive supranuclear palsy (PSP), typically downward > upward; “atypical parkinsonism”
- Additional variable neurological symptoms

**Additional variable neurological symptoms**

<table>
<thead>
<tr>
<th>Ocular tilt reaction: skew deviation (vertical squinting), head tilt, binocular concordant cyclorotation, tilt of subjective vertical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral: Horner syndrome, ataxia, facial sensory deficits (CN V); contralateral: hypalgesia; dysphagia, dysarthria (Wallenberg syndrome)</td>
</tr>
<tr>
<td>Downward deviation of both eyes with/without convergence, miosis</td>
</tr>
<tr>
<td>Thalamus</td>
</tr>
<tr>
<td>Ischemia, hemorrhage, infection, tumor, other</td>
</tr>
<tr>
<td>Dorsolateral medulla oblongata</td>
</tr>
<tr>
<td>Ischemia, hemorrhage, infection, tumor, other</td>
</tr>
<tr>
<td>Metabolic diseases</td>
</tr>
<tr>
<td>M. Whipple</td>
</tr>
<tr>
<td>Other, e.g., paraneoplastic brainstem encephalitis</td>
</tr>
</tbody>
</table>

**CN cranial nerve, MLF medial longitudinal fascicle, PPRF paramedian pontine reticular formation, PSP progressive supranuclear palsy (Steele Richardson Olszewski- or Richardson syndrome), PTPA posterior thalamoperforating arteries, rMLF rostral interstitial nuclei of the medial longitudinal fasciculus**
retraction syndrome caused by hypo- or aplasia of the ICA aneurysms with involvement of the clivus and Dorello inflammation (Fig. 1). Inflammation can also be caused by pseudo-Duane syndrome.

In up to 35%, painful oculomotor nerve palsy precedes subarachnoid hemorrhage (SAH) as a “warning leak” or sentinel leak [26, 29]. However, most often, clinical presentation of ruptured distal ICA aneurysms is the apoplectic type with SAH.

Another emergency situation represents CN III paresis with initial mydriasis in case of supratentorial space occupying lesions leading to transtentorial herniation with ipsilateral nerve compression at the level of the plica petroclinoidea. If possible, acute neurosurgical intervention is required [5, 6].

In contrast to CN IV paresis but similar to CN III affection, lesions of the abducens nerve (CN VI) are also common (Fig. 4) [1, 7]. Besides disturbance of microcirculation in patients suffering from diabetes, possible etiologies include inflammation (Fig. 4), pathological processes of the skull base with involvement of the clivus and Dorello’s canal (Fig. 1) [1, 2, 7, 17], and in rare cases also infracavernous intracavernous ICA aneurysms [7, 31].

Differential diagnosis of CN VI palsy include Duane’s retraction syndrome caused by hypo- or aplasia of the abducens nerve and/or the CN nucleus [32]. Due to paradoxical coinnervation of the lateral and medial rectus muscles, clinical examination exhibits retraction of the globe and narrowed palpebral fissure in attempted adduction [1, 32]. Based on ocular muscle electromyography, three subtypes could be differentiated [33]. Type I is the most common pattern characterized by impaired abduction, normal adduction, and retraction of the adducted globe [34]. MRI typically shows absence of the CN VI (see Fig. 5) [35–37]. Type 2 is rare going ahead with normal abduction and impaired adduction, and in type 3 both abduction and adduction are impaired [1, 33]. High-resolution MRI using heavily T2 WI may provide additional information of innervation abnormalities of the extraocular muscles (EOM) [35]. However, also orbital blow-out fractures with entrapment of the medial rectus muscle may mimic Duane’s syndrome, i.e., pseudo-Duane’s retraction syndrome [1].

In OP due to CN paresis occurs in nearly one-third of patients suffering from intracranial hypotension (ICH), when cerebrospinal fluid volume is reduced via spinal meninges caused by spontaneous leakage or iatrogenic procedures, e.g., lumbar puncture (see Fig. 6) [38–42]. Uni- or bilateral abducens nerve paresis (> 80%) is the most common in symptomatic spontaneous ICH [39]. Although the precise etiology of CN palsy is unclear, one reason therefore may be traction of the CN due to downward displacement of the brainstem [39]. From pathophysiological point of view, the abducens nerve is favored to traction-related injury due to the long preoptine subarachnoid course, the subsequent travel through Dorello’s canal, and attachment to the Gruber ligament [43, 44]. CN III and CN IV palsies are less common and in advanced cases with progressive herniation, CN compression as well as brainstem injury may be likely consequences [38, 39, 42].

**Table 3** Disorders of the extraocular eye muscles (EOM) and intraorbital pathologies

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid-associated orbitopathy (Graves or endemic ophthalmopathy)</td>
</tr>
<tr>
<td>Primary ocular myopathies (e.g., Kearns Sayre syndrome, chronic progressive external ophthalmoplegia)</td>
</tr>
<tr>
<td>Neuromuscular junction/myasthenia gravis</td>
</tr>
<tr>
<td>Orbital inflammatory pseudotumor, i.e., IgG 4-related ophthalmic disease (IgG-4ROD; idiopathic orbital inflammation)</td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Neoplasia</td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
<tr>
<td>Trauma/blow-out fractures (“pseudo-Duane syndrome”)</td>
</tr>
</tbody>
</table>

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**Table 4** Different Horner syndromes (HS)

<table>
<thead>
<tr>
<th>Form</th>
<th>Localization</th>
<th>Etiology</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central (first-order neuron)</td>
<td>Uncrossed: hypothalamus–pons–dorsolateral medulla oblongata–lower cervical spinal cord at the level of the internal carotid artery (C8–Th2)</td>
<td>Hemorrhage, infarct, tumor</td>
<td>Wallenberg syndrome: ipsilateral: CN V, IX, X with Horner syndrome, ataxia, hypo-/anhidrosis; contralateral: hypalgiesia</td>
</tr>
<tr>
<td>Preganglionic (second-order neuron)</td>
<td>Spinal nerve roots C8–Th2, aortic arch (le.) and subclavian artery (ri.)—superior cervical ganglion at the level of the ICA origin</td>
<td>Traumatic spinal nerve root lesion, pancoast-tumor, aortic arch dissection</td>
<td>Horner syndrome; Ggl. stellatum: hypo-/anhidrosis arm and face; superior cervical ggl.: facial hypo-/anhidrosis</td>
</tr>
<tr>
<td>Postganglionic (third-order neuron)</td>
<td>Superior cervical ganglion: as internal carotid plexus in the arterial wall of the ICA—as external carotid plexus (sudomotoric fibers towards the facial sweat glands on the surface of the ICA wall)</td>
<td>ICA dissection, cervical tumor, lesions of the skull base or cavernous sinus</td>
<td>Painful Horner syndrome, often without facial anhidrosis</td>
</tr>
</tbody>
</table>

**CN cranial nerve, ICA internal carotid artery, Ggl ganglion**
Combined CN III, IV, and VI palsies

Whereas the CN III, IV, and the first and second branch of the trigeminal nerve (CN V; ophthalmic nerve and maxillary nerve) run in the lateral wall of the cavernous sinus [22], the abducens nerve (CN VI) partially accompanied by additional sympathetic ocular fibers and the ICA are located in the venous compartment of the cavernous sinus itself [22, 45, 46]. Therefore, pathological processes in the cavernous sinus may result in different combinations of CN paresis, often accompanied by retro- or periorbital pain (Figs. 7 and 8; see Table 1) [1, 2, 5, 7].

Tolosa-Hunt syndrome

The Tolosa-Hunt syndrome (THS) represents a painful OP characterized by paresis of the CN III, IV, and VI and severe unilateral retro- or periorbital pain, quickly responding to steroids [47–49]. In addition, the first and second branch of the trigeminal nerve may be involved, and in rare cases, also the optic nerve (CN II). THS is caused by a nonspecific granulomatous lymphocytic inflammation with the soft-tissue mass involving the cavernous sinus with possible extension towards the superior orbital fissure and the orbital apex (Fig. 9) [47–49]. Per
 definition, the inflammation may also involve the ICA wall, i.e., periarteritic granuloma [47]. Diagnostic criteria for the THS given by the International Headache Society (IHS) are the following: (1) one or more episodes of unilateral orbital pain persisting for weeks if untreated; (2) singular or combined paresis of the CN III, IV, and VI and/or detection of granuloma by MR imaging or biopsy; (3) paresis within a 2-week period after pain onset; (4) remission of pain and paresis within 72 h when treated adequate with steroids; and (5) exclusion of other causes by accurate investigation [49, 50].

MRI features could be classified into primary and secondary criteria [22, 51]. Primary criteria include (1) presence of a lesion within the anterior cavernous sinus (Fig. 9), (2) local increasing size of the cavernous sinus, and (3) bulging of the dural contour of the cavernous sinus. Secondary criteria include (1) involvement of the orbital apex and the optic nerve, (2) extension toward the superior orbital fissure, (3) involvement of the ICA, and (4) blurred dural boarder on T2 WI. If solely intraorbital masses are present, differential diagnosis should include idiopathic inflammatory orbitopathy (orbital pseudotumor; Fig. 10). However, with regard to histopathological findings, it is supposed that THS [11, 52–54], orbital pseudotumor [10, 55–57], and hypertrophic pachymeningitis [58, 59] are three different manifestations of a common underlying pathology, i.e., IgG 4-related diseases [54].

Carotid-cavernous fistula

According to the Barrow classification, carotid-cavernous fistula (CCF) can be differentiated into direct (Barrow type A) and
Fig. 6  Spontaneous intracranial hypotension (ICH) due to CSF leakage in a 45-year-old man suffering from postural headache and bilateral CN VI palsy. Axial T2 WI (a, b) showing bilateral SDH (a), narrowing of the basal cisterns (b, arrow); (c) sag. T1 WI pc: downward displacement of cranial contents.

Fig. 7  Combined cranial nerve paresis right sided with external oculomotor nerve (CN III) paresis (a: adduction deficit right), abducens nerve (CN VI) paresis (b: lateral rectus muscle palsy right), and trochlear nerve (CN IV) paresis (c: superior oblique muscle palsy) due to a space occupying lesion (metastasis) in the anterior lateral cavernous sinus (d: ax. T2 WI; e, f: ax. T1 WI; arrow) and the superior orbital fissure (f, arrowhead) with accentuated peripheral enhancement (f, g: arrow; g: cor. pc T1 WI)

Fig. 8 Right-sided acute incomplete cavernous sinus syndrome in an 84-year-old woman with abducens nerve palsy (a) and oculomotor nerve palsy (b) including ptosis and mydriasis. Axial T2 WI (c) and ax. T1 WI pc (d) 5 years before showing enlarged cavernous sinus (c, d: arrow) with inhomogeneous flow void (e, arrowhead). Actual pc CT (e, f) disclosing impressive extension of the intracavernous internal carotid artery (ICA) aneurysm (white arrow) with partial thrombosis (e, white arrowhead) and partial enhancement (e, f: black arrow). Note also ectasia of the basilar artery and the left ICA (e, f: black arrowhead).

Fig. 9 Tolosa-Hunt syndrome. Axial (a, b) and coronal (c, d) T1 WI disclosing slight enlargement of the anterior lateral cavernous sinus left (arrow) with inhomogeneous enhancement (b–d, arrow). Complete remission after four weeks of high dosage steroid therapy (not shown).
indirect fistula (Barrow type B–D) [60]. Direct CCF are defined by a direct vascular connection between the ICA and the cavernous sinus and are often caused by traumata involving the skull base [60, 61]. However, also intracavernous ICA aneurysm rupture or iatrogenic lesions caused by surgical or neurointerventional procedures may lead to direct CCF [31, 62]. Neurological examination discloses (in-)complete combined paresis of the CN III, IV, and VI resulting in (in-)complete internal and external OP on the affected side (Fig. 11a, b). In addition, patients typically suffer from orbital pain, progressive proptosis, conjunctival injection, chemosis, and secondary glaucoma [5, 7, 63].

Fig. 10 Orbital pseudotumor. Coronal T2 W1 (a) and T1 W1 pc (b) showing a space occupying lesion (a, b; arrow) with inhomogeneous contrast enhancement (b, arrow) and involvement of the optic nerve (a, b; arrowhead)

Fig. 11 Painful complete ophthalmoplegia left accompanied by exophthalmos, chemosis, and conjunctival bleeding (a) due to traumatic direct carotid cavernous sinus fistula (CCF). b After CCF occlusion declined exophthalmos and conjunctival bleeding, but persisting complete ophthalmoplegia with mydriasis. c Ax. CT pc showing enlarged cavernous sinus (arrow) and dilated superior orbital vein (arrowhead). d, e Digital subtraction angiography (DSA) disclosing direct CCF (d, arrow) and early retrograde filling of the dilated superior orbital vein (d, arrowhead). e Coil embolization (white arrow) and normal filling of the ophthalmic artery (black arrow). Note also regular filling of middle cerebral artery (MCA) and anterior cerebral artery (ACA) branches after endovascular CCF occlusion
Characteristic MRI features include asymmetric dilation of the cavernous sinus with increased flow void, dilatation of the superior orbital vein, and sometimes protrusion of the eyeball (Fig. 11) [63]. Time-resolved CT and MR contrast-enhanced angiography could demonstrate early enhancement of the cavernous sinus, and MR time of flight (TOF) angiography may show arterialized flow signal in the cavernous sinus [60, 61, 64–66]. In contrast, indirect vascular connection between the ICA and cavernous sinus (CCF Barrow types B–D) caused by dural arterial branches are often low-flow fistula [60]. In many cases, these CCF are only detectable on digital subtraction angiography (DSA), which is the gold standard [62]. CCF Barrow type B show arteriovenous fistula by meningeal branches of the ICA, Barrow type C meningeal branches of the external carotid artery (ECA), and type D of both ICA and ECA [60, 67].

**Anti-GQ1b antibody syndrome**

OP is also a core clinical feature in (Miller) Fisher syndrome (MFS) [68] and Bickerstaff’s encephalitis (BE) [69], both representing different conditions of the anti-GQ1b antibody syndrome [70, 71]. While in MFS the peripheral nervous system (PNS) involvement is more prominent, in Bickerstaff’s encephalitis as the so-called central nervous system (CNS) variant of the anti-GQ1b antibody syndrome, the alteration of the reticular formation with impaired consciousness is a typical clinical feature (see Fig. 12) [70–73]. However, neurological presentation may be incomplete and a continuous spectrum with variable PNS and CNS involvement exists [70]. Moreover, there is also an overlap between MFS and an axonal subtype of the Guillain-Barré Syndrome, i.e., acute motor axonal neuropathy (AMAN) [74, 75].

**Erdheim-Chester disease**

In case of unclear intracranial lesions and additional bony changes of the facial skull, in particular sinus walls and orbit, the differential diagnosis should include ECD, a rare systemic non-Langerhans cell histiocytosis of unknown etiology [76–78]. Erdheim-Chester disease (ECD) is characterized by bilateral symmetric long-bone involvement; however, in a recent study, up to 47% of patients had additional neurological symptoms [78, 79]. The widespread spectrum of neurological disorders encompasses cerebellar and pyramidal signs (41 resp. 45%), sensory disturbances, CN palsies, and ocular symptoms including DV and visual field defects [77–79]. Neuroimaging most often exhibits extraaxial mass lesions by foamy histiocytes with involvement of the meninges, the hypotalamic-pituitary axis, the orbit, and facial and/or skull base bone thickening [76, 80–82]. Intraaxial lesions are less common (17–23%) and MRI often shows infratentorial hyperintense signal abnormalities on T2 WI especially in the brainstem, the dentate nucleus, and the middle cerebellar peduncle [76–78, 81–84].

**Conjugate gaze abnormalities (internuclear and supranuclear disorders)**

**Horizontal gaze deficits**

**Internuclear ophthalmoplegia**

The medial longitudinal fascicle (MLF) is an internuclear pathway between the nuclei of CN III and VI, providing

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**Fig. 12** Autoimmune (Bickerstaff) encephalitis. A 36-year-old male suffering from progressive double vision, cranial nerve palsies III, IV, and VI, and gait ataxia. Ax. T2 WI (a, b) showing nearly symmetrical hyperintense signal changes of the mesencephalon and tegmentum (arrow) with inhomogeneous enhancement on pc T1 WI (c, arrow)
conjugated sideways gaze [1, 3–5]. MLF travels from the rostral midbrain along the pontine tegmentum to the cervical spinal cord (Fig. 1). Circumscribed lesion in the course of the MLF causes internuclear ophthalmoplegia (INO) and neurological examination shows impaired bulb adduction ipsilateral and dissociated nystagmus of the abducted bulb contralateral, resulting in collocate DV during lateral gaze (Fig. 13) [1, 3–5]. Both MLF are located close together, therefore INO is often bilaterally. In younger patients, etiology is most often multiple sclerosis (MS; Fig. 13) [85–89], whereas in the elderly, vascular lesions according to ischemia are more common (Fig. 14) [90–92]. Beside atherosclerosis of the basilar artery leading to occlusion of the orifices of the median and paramedian pontine perforators, microangiopathy may also cause lacunar infarcts in the dorsal brainstem (Fig. 14) [21, 90–92]. Lesions at the level of the paramedian pontine reticular formation (PPFR) (Fig. 1) additionally involve the nucleus of the abducens nerve (CN VI), and the clinical feature is “one and a half syndrome” [1, 3, 5, 93, 94]. In neurological examination, ipsilateral bulb adduction and abduction as well as contralateral bulb adduction is nullified, and only abduction of the contralateral eyeball with dissociated nystagmus is preserved (see Fig. 15) [1, 93, 94]. Moreover, additional facial nerve involvement during his course around the CN VI nucleus (inner CN VII knee) will cause the so-called eight and a half syndrome with additive ipsilateral peripheral CN VII palsy [95–97].

Wernicke encephalopathy

Wernicke encephalopathy (WE) is characterized a global state of confusion, ataxia, OP, and nystagmus [98]. However, clinical presentation is often incomplete and isolated oculomotor disorders or disturbance of consciousness may be present [98–100]. The underlying etiopathology of this serious disease is thiamine (vitamin B1) deficiency often caused by malnutrition, e.g., chronic alcoholism, and if untreated, WE may be followed by an irreversible amnestic syndrome, i.e., Korsakow psychosis [98]. Oculomotor disturbances most often consist of an incomplete horizontal gaze palsy with accentuated abduction deficits and horizontal nystagmus (Fig. 16a–c) [4, 98]. The accountable lesions are located in the periaqueductal gray matter and the tectal plate (Fig. 16d–f) [84, 98–101]. In addition, MRI may show often symmetrical lesions in the periventricular regions of the hypothalamus and thalamus with a high rate of thiamine-related glucose and oxidative metabolism, the pulvinar, the mammillary bodies, the bottom of the forth ventricle, and midline structures of the cerebellum [99–101]. Due to the severe irreversible cause of the disease without sufficient thiamine (vitamin B1) substitution, the knowledge of typical MRI features of WE is of critical importance [99, 100]. Moreover, MRI may be the key for correct diagnosis especially in patients showing only psycho-pathological abnormalities or incomplete symptoms on neurological examination [100, 102]. Whereas in the acute stage of the disease within the first 6 days, contrast enhancement of

Fig. 13 Bilateral internuclear ophthalmoplegia (INO) in a 32-year-old man suffering from primary progressive multiple sclerosis (MS). a INO left with adduction deficit left; see also divergent eyeballs on ax. T2 WI; b black arrow. b INO right presenting with adduction deficit right. c bilateral hyperintense lesions (white arrows) along the course of the medial longitudinal fascicles (MLF) in the pontine tegmentum
the above-mentioned structures may be detectable, in the sub-
acute and chronic phase hyperintense signal changes on T2
WI and FLAIR accompanied with different degrees of
circumscribed atrophy are detectable (Fig. 16) [99]. In addi-
tion, DWI may exhibit slight lowering of ADC values in
the acute phase [103, 104]. When treated sufficiently in
due time, clinical syndromes as well as MRI abnormalities
may resolve completely. However, residual slight hyperin-
tense signal changes on T2 WI and FLAIR may persist
over time [99, 103].
Also affecting respective mesencephalic and other
brainstem regions, other inflammatory diseases, e.g.,
Bickerstaff encephalitis [69–73, 105], Beh et’s disease,
and paraneoplastic brainstem encephalitis, metabolic

Fig. 14  Axial (a) and sag. (d) T2 WI showing a small hyperintense lesion of the MLF in the pontine tegmentum paramedian right (a, arrow) due to acute
infarction (b, c: ax. and cor. diffusion-weighted images, DWI; b = 1000 s/mm²; arrow) in a 66-year-old man suffering from INO right

Fig. 15  One-and-a-half syndrome in a 41-year-old woman. Axial (a) and sag. (d) T2 WI demonstrating lacunar infarct (arrow; b, c: ax. and
cor. DWI; b = 1000 s/mm²; arrow) in the lower pontine tegmentum
paramedian right at the level of the abducens nucleus (see also
Fig. 14d). Right (e) and left (f) gaze exhibiting complete horizontal paresis of the right eye and adduction deficit of the left eye
disorders including mitochondriopathies, e.g., Kearns Sayre Syndrome [19, 106], Wilson disease, and neoplastic lesions, e.g., brainstem glioma, may cause gaze palsy and/or combined CN palsies [19]. However, detailed description goes beyond the scope of this review, and it is referred to further specific literature.

Abnormal horizontal conjugate gaze deviations

The frontal eye fields located in the prefrontal cortex, i.e., cortical Brodman’s area 8, initiate and regulate the contralateral gaze movements [1, 5]. Therefore, lesions affecting the cortical frontal eye fields result in a gaze preference toward the
side of lesion due to preponderance of the contralateral cortical eye fields [1, 2, 5]. This “deviation conjuguée” is also called “right way eyes” sign, and depending on to the extent of the lesion, additional contralateral neurological symptoms such as hemiparesis and sensation deficits may be present. Most often, large infarcts in the middle cerebral artery (MCA) territory with involvement of the prefrontal branches (anterior M2 segment) cause a “deviation conjuguée” toward the side of lesion [1, 2, 5]. However, exceeding stimulation of the frontal eye fields may provoke preponderance for the contralateral gaze, so-called “wrong way eyes” sign [1, 2, 5]. Etiology for the more rarely contralateral “deviation conjuguée” includes seizures especially with focal epileptic activity and atypical located intracerebral hemorrhages [1, 2]. Regarding acute stroke management, it is of interest if the horizontal conjugate gaze deviation is conquerable or not and therefore represents an important item in the National Institute Health Stroke Scale (NIHSS).

**Vertical gaze deficits**

**Paramedian rostromesencephalic and inferomedial thalamic infarcts**

Vertical gaze palsy may be due to bilateral paramedian rostromesencephalic and inferomedial thalamic infarcts (Fig. 17) leading to dysfunction of the rostral interstitial nucleus of the MLF (Bender’s theory) [22–24, 107–112]. The infarcts are located in the territory of the posterior thalamoperforating arteries (PTPA) originating from the P1-segment (precommunicating segment) of the posterior cerebral artery (PCA) [23, 24, 111–117]. Bilateral inferior paramedian infarcts are a likely consequence, when the origin of the PTPA is a common trunk according to type II of Percheron (Percheron’s artery) [113, 114]. Due to the highly variable vascular supply of the rostromesencephalic and paramedian thalamic nuclei [90, 115, 116], additional neurological symptoms such as impairment of consciousness, somnolence up to coma, cognitive deficits, hemis syndromes, and oculomotor nerve palsy may occur (“top of the basilar artery syndrome”) [110]. Besides Bender’s theory with bilateral innervation of vertical eye movement, also unilateral paramedian thalamic infarcts may cause vertical gaze palsy [8, 118–120]. One reason therefore might be that frontocortical neuronal pathways decussate in the medial thalamus and unilateral infarcts may cause interruption of supranuclear input [118].

**Progressive supranuclear palsy**

In the first clinical description by Steele, Richardson, and Olszewski [121], this neurodegenerative disease was characterized with the neurological triad of (1) supranuclear vertical gaze palsy, (2) slowing of vertical saccades, and (3) postural instability (Fig. 18). However, for clinical diagnosis of progressive supranuclear palsy (PSP), new criteria have been established, because two-third of all patients suffering from PSP lack to show characteristic oculomotor disorders [122–124]. The Richardson syndrome (PSP–RS) is consistent with the initial description mentioned above [123]. In addition, different clinical phenotypes of PSP were defined including corticobasal syndrome, PSP with Parkinsonism (PSP–P), semantic variant of primary progressive aphasia (PPA), and the non-fluent agrammatic variant of PPA [122, 123]. These new diagnostic PSP criteria defined by the Movement Disorder Society differentiate three levels of diagnostic certainty, i.e., probable, possible, and suggestive PSP [123]. However, definite diagnosis of PSP requires neuropathological conformation of protein tau aggregates. The different clinical features of PSP may be a likely consequence of different anatomic seeding and spreading properties of intracellular aggregates of protein tau.

Structural MRI in PSP presenting with the classical Richardson syndrome (PSP–RS) disclose midbrain atrophy with reduction of the midbrain anterior-posterior (ap.) diameter and concavity of the dorsolateral midbrain margins (Mickey Mouse or Morning Glory sign; Fig. 18) [125–127]. The reduction of the ap. diameter below 15 mm at the level of the interpeduncular fossa was described to be specific for PSP [125–128]. However, reduction of the midsagittal midbrain area in manual performed measurement seems to be a sensitive tool for PSP identification and differentiation from other multisystem atrophies (MSA), e.g., cerebellar type of MSA (MSA-C; formerly: olivo-ponto-cerebellar atrophy; OPCA) [124, 128]. Moreover, the MR Parkinsonism index (MRPI), which includes also evaluation of the superior and middles cerebellar peduncles, is a very reliable MR biomarker for the diagnosis of PSP–RS [123, 124, 128, 129]. Additionally, T2 WI may show also symmetrical planar hyperintense signal changes in the dorsolateral mesencephalon caused by the neurodegenerative process [126].

**Parinaud syndrome**

Characteristic neurological presentation in Parinaud syndrome includes vertical gaze palsy, disturbance of the pupillary motoric going along with mydriasis, light–near–dissociation, and convergence–retraction nystagmus [1, 5, 130, 131]. The syndrome is often caused by compression of the dorsal midbrain and pretectal area, e.g., space- occupying lesions of the pineal gland and the tectal plate. Most often, tectal tumors are gliomas, but also focal dysplasias as well as ganglioneural tumors may occur [130, 131]. However, also hydrocephalus and periaqueductal lesions may generate Parinaud syndrome [5, 9].
Widespread different pathological processes in the orbit can cause OP, such as inflammatory diseases including IgG4-related orbital diseases (IgG4-ROD) and other systemic autoimmune associated pathologies, tumors, e.g., lymphoma, meningioma, and hemangioma, and also traumatic orbital lesions (see Table 1) [132, 133]. Besides isolated orbital myositis or systemic myositis (Fig. 19) [134–137], the extraocular
muscles (EOM) may be affected by myasthenia gravis or metabolic disorders. Typical metabolic etiologies include endocrine orbitopathy (Fig. 19) and mitochondrial related disorders, the latter often manifesting as chronic progressive external OP. In Kearns-Sayre Syndrome, MR imaging may show hyperintense brainstem lesions on T2 WI especially in the pontine tegmentum.

An important differential diagnosis of orbital inflammatory processes is the IgG4-ROD (Fig. 9). Histopathology of this multifocal inflammatory disease exhibits dense lymphocytic infiltrates especially containing IgG-4 plasma cells and fibrosis causing tumefactive lesions. Usually, the disease responds promptly to systemic steroid therapy, but relapses may occur and escalation of immunosuppressive therapy using monoclonal antibodies, e.g., Rituximab, is a likely consequence. IgG4-ROD may involve the lacrimal glands, the EOM, and the orbital soft tissue. Most often, the so called orbital inflammatory pseudotumor is an IgG4-ROD. In orbital trauma and OP, differential diagnosis should include fracture of the orbital bottom with herniation and entrapment of the inferior rectus muscle and also pseudo-Duane syndrome.

**Oculosympathetic paresis (Horner syndrome)**

The Horner syndrome (HS) is defined by ptosis and miosis but normally reactive pupil, and facultative anhidrosis due to ipsilateral disturbance of oculosympathetic fibers. Failed sympathetic innervation of the iris dilator muscle on the affected side caused miosis with consecutive anisocoria, and paresis of the Müller’s muscles of the eyelids results in ptosis, also called “upside down ptosis” or “reverse ptosis” (Fig. 20a). The combination of the upper eyelid ptosis and the lower eyelid elevation visually is suggestive of enophthalmus. However, this is not a true enophthalmus. Due to synaptic interconnections, three topographic locations of the disturbed oculosympathetic pathway can be differentiated: (1) central or first-order neuron HS, (2) preganglionic or second-order neuron HS, and (3) postganglionic or third-order neuron HS (see Table 4).

**Central or first-order neuron HS**

In central HS, the lesion of the uncrossed sympathetic fibers is located in their course beginning at the posterior hypothalamus, passing through the lateral brainstem and the medulla oblongata downwards to the spinal cord at the level C8–T2. The heterogeneous etiology includes hypothalamic bleedings, tumors, brainstem infarcts, and inflammatory or infectious myelitis of the spinal cord. Typical clinical presentation of dorsolateral medulla oblongata infarcts (Fig. 20) is the Wallenberg Syndrome, defined by ipsilateral HS, ataxia, dysfunction of the CN V, IX, X, and contralateral hypalgesia.
Most often, Wallenberg’s syndrome is caused by ipsilateral distal vertebral artery occlusion at the level of the intradural V4 segment, but also diseases of the proximal posterior inferior cerebellar artery (PICA) compromising the circumferential branches supplying the lateral and especially the dorsolateral medulla oblongata are possible pathologies [149].

**Preganglionic or second-order neuron HS**

The lesion of the sympathetic fibers is located between the exit from the ciliospinal center and the synapses in the superior cervical ganglion at the level of the proximal ICA [5, 45, 148]. Beside traumatic spinal root and/or brachial plexus lesions, also apical lung diseases, e.g., Pancoast tumor or other space-occupying processes (e.g., metastasis or lymphoma) in the neighborhood of the fiber course toward the superior cervical ganglion as well as inflammatory etiologies may cause HS (see Table 4). Neuroimaging should encompass complete course of preganglionic fibers including the aortic arch [45, 146, 150].

**Postganglionic or third-order neuron HS**

The postganglionic oculosympathetic fibers run in the ICA wall, i.e., the internal carotid plexus, whereas the sudomotoric fibers, which innervate the facial sweat glands, travel along the external carotid plexus on the surface of the arterial wall [45]. Therefore, HS caused by ICA dissection is often referred to as an incomplete HS, because facial anhidrosis does not occur due to spared sympathetic sudomotoric fibers in the external carotid plexus (Fig. 21) [45, 151–154]. Within the cavernous sinus, the oculosympathetic pathway travel a short distance along with the CN VI and then switch over to the first portion of the trigeminal nerve (CN V), i.e., the ophthalmic nerve. Therefore, the combination of CN VI palsy and HS is highly suggestive for a lesion in the dorsolateral portion of the cavernous sinus [45, 155]. More peripherally located pathologies of the ophthalmic nerve, e.g., Herpes zoster ophthalmicus, may cause HS. In addition, besides ICA dissection, also neck tumors, skull base lesions, and diseases of the cavernous sinus may induce postganglionic HS [45, 146, 148].

In a large case series of 450 patients, Maloney WF et al. [147] reported 65% (270 pat.) to have a demonstrable cause for the HS. These 270 patients showed preganglionic HS in 44%, postganglionic HS in 43%, and the remaining 13% suffered from central HS. In isolated HS, neuroimaging detects underlying pathology in 20%, most often ICA dissection (Fig. 21) [153]. Therefore, especially painful isolated HS constitutes a red flag, implicating diagnostic clarification in an emergency setting [146, 153]. However, when planning the MRI scan, it should be kept in mind that in the acute stage of ICA dissection within day 1–4, especially proton density-weighted images (PD WI) are sensitive for intramural hematoma with hyperintense signal changes [151, 153]. In contrast, unenhanced T1 WI with fat suppression (FS) disclose isointense signal of the hematoma due to absent intracellular methemoglobin within the first days after dissection onset. Hyperintense signal of the intramural hematoma will appear after day 4 caused by metabolism of desoxyhemoglobin into methemoglobin [151, 153].
Key learning points

1. OP and HS can be the overture to a life-threatening neurological disorder, especially when pain is present at the same time. In this respect, imaging plays a central role in the clarification of OP or HS at acute onset.

2. A precise neurological diagnosis with topical assignment of the anatomical structures involved is essential for a targeted neuroimaging using specialized investigation protocols.

3. Diseases going ahead with OP can be divided into (a) efferent peripheral neuroophthalmic disorders involving oculomotor CN, (b) conjugate gaze abnormalities due to internuclear or supranuclear disorders, and (c) diseases of the orbit and the EOM.

4. Isolated or combined oculomotor CN palsies may occur particularly in the subarachnoid, cavernous, and orbital compartments, and have heterogeneous etiologies.

5. Painless induced CN III palsy may be caused by impaired microcirculation within the CN as well as by circumscribed paramedian mesencephalic infarcts.

6. Due to its long cisternal course and subsequent entry into the Dorello canal with ligamentary fixation, the abducens nerve is particularly vulnerable to intracranial hypotension.

7. Horizontal gaze deficits are often caused by lesions of the MLF.

8. Differential diagnosis of acute vertical gaze deficits should include paramedian rostomesencephalic and inferomedial thalamic infarcts, most often bilaterally.

9. Widespread different pathological processes in the orbit can cause OP, such as inflammatory diseases including IgG4-ROD and other systemic autoimmune associated pathologies, tumors, and also traumatic orbital lesions.

10. The knowledge of pathophysiologic aspects of OP is crucial, especially since some entities of OP cannot be identified by imaging, e.g., in neuromuscular junction disorders.

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Compliance with ethical standards

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Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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