arise at different times, and they also follow completely independent courses. Apart from a small subset of patients who die at birth, or in the first 6 months of life from hepatic or respiratory failure, and exceptional adult cases, all patients ultimately will develop a progressive and fatal neurological disease. Systemic disease, when present, always precedes onset of neurological symptoms, but the systemic component may be absent or minimal in approximately 15% of all patients, and close to half of the adult-onset patients, at least at the time of diagnosis. In typical patients, the neurologic disorder consists mainly of cerebellar ataxia, dystarthisa, dysphagia, and progressive dementia, and the majority of cases show a characteristic vertical supranuclear gaze palsy (VSGP) [36]. Cataplexy, seizures, and dystonia are other quite common features, and psychiatric disturbances are frequent in late-onset patients. The proper recognition of VSGP is essential but this sign is often overlooked at an early stage, because slow pursuit is often maintained although saccade velocity is already impaired. Cataplexy (with or without narcolepsy), usually laughter-induced, is another more specific symptom [37,38]. Except for the perinatal period, the systemic disease is usually not very severe and is well tolerated. The splenomegaly has been described to fluctuate and to decrease with time. Severe lung involvement has been reported in a few patients but is not frequent.

A description of the various clinical forms by age categories has been used in recent reviews [10,11,27] and will also be followed in this summary. Detailed complementary information can be obtained in [27]. For each age category except for the perinatal presentations, one should however distinguish patients entering the disease by systemic involvement [39] from those who are starting then their neurological disease (although they may have presented earlier with visceral symptoms). Of essential importance is to note that the age of onset of the systemic symptoms is not related with that of the neurological disease (the latter can occur many years or even decades later), while there is a correlation between the age of onset of the neurological symptoms and the general further course of the disease and lifespan (Fig. 1). Categorizing patients by forms based on the age range of onset of the neurological symptoms [11,32,40], irrespective of the age of the first symptom, is very useful for genetic counseling, natural history studies and also in clinical practice. With an exception for the severe early infantile neurological form which is quite significantly distinct, recent large studies have however demonstrated an overlap between the neurological forms, and thus a continuum [27]. A schematic representation is proposed in Fig. 2.

**Perinatal presentation**
Nieman-Pick C disease is now recognized as a relatively common cause of liver disease in early life. Fetal hydrops or fetal ascites can be observed [28]. Above all, a prolonged neonatal cholestatic icterus, appearing in the first days or weeks of life and usually associated with progressive hepatosplenomegaly is present in close to half of patients, although with very variable intensity [29,41,42]. In most cases, the icterus resolves spontaneously by 2 to 4 months of age, and only hepatosplenomegaly remains for a highly variable period, preceding onset of neurologic symptoms (see below). In about 10% of these patients, however, the icterus quickly worsens and leads to liver failure. Children with this dramatic "acute" neonatal cholestatic rapidly fatal form usually die before the age of 6 months [29]. Some other infants, especially (but not exclusively) those having mutations in the NPC2 gene, present with a severe respiratory insufficiency (together with hepatosplenomegaly or more severe liver disease) that may also be fatal. In two patients, lung lavage, radiology and histology showed signs of pulmonary alveolar lipoproteinosis [43,44]. Patients with NP-C do not show neurological manifestations during the neonatal period (important for differential diagnosis). But there are many examples of patients dying from a severe perinatal form having siblings with a neurologic infantile or juvenile onset form [11,29].

**Early infantile period (2 months-2 years)**

**Systemic stage**
An isolated hepatosplenomegaly can be discovered at this age period, which may well stay isolated for many years, in spite of the early onset. Once the diagnosis of NP-C is made, a regular neuropaedic follow up should be initiated.
Severe early infantile neurologic onset form
In these infants, hepatosplenomegaly has almost invariably been present since birth or the first months of life. Delay of developmental motor milestones from the age of 8-9 months and central hypotonia constitute the first neurologic symptoms, which become evident between the age of 1 and 2 years. Subsequent clinical course includes a loss of acquired motor skills, proportionally less marked mental regression, followed by pronounced spasticity with pyramidal tract involvement. Many of these children never learn to walk. Intention tremor is frequently present; supranuclear gaze palsy is usually not recognized. Seizures are uncommon. Brain imaging (MRI and MRS) shows signs of leukodystrophy and cerebral atrophy. Survival rarely exceeds 5 years. This form seems to be more frequent in Southern Europe (where it constitutes >20% of the cases) and the Middle East [11,29,32].

Late infantile period (2 to 6 years)
Systemic stage
Many patients start their disease by discovery of an isolated hepatosplenomegaly or splenomegaly during this period. Regular neuropediatric follow-up should be initiated, as above.

Late infantile neurologic onset form
Hepatosplenomegaly has almost invariably been present for a varying length of time. Language delay is frequent. The child often presents with gait problems, frequent falls and clumsiness between 3 and 5 years of age, due to ataxia. VSGP is usually present but may not be recognized at an early stage. Hearing loss has also been described. Cataplexy develops relatively frequently and may occasionally be the presenting symptom. The motor problems worsen, and impairment in mental development becomes more obvious. A significant proportion of patients develop seizures which may be partial, generalized, or both. They generally respond to standard treatment but refractory cases may occur, with some patients dying from status epilepticus or complications of seizures. Severe epilepsy has a bad prognosis and significantly shortens the lifespan of the patients. As ataxia progresses, dysphagia, dysarthria, and dementia develop. At later stages, the patients develop pyramidal signs and spasticity, and pronounced swallowing problems. Most
require gastrostomy. Death most often occurs between 7 to 12 years in this form.

**Juvenile period (6-15 years) (classical form)**

**Systemic stage**

Discovery of an isolated splenomegaly (or, rarely, of a hepatosplenomegaly) at this period may again be the inaugural sign of the disease, and these patients should later be appropriately monitored.

**Juvenile neurologic onset form**

This constitutes in most countries the most common form of the disease. A moderate splenomegaly (or hepatosplenomegaly) is frequent, and may have been detected at any earlier time, including the neonatal period. However, cases in whom a splenomegaly had been noted in early childhood but is hardly detectable at the time first neurological symptoms arise are not rare; and absence of a detectable organomegaly has been reported to occur in at least 10% of cases. School problems with difficulties in writing and impaired attention are very common and may lead to misdiagnosis. The disease may also mimic dyspraxia. VSGP is almost invariably present and often the initial sign. The child becomes clumsy and shows more learning disabilities. Cataplexy, with or without narcolepsy, typically laughter-induced, is another common symptom. Ataxia soon becomes obvious, with frequent falls and difficulties to run, and progresses at a variable rate. Dysarthria develops, as well as dysphagia. Action dystonia is also frequent. Motor impairment is major and intellectual decline may be variable. About half of the patients with the classic form develop seizures of variable type and severity (see above). At a later stage, dysarthria worsens and patients often stop talking. At a late stage, patients develop pyramidal signs and spasticity, and pronounced swallowing problems, requiring gastrostomy. The lifespan is quite variable, some patients being still alive by age 30 or later [27].

**Adolescent and adults (>15 years)**

**Systemic adult form of NP-C**

The finding of three patients aged 53-63 years with isolated splenomegaly and a biochemical and molecular diagnosis of NP-C [45-48] suggests the existence of a rare non-neuropathic form of the disease (possibly corresponding to the ill-described historical "type E"). Nevertheless, apart from these exceptional cases and from infants with early death, as stated above, all NP-C patients develop neurologic symptoms.

**Adult neurologic onset form**

More patients with a neurologic adult onset form of the disease (often in the second or third decade, but as late as 50 years or older) have been described in recent years [30,35,49-53] This diagnosis is probably underestimated. Absence of clinically detectable splenomegaly has been reported in a significant proportion of patients but abdominal sonography may reveal a slightly enlarged spleen. VSGP is usually present but may also be missing. The most common symptomatology is that of an attenuated juvenile form with an insidious onset, with in at least one third of cases, a psychiatric presentation that may be isolated for several years before the onset of motor and cognitive signs. Psychiatric signs are most often consistent with psychosis, including paranoid delusions, auditory or visual hallucinations, and interpretative thoughts. Onset may be acute or progressive, eventually with relapses. At this stage the neurologic examination may be normal. Other types of psychiatric disturbances are depressive syndrome, behavioral problems with aggressiveness, or social isolation. Cases have also been reported with bipolar disorders, obsessive-compulsive disorders, or transient visual hallucinations. From compilation of the literature [35] the most common features are: cerebellar ataxia (75%), vertical supranuclear ophthalmoplegia (75%), dysarthria (63%), cognitive troubles (61%), movement disorders (58%), splenomegaly (54%), psychiatric disorders (45%) and dysphagia (37%). Movement disorders (dystonia, Parkinsonism, chorea) are more frequent than in the juvenile form. Some patients show severe ataxia, dystonia, and dysarthria with variable cognitive dysfunction, whereas psychiatric symptoms and dementia dominate in others. Epilepsy is rare in adult onset NP-C (15%). Later course is similar to that in the juvenile form.

**Etiology**

Mutations in either of the two genes, NPC1 or NPC2, may cause the disease [13-16]. Approximately 95% of patients have mutations in the NPC1 gene, which encodes a large membrane glycoprotein with mostly a late endosomal localization [54]. The remainder have mutations in the NPC2 gene, which encodes a small soluble lysosomal protein that binds cholesterol with high affinity [16,55,56]. Mutations in the NPC1 or NPC2 genes result in a similar cellular lesion, including a unique impairment in processing and utilization of endocytosed cholesterol that could explain cholesterol storage and secondary alterations of sphingomyelin metabolism in extra neural tissues. Glycolipids and free sphingosine/sphinganine storage also occurs. In brain, - more specifically in neurons - the dominant lipid accumulation is in fact that of GM2 and GM3 gangliosides, with only limited apparent abnormalities of cholesterol (see below). Early studies in cells and tissues from NP-C1 and NP-C2 patients could not disclose any biochemical marker that was specific to any of the groups, suggesting that both proteins may function in tandem or sequentially [14]. Comparison between double mutant mice deficient in both NPC1 and NPC2 and the single mutants demonstrated a non-
redundant functional cooperativity of the two proteins in a common pathway for lipid cellular transport, which strengthened this concept [18]. The exact functions of the NPC1 and NPC2 proteins are still unclear [10-12,56,57], which greatly complicates understanding of the pathophysiology. Neuronal storage with megalurite formation and extensive growth of ectopic dendrites, as well as formation of neurofibrillary tangles, are important neuropathological features together with neuroinflammation and neuroaxonal dystrophy. As the disease progresses, neuronal death becomes prominent, affecting more specifically certain regions, particularly Purkinje cells of the cerebellum, but the basis of this selective neuronal vulnerability is still unknown [10,58].

Lipid accumulation in tissues

Similar profiles have been observed in NP-C1 and NP-C2 patients (and animal models), but the pattern of accumulating lipids is different in brain and in non-neural organs [10,18,20,40,59-64]. In liver and spleen, a complex pattern, with no predominating compound, is observed. Accumulated lipids include unesterified cholesterol and sphingomyelin (2- to 5-fold increase in human patients), bis(monoacylglycerol) phosphate (also named LRP or BMP), glycolipids (essentially glucosylceramides and lactosylceramide), and free sphingosine and sphinganine. In human patients, the level of storage is more pronounced in the spleen than in the liver, where changes may be subtle. In brain tissue, neither cholesterol nor sphingomyelin overly accumulate, but significant alterations of glycosphingolipids occur, especially for gangliosides GM2 and GM3 (10-20 fold increase). Free sphingolipids levels are much less elevated in brain (x3) than in liver or spleen (x20) [62,64]. Myelin lipids are markedly affected in the NPC1 mouse model but in patients, a significant decrease is only seen in the early infantile neurological onset form [18,60].

Cell biology and cholesterol transport, and the brain enigma

Initial studies by Peter Pentchev and associates and further work from several laboratories (reviewed in [10,20]) demonstrated, in cultured skin fibroblasts of Niemann-Pick C disease patients, a disruption in intracellular transport of endocytosed cholesterol. Endocytosed low density lipoproteins are delivered to late endosomes/lysosomes, where they are hydrolyzed, so that free cholesterol is released. In normal cells, this cholesterol is transported rapidly out of endosomes to the plasma membrane and the endoplasmic reticulum. In Niemann-Pick C disease cells (either NPC1 or NPC2), the cholesterol does not exit the endocytic pathway but accumulates within lysosomes. This anomaly constitutes the cellular hallmark of the disease. Due to this sequestration, the subsequent induction of all low-density lipoprotein cholesterol-mediated homeostatic responses (more specially cholesteryl ester formation) is retarded in Niemann-Pick C disease cells. Normal responses can be induced by membrane-permeable oysterol and by mevalonate, showing that the ability of the cell to respond is maintained. Very recently, it was further shown that the block in cholesterol delivery to the ER can also be overcome by 2-hydroxypropyl-beta-cyclodextrin [65], and that this compound added to fibroblasts reduces the lysosomal cholesterol accumulation [66]. Studies in patients’ cells showed that lysosomal storage of unesterified cholesterol may show a variable intensity, and a “variant” biochemical phenotype with mild abnormalities has been described [67,68]. Later work showed that this phenotype was underlined by specific NPC1 mutations (see below). Unexpectedly, fibroblasts from a large proportion of obligate heterozygotes have been found to show mild but definite changes [67-70].

This unique impairment in processing and utilization of endocytosed cholesterol obviously plays a key role in the pathogenesis of Niemann-Pick C disease, and, at least in extraneural organs, could actually explain a more general dysfunction of intracellular metabolism of lipids [63]. Sphingomyelin accumulation appears related to lysosomal cholesterol storage, since sphingomyelinase activity can be strongly modulated in fibroblast cultures of Niemann-Pick C disease patients by incubation in presence or absence of low-density lipoprotein. Cholesterol accumulation might also modulate glucosylceramide hydrolysis [71], as well as the trafficking of late endosomal proteins such as Rab 9 and mannose-6-phosphate receptors [72], two key players in the normal function of the endosomal/lysosomal system. There is thus good evidence that cholesterol accumulation in the late endosomal/lysosomal compartment can impair vesicular trafficking pathways.

The pathogenesis of the neuronal dysfunction appears by far more complex, since brain cholesterol is synthesized locally, mostly by oligodendroglial cells and to a lesser extent by astrocytes and neurons. Neurons might also acquire a small amount of cholesterol by glial delivery through apo-E uptake [73]. By chemical measurement, no significant increase of cholesterol concentrations can be found in dissected cerebral grey matter from human patients [60]. In situ labeling using filipin histochemistry, however, reveals a sequestration of unesterified cholesterol in cell bodies of neurons and glia of single NPC1 or NPC2 mutant mice as well as those of the double mutant [18,58,73-75]. These observations are not necessarily contradictory, since studies on cultured sympathetic neurons from NPC1 mutant mice gave indication that cholesterol did accumulate in cell bodies, but was decreased in distal axons, leading to a distribution imbalance [76,77]. One group has reported that endoge-
ously synthesized cholesterol may significantly contribute to the overall cholesterol accumulation observed in Niemann-Pick C disease in various cell types, including glial cells [78]. Nevertheless, since abnormal filipin staining of neurons is also observed in a wide spectrum of other lysosomal storage disorders [discussed in 63], the exact participation of cellular cholesterol transport abnormalities in the pathophysiology of the neurodegenerative NP-C disease remains elusive. Of note, fibroblasts from patients with an adult-onset of neurological symptoms may show either a severe cholesterol trafficking defect or only minimal alterations (biochemical variant) [35,69,70]. Conversely, in two "variant" siblings who had died from a juvenile form, the liver showed no lipid accumulation (spleen did), but the brain showed typical accumulation of GM2 and GM3 gangliosides [79].

The NPC1 and NPC2 proteins
The mature native NPC1 is a large (1252 amino acids) glycoprotein with 13 transmembrane domains, that resides primarily in late endosomes and interacts transiently with lysosomes and the trans-Golgi network [54,80]. It possesses a sterol-sensing domain (amino acid residues 615-797) showing homologies with those of HMG-CoA reductase, SCA1, patched and NPC1L1, the exact role of which is still unclear although it appears necessary for protein function. Two luminal domains may play a role in protein-protein interactions: a cysteine-rich loop with a ring-finger motif which harbors about 1/3 of the mutations described in patients (amino acid residues 855-1098), and a highly conserved domain with a leucine-zipper motif, located in the N-terminal tail (amino acids 25-264) [81]. Importantly, the latter has been shown to possess a cholesterol-binding site (reviewed in [56]). Contrary to the NPC1 protein, the NPC2 protein is small (132 amino acids), soluble, secreted and recaptured. It is transported to the lysosome via the mannose-6-phosphate receptor and binds cholesterol with submicromolar affinity [56]. The mutation p.S120P (observed in a patient with a juvenile neurological onset and slowly progressive form [82]) has been instrumental to confirm the functional significance of the cholesterol-binding site of the NPC2 protein [83]. Studies in patients and animal models have shown that both NPC2 and NPC1 are required for cholesterol egress from the lysosome. Binding of cholesterol to NPC1 and dissociation both appear accelerated by NPC2 [83]. Based on the current stage of knowledge but fully compatible with earlier studies (reviewed in [56]) a "handoff" model has recently been proposed for the coordinated role of the two proteins [19]. In this model, cholesterol released within the lysosome binds to NPC2 with its hydroxyl group exposed; a transfer to the N-terminal domain of NPC1 occurs reversing its orientation, so that the hydrophobic side chain could lead the way into the membrane and/or the glyocalyx. The most recent studies [65] indicate that the role of NPC2/NPC1 proteins in cholesterol transport is restricted to lysosomal export. Current data suggest that retrograde cholesterol movement from the plasma membrane to the ER does not require NPC1 [65] and implication of these proteins in cell processing of endogenously synthesized cholesterol [84] is still a matter of discussion.

Many uncertainties thus remain regarding the precise and complete functions of the NPC1 and NPC2 proteins. It has also been suggested that they could be involved in fusion/fission events between the late endosome and the lysosome. One important (and yet unanswered) question is whether these proteins – at least NPC1 - also directly regulate or mediate retrograde transport of other lysosomal cargo. Glycolipids, which constitute the main lipid accumulation in the brain, by opposition to the quantitatively minor cholesterol imbalance in neurons, are good candidates. The storage of GM2 and GM3 gangliosides in brain is not specific. Yet, the increase of GM2 occurs much earlier and is more prominent in NP-C than in other lysosomal diseases [63]. But no data supportive of a glycolipid transport by NPC1 or NPC2 have been published so far. It has also been postulated that sphingosine storage could be the primary trigger of a pathogenic cascade in NP-C since this lipid can disrupt calcium homeostasis in NPC1 lysosomes [85,86]. The latter studies, however, were conducted in non neural NP-C cells or in a drug (U18666A)-induced model. In brain, currently available data show a close link between accumulation of the different lipids, both in developmental terms and after therapeutic attempts [63,64]. No ganglioside or sphingosine accumulation can be detected in the brain of human fetuses at 24 gestational weeks, although the liver already shows a pronounced storage. Arguments for and against each of the accumulated lipids as the offending metabolite have recently been discussed [86]. Most likely, stored lipids (and possibly other metabolites) collectively contribute to the pathology. More work is clearly needed to better understand the cause of brain dysfunction in Niemann-Pick C disease. In particular, the mechanisms by which Purkinje cells and other neurons degenerate remain unclear.

Disease-causing mutations and genotype-phenotype relationships
The Niemann-Pick type C disease variation database [87] listed by January 2010 248 NPC1 and 18 NPC2 gene sequence variants. Reporting from diagnostic laboratories, however, has not been exhaustive, and the current number for identified NPC1 disease-causing mutations is most likely close to 300. More than 60 polymorphisms of NPC1 have also been described, some of them very common. In early genetic complementation studies, it was
stated that about 95% of the families had mutations in the NPC1 gene [14]. In France, among the 132 families genotyped so far, 9 had NPC2 mutations. To date, only ca 30 families have been identified worldwide with mutations in the NPC2 gene. Several large mutational studies have been published [33,47,82,87-97], but only few functional studies [47,82,91,98-101].

The NPC1 gene, mapped to chromosome 18q11-q12, spans 56 kb and contains 25 exons. One mutant allele, p.I11061T, is particularly frequent [26] (approximately 20-25% of alleles in patients diagnosed in France or the United Kingdom). This mutation is also highly prevalent in patients from a Spanish-American isolate from the upper Rio Grande valley, but much less frequent in Portugal, Spain or Italy [91,94,96]. In the homozygotic state, it is associated with prominent cellular cholesterol trafficking abnormalities in fibroblasts of patients, and it correlates with a juvenile neurologic onset form of the disease [26]. In the heterozygotic state, so far it has never been found associated with the most severe infantile neurologic onset form. The I11061T mutant was shown to be a functional protein selected for endoplasmic reticulum-associated degradation due to protein misfolding and thus a potential target for chaperone therapy [98]. The second most recurrent NPC1 mutation in Europe, p.P1007A, is the prototype of a "biochemical variant" mutation [47,89,95]. In the homozygotic state, it has been described in a family with two adult onset siblings [91]. A number of other recurrent NPC1 mutations seem to be associated with adult neurological onset of the disease [35,95]. The mutation p.G992W, typical of Nova-Scotian patients [17] is sporadically (but rarely) found in patients of other origin. As more patients are genotyped, a larger number of recurrent mutations are observed, some of them preferentially found in patients from defined ethnic origin.

The ten genotype-phenotype studies published so far in NP-C patients generally showed good correlation between nonsense or frameshift mutations and the most severe neurologic course. Missense mutations have emphasized the functional significance of two particular domains of the NPC1 protein. Homozygotic mutations in the sterol-sensing domain were found to be very deleterious, corresponding to a lack of mature NPC1 protein and to a very severe disease phenotype, biochemically and clinically [47]. The cysteine-rich luminal loop contains approximately one third of all described mutations, with a variable cellular and clinical impact [47,89,93,95]. Among others, it harbors the three most frequent mutations discussed above. Interestingly, mutations leading to a less severe impairment of cellular trafficking ("variant" phenotype) are typically located on this loop [47,90,91,93-95]. Genotype-phenotype correlations for more specific mutations have been discussed in earlier reports [11,88,95].

The NPC2 gene (initially known as HEI), mapped to chromosome 14q24.3, spans 13.5 Kb and contains 5 exons [16]. One nonsense mutation (E20X) appears relatively frequent [82,92], and many other mutations also lead to a truncated protein. They have so far been associated with very severe clinical phenotypes. Described missense mutations have corresponded to more varied phenotypes, including juvenile and adult onset patients [82,92,93,101].

Finally, for both NPC1 and NPC2, the study of a large number of multiplex families has clearly shown that mutations correlate with the neurological form of the disease, but not with the systemic manifestations [11].

**Diagnostic methods**

The laboratory diagnostic algorithm proposed in a recent consensus report [27] is given in Fig. 3.

**Initial clinical assessment**

Suspecting Niemann-Pick disease type C is relatively easy in patients with the most typical symptoms, such as combined splenomegaly, ataxia, and supranuclear vertical gaze palsy. However, as described earlier, strikingly different clinical presentations exist, especially in infants and neonates. The fact that isolated spleno- or hepatosplenomegaly can be the presenting symptom long before neurologic onset has not been emphasized enough. Finally, the diagnosis is often very delayed (and probably often not made) in neurological cases lacking organomegaly, and in psychiatric cases. Consequently, the age at which the diagnosis is established is very variable. This is illustrated by data obtained in the author's laboratory for a representative cohort of patients (Fig. 4).

The characteristic key signs and symptoms in the systemic, ophthalmological and neuropsychiatric areas have been discussed above and the reader is also referred to a recent review [27]. A comprehensive clinical examination should be performed. The neurological evaluation must include muscle tone and strength tests, motor reflexes, assessment of movement (ataxia and dystonia) and swallowing testing [27]. Psychometric assessment is also important.

The ophthalmological assessment is of particular importance, because abnormal saccadic eye movements (SEM) are often the earliest neurological sign in NP-C. Proper examination is not always done, and reported findings are sometimes neglected in the global evaluation of the patient. The initial SEM deficit is in the vertical plane (downward, upward, or both). VSGP can be described as an increased latency of initiation of vertical saccades, with gradual slowing and eventual loss of saccadic velocity [27,102,103]. Subsequently, horizontal gaze is also affected. Cataplexy ranges from subtle signs (minor
head-drop or falls, often confused with seizures) to full collapse in response to lumbar stimuli [27].

Neurophysiologic and neuroradiologic studies
Hearing tests (audiogram and/or brainstem evoked potentials) often show abnormalities. MRI and CT scans are not very useful for diagnosis, as they may be normal or show cerebellar or cortical atrophy, or, in the severe infantile form, white matter changes. Some rare patients have been described with a peripheral neuropathy.

Histology
Foam cells and sea-blue histiocytes are usually - but not always - present in bone marrow. Foam cells stain strongly positive with filipin. Ultrastructural studies on skin [104], conjunctival, or liver biopsies can provide strong support for the diagnosis, but false-negative results often occur on liver biopsy studied by light microscopy only [41].

Non-specific laboratory analyses
Routine laboratory tests usually give normal results, except in patients with cholestatic jaundice or hypersplenism. Low HDL-cholesterol is a frequent but not universal finding. Plasma lipid profiles seem correlated to severity of cholesterol trafficking abnormalities [97]. Cholesterol and ester activity is usually mildly elevated [105] but can be normal. Acid sphingomyelinase activity is normal or elevated in leukocytes (differential diagnosis with Nie-
mann-Pick type B or atypical type A) but often partially deficient in fibroblasts [11,25,29,67].

Specific laboratory diagnosis
Biochemical/cell biology study: the "filipin" test
The demonstration of impaired intracellular cholesterol transport and homeostasis is considered the primary diagnostic test for NP-C. These studies require living cells and thus a skin fibroblast culture. They should be conducted in specialized centres with the required experience. The "filipin test" is the most sensitive and specific assay. Fibroblasts are cultured in a LDL-enriched medium, then fixed and stained with filipin (a compound forming specific complexes with unesterified cholesterol). Fluorescence microscopic examination of NP-C-positive cells typically reveals numerous strongly fluorescent (cholesterol-filled) perinuclear vesicles. This "classical" storage pattern is observed in approximately 80-85% of cases. A lesser (and variable) level of storage is seen even under optimized conditions [67] in the remaining cases, described as having a "variant" biochemical phenotype [67,68]. As discussed above, several recurrent NPC1 mutations are known to result in this "variant" biochemical phenotype. Note that a similar, mildly abnormal filipin pattern, has been observed in a number of heterozygotes [69,70], but also not infrequently in acid sphingomyelinase deficiencies. Measurement of the LDL-induced rate of cholesteryl ester formation was until recently systematically used as a secondary test, showing very low levels in cell lines with a "classical" biochemical phenotype but only a mild or non-significant impairment in those with a "variant" phenotype [67,68]. As this test is complex, costly and time-consuming, mutation analysis is now often initiated directly when the filipin study is clearly positive.

From the experience of the author, based on the study of cells from more than 600 NP-C patients, demonstration of cholesterol accumulation in cultured fibroblasts provides a clear-cut diagnosis in a majority of cases, but making a decision can be very difficult in some cell lines showing only minor abnormalities. In such cases, (and eventually in cases with apparently negative filipin but a history highly suggestive of NP-C), complementary mutation analysis is very useful to reach a definitive diagnosis.

Genetic testing
It is highly advisable to undertake gene testing in every newly diagnosed patient, since molecular genetic study is today the highly preferred strategy for prenatal diagnosis, and the only reliable one for identification of carriers in blood relatives. Furthermore, as discussed above, gene testing can sometimes be necessary to confirm or disprove the diagnosis of NP-C. Genetic complementation studies - performed earlier in a few laboratories to define which gene was affected - are no longer used today, because cell hybridization and further testing are more elaborate than gene sequencing. Sequencing of all exons and boundaries is more laborious for the NPC1 gene (25 exons) than for the NPC2 gene (5 short exons), which is unfortunate, since over 95% of NP-C patients have pathological NPC1 mutations. Rapid methods have been published to test for the two most frequent mutations [26,47]. Identification of NPC1 mutations can, in some instances, be difficult and may require combined studies of gDNA and cDNA. All groups have met a common problem, namely that in some patients mutations could be identified in only one allele, and in a few of them, no mutation at all. The latter patients have raised the question of a potential third gene causing NP-C. This cannot be excluded, but often the possibilities of large deletions, or of deep intronic mutations [106] have not been investigated. Finally, due to the highly polymorphic nature of NPC1, interpretation of new missense mutations should be undertaken with caution.

Differential diagnosis
In the neonate and young infant, Niemann-Pick disease type C must be differentiated from idiopathic neonatal hepatitis, and other causes of cholestatic icterus. Onset of cholestasis usually occurs in the early neonatal period. Associated splenomegaly is a useful orientation sign. In case of isolated splenomegaly or hepatosplenomegaly, NP-C should be considered as a possible cause. Among other lipidoses, the most obvious differential diagnoses are Niemann-Pick type B (similar foam cells in bone marrow) and Gaucher disease. In older children and adults, depending on the symptoms, other conditions with cerebellar ataxia, dystonia, catalepsy and supranuclear gaze palsy need to be considered [27,31].
Genetic counseling
Niemann-Pick C disease is genetically inherited following an autosomal recessive mode. The genetic status of a blood relative can be reliably established if mutations have been identified in the family index case. However, it is not currently possible to ascertain the status of a person from the general population, due to the complexity of NPC1 gene sequencing and its polymorphic nature. Antenatal diagnosis is possible under the conditions described below.

The possibility of symptomatic heterozygotes has been raised in three families known to the author but ruled out in two of them (no further study in the third one). Two disease-causing NPC1 mutations had been identified in each index case. In both families, the father of the proband developed progressive symptoms compatible with an adult onset neurologic form of NP-C. Subsequent complete gene sequencing revealed one allele carrying the mutation transmitted to the affected child, and another (not transmitted) disease-causing mutation on the other allele (M.T. Vanier and K. Harzer; M.T. Vanier and A. Ivanou, unpublished). These individuals were thus NP-C1 homozygotes with an adult onset form. These exceptional histories illustrate some of the problems eventually posed by the clinical heterogeneity of NP-C and the possible underestimation of adult-onset form of the disease.

Antenatal diagnosis
Prenatal diagnosis of NP-C should be offered to couples at risk [27,107,108]. It is best achieved using chorionic villus sampling (CVS) at 10-12 weeks, but is also possible on amniotic cells. Molecular genetic analysis is today by far the preferred strategy [27], for several reasons. Unlike the cellular biology testing using flupin-staining, it does not require cultured cells and a lengthy elaborate work up. The results can be obtained much earlier in pregnancy, and the tests can in principle be set up in any good molecular biology laboratory. It however requires that mutations have been identified on both alleles in the index case, or at least that suitable intragenic markers have been identified in the nuclear family. Today, few laboratories offer a prenatal test using the cellular biology strategy, which should be considered as a last resort due to its many drawbacks. Results will not be reached until 5-7 weeks after the sampling; the tests are technically difficult; besides, they are fully reliable only when the proband has shown severe abnormalities, thus excluding 15-20% of the families.

Management including treatment
To date, management remains largely symptomatic. Information and support to families can be obtained through organizations specifically devoted to Niemann-Pick diseases (in the United States, United Kingdom, Germany, Spain, Italy, Argentina, Australia, Poland), to lysosomal diseases (France) or to inherited metabolic diseases (The Netherlands) [see appendix for websites]. Genetic counseling should be made available for family members. For detailed guidelines on current management of patients, the reader is referred to a recent publication compiled by an International Working Group [27]. A study on the cost of illness associated with NP-C in the UK has recently been published [109].

Symptomatic management
Seizures generally respond at least partially to antiepileptic drugs until a fairly advanced stage of the disease. Catalepsy can usually be controlled by clonipramine, protriptyline, or modafinil. Anticholinergic agents have been reported to improve dystonia and tremor in some patients. Physiotherapy is useful in the management of spasticity and the prevention of contractures. Melatonin may be used to treat insomnia. Patients with a slow disease course may benefit from special schooling for handicapped children. Proper management of infections and of feeding difficulties (gastrostomy) is essential at an advanced stage of the disease.

Specific treatment
In the murine and feline NPC1 models, bone marrow transplantation (BMT) did not improve the neurological disease, not unexpectedly considering the properties of the NPC1 protein; similarly, after BMT the neurologic status of a child continued to deteriorate, although there was a regression of hepatosplenomegaly and lung infiltration [110]. In addition, liver transplantation performed in a few cases with cirrhosis did not influence the course of neurologic deterioration [111]. On the contrary, because the NPC2 protein is soluble, secreted and recaptured, there is a rationale supporting early hematopoietic stem cell transplantation in NP-C2 patients [82]. The long-term outcome is yet unknown, but encouraging results have recently been obtained in one patient transplanted at 18 months and followed up until 3 years of age [112].

Treatment strategies based on the hypothesis that cholesterol is the offending metabolite were first proposed in the early 90’s. The combination of hypcholesterolemic drugs and a low-cholesterol diet seemed to partially reduce the cholesterol load in liver, but no amelioration of the neurological disease was seen in patients after 2 years of treatment [31].

Since glycolipid storage appears to contribute to at least some of the neuropathologic features, an iminosugar inhibitor of glucosylceramide synthase (miglustat, also known as N-butyl-deoxyxojirimycin, NB-DNJ and OGT 918, later approved for substrate reduction therapy of mild to moderate type 1 Gaucher disease), was admini-
tered to *npc1* mutant mice and cats. It resulted in delayed onset of the neurological symptoms in both species, and a 20% longer survival of the mice [113]. A controlled clinical trial was thus initiated in neurologically symptomatic patients, first in adolescents and adults (12 years and above) [114], then in children (4-12 years). Long-term data from open-label extension treatment (up to 66 months) have now been reported in children [115] as well as in juvenile and adult patients [116] (reviewed in [27]). Overall, the disease course stabilized in 72% of patients treated for one year or more, based on a composite assessment of horizontal saccadic eye movement velocity, ambulation, swallowing and cognition. In January 2009, the European Union has extended the indication of miglustat to the treatment of progressive neurological manifestations in adult and pediatric patients with NP-C, and the drug is now approved for this indication in several other countries. This represents the first specific treatment for NP-C. Apart from single case reports [117,118], an international, multicenter observational cohort study in 66 patients treated off-label with miglustat has been published [119]. Evaluation made with a modified disease-specific disability scale [32] further showed a significant reduction in the annual rate of progression of the disease in a majority of patients: Late-onset forms generally appeared as the best responders. A further case series from Spain has been documented [120]. Longer term studies will be important to better evaluate the disease progression following the stabilisation phase [121]. Indication, clinical utility and monitoring of treatment with miglustat have been recently discussed [27,122]. In short, it has been recommended to treat patients as soon as they show neurological manifestations of any type. Due to the known adverse effects, such as diarrhea, flatulence, weight loss and tremor, it is not recommended today to treat patients with systemic disease only. Note that miglustat is not expected to have an effect on the systemic manifestations of NP-C.

**Disease monitoring**

In order to monitor disease progression and, if applicable, patient responses to treatment, it is important to regularly quantify the degree of disability resulting from neurological impairment. Two disease-specific disability scales have recently been proposed [32,123]. The first one [32] (Table 1) evaluates four key parameters: ambulation, manipulation, language and swallowing, with a 4 to 5 point scale for each. This allows calculation of a composite score representing overall "functional disability". Although not formally validated, it has already been used successfully in several cohort studies. Recent natural history surveys using these different scales both concluded to a linear clinical progression over time [123,124]. The cohort including a broader - and thus more representa-

tive - range of clinical phenotypes [124] showed a more rapid course in the patients with an early onset.

Useful monitoring tests have been recently discussed in detail [27]. Several methods for analysis of movement abnormalities [125,126] or neuropsychological profiles [127] have also been proposed. Results on these patients indicated that longitudinal MRS studies [128] might prove useful for follow up of therapy [129]. Diffusion tensor imaging has also been proposed [130].

**Experimental therapeutic approaches in animal models**

Extensive research towards other therapeutic avenues is currently underway on animal and cellular models. These approaches have been reviewed in [27]. Various transgenic mice have been generated, such as mice over expressing Rab9, a protein involved in intracellular trafficking [131-133], or mice expressing NPC1 only in one particular brain cell type [134]. Most studies have however been conducted on the *npc1*Δm mouse and a cat model (both spontaneous *npc1* mutants) [135,136], as well as a transgenic *npc2* mouse mutant [18]. These animals are particularly useful to study brain dysfunction, and facilitate various types of experiments, including administration of various compounds with a therapeutic goal. Data have been published in the mouse using imatinib [137], curcumin [65], non-steroid anti-inflammatory drugs [138], neurosteroids (allopropregnanolone) in combination with 2-HP-β-cyclodextrin [139], and with 2-HP-β-cyclodextrin alone [64,140]. Chronic subcutaneous administration of high doses of 2-HP-β-cyclodextrin resulted in a striking reduction of the various stored lipids both in the liver and the brain of NP-C mice, as well as a very significant effect on their lifespan [64]. An orphan drug designation has been sought for this compound from the US-FDA. However, translation of most of these studies to human patients is not straightforward. Even neglecting adverse effects [141] or the purity or homogeneity of certain compounds, a quite general and major limitation is the usual early timing of treatment (usually long before symptoms appear). Such experimental work in the whole animal is, however, important as it is generally felt that future treatment plans will combine several approaches and will be tailored to the individual.

**Prognosis**

NP-C is a severe disorder that invariably leads to premature death, with few exceptions (three proven cases aged 53 years or more with isolated splenomegaly are known) [45-48]. However, as discussed above, the rate of progression and life span show considerable variation. The systemic disease can be fatal in early infancy. Patients with fetal hydrops survive at most a few days. Liver failure causes rapid death (before 3-6 months of age) in approxi-
Table 1: NP-C functional disability scale (from [32] and [27])

<table>
<thead>
<tr>
<th>Ambulation</th>
<th>Score</th>
<th>Language</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>Autonomous ataxic gait</td>
<td>2</td>
<td>Mild dysarthria(^d)</td>
<td>2</td>
</tr>
<tr>
<td>Outdoor assisted ambulation</td>
<td>3</td>
<td>Severe dysarthria(^d)</td>
<td>3</td>
</tr>
<tr>
<td>Indoor assisted ambulation</td>
<td>4</td>
<td>Non-verbal communication</td>
<td>4</td>
</tr>
<tr>
<td>Wheelchair bound</td>
<td>5</td>
<td>Absence of communication</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manipulation</th>
<th></th>
<th>Swallowing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>Slight dysmetria/dystonia(^a)</td>
<td>2</td>
<td>Occasional dysphagia</td>
<td>2</td>
</tr>
<tr>
<td>Mild dysmetria/dystonia(^b)</td>
<td>3</td>
<td>Daily dysphagia</td>
<td>3</td>
</tr>
<tr>
<td>Severe dysmetria/dystonia(^c)</td>
<td>4</td>
<td>NG tube or gastric button feeding</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NG, nasogastric; \(^a\) autonomous manipulation; \(^b\) requires help for tasks but able to feed self; \(^c\) requires help for all activities; \(^d\) understandable; \(^e\) only comprehensible to certain family members.

Maturely 10% of neonates presenting with a cholestatic icterus, and a few patients (most of them with a severe NPC2 mutation) have died from severe pulmonary insufficiency. Neonatal cholestatic icterus is otherwise transient and usually resolves spontaneously by 4 months of age. Splenomegaly very rarely leads to hypersplenism. An important observation is that the age of onset of the systemic disease is generally unrelated to the subsequent neurological involvement and cannot be used as a predictor. This is well illustrated in Fig. 4, where several patients diagnosed in their first months of life are now teenagers. In the vast majority of patients, the lifespan is in large part determined by the age of onset of nervous system involvement. Data on large cohorts of patients recently compiled for Spain, the UK and France [27] are well in line with earlier reports. Patients with the severe neurologic early infantile form often die between 3 and 5 years of age, those with a late-infantile neurologic onset usually between 7 and 12. Patients with a juvenile neurologic onset survive until adolescence or later, with a sizable proportion reaching the age of 30. In a review of 68 cases with adult onset [35], the mean age at death (on 20 patients) was 38 ± 10.2 years, but some patients have reached the age of 70. Motor involvement is often more severe and more rapidly progressive than mental retardation. Progressive and severe dysphagia requiring gastrostomy is a common complication. Severe and intractable epilepsy accelerates the downhill course of the disease. Psychiatric disturbances, in rare cases, may be prominent or even dramatic.

Regarding recurrence within a sibship, the study of many multiplex families has shown that as a rule, the neurological form - as defined by age of onset of neurological symptoms, and irrespective of the age of onset of the systemic disease - is similar between siblings. The subsequent course can however show variations, especially for cases developing severe epilepsy. On the other hand, there are many examples of families with one case of fetal hydrops or fatal neonatal liver disease and a sibling having a more classical neurovisceral form - more often of the early infantile type, but also of the late infantile or juvenile type.

Correlations between the neurological form and the severity of the cholesterol trafficking lesion as found by the filipin test has been discussed previously [11,67,70]. In brief, in the experience of the author, a "variant" biochemical phenotype tends to correlate with a less rapid course, since it has so far never been found in the most severe early infantile neurological form, is rare in late infantile forms, but seen in a number of juvenile and nearly half of the adult onset patients. On the other hand, finding a very severe cholesterol trafficking impairment (massive cholesterol accumulation in lysosomes) is not predictive of any form of the disease (seen in the other half of adult-onset patients).

Finally, although genotype-phenotype correlations are limited, in NP-C1, some degree of prediction is often possible. Thus far, the p.I1061T allele has not been associated with the most severe infantile neurological form [11,47]. Frameshift or nonsense mutations, as expected, but also
misse mutations affecting the sterol sensing domain usually have a severe impact. On the other hand, association with a mutation leading (when in the homozygous state) to an adult onset form usually results in a slowly progressive juvenile or early adult onset form [95].

Unresolved questions
NP-C is a disease with many unresolved questions. To begin with, the precise and complete function(s) of the NPC1 and NPC2 proteins are still largely unknown. Only few studies on cholesterol transport and metabolism have addressed the brain, in spite of the fact that brain has a cholesterol metabolism that is different from that in cells from systemic origins [142]. The nature of the primary offending metabolite in brain is also unknown. For these reasons, meaningful high throughput drug screening strategies are difficult to set up.

A major practical problem is the current lack of a biochemical test with sufficient specificity to be used for screening- or even better, diagnosis - that could be carried out on a blood sample. Having to start from a skin biopsy excludes NP-C from all 'metabolic screens' and significantly contributes to the delay in diagnosis. Importantly, recent pilot study indicates that plasma of patients with NP-C show a specific oxyester profile that could be used as a biomarker [143]. This observation may impact the future diagnostic strategy.

As regards therapy, because the NPC1 protein, unlike many other lysosomal proteins, is not secreted and recaptured, many therapeutic strategies that are currently holding promises for the future seem not easily applicable to NP-C, including cell and gene therapy. Another difficulty to treat the brain dysfunction is the unknown nature of the primary target. Along line, the potential mode of action of some experimental compounds (among which is β-cycloxdextrin) remains a puzzling question. Finally, the broad clinical spectrum, as well as the lack of good disease markers and clinical endpoints, makes evaluation of therapeutic trials particularly difficult.

List of abbreviations

CT: computed tomography; 2-HP-β-cycloxdextrin: 2-hydroxypropyl-β-cycloxdextrin; LDL: low-density lipoproteins; NP-C: Niemann-Pick type C; NP-C1: Niemann-Pick type C disease with mutations in the NPC1 gene; NP-C2: Niemann-Pick type C disease with mutations in the NPC2 gene; MRS: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; VSGP: vertical supranuclear palsy.

Appendix

Niemann-Pick diseases support groups and corresponding websites

1. Specific Niemann-Pick diseases support groups:
   - UK: Niemann-Pick disease Group (UK) http://www.niemannpick.org.uk
   - Germany: Niemann-Pick Selbsthilfegruppe Deutschland http://www.niemann-pick.de
   - Spain: Fundacion Niemann-Pick de España http://www.fnp.es
   - Italy: Associazione Italiana Niemann-Pick http://www.niemannpick.org
   - Australia: Australian NPC disease Foundation http://www.npdc.org.au
   - Poland: Stowarzyszenie Chorych na NPC
   - France (with antennas in French speaking areas of Belgium and Switzerland): Vaincre les Maladies Lysosomales http://www.vml-asso.org
   - The Netherlands: Volwassenen Kinderen en Stofwisselingsziekten http://www.stofwisselingsziekten.nl

Competing interests

In the past 3 years, MEY has been an invited speaker in meetings organized and sponsored by Actelion, in postgraduate courses sponsored by Shire educational grants, and has served in an advisory board for Actelion. She has received occasional honoraria from Actelion and Shire.

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References


Central ocular motor disorders, including gaze palsy and nystagmus

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Abstract An impairment of eye movements, or nystagmus, is seen in many diseases of the central nervous system, in particular those affecting the brainstem and cerebellum, as well as in those of the vestibular system. The key to diagnosis is a systematic clinical examination of the different types of eye movements, including: eye position, range of eye movements, smooth pursuit, saccades, gaze-holding function and optokinetic nystagmus, as well as testing for the different types of nystagmus (e.g., central fixation nystagmus or peripheral vestibular nystagmus). Depending on the time course of the signs and symptoms, eye movements often indicate a specific underlying cause (e.g., stroke or neurodegenerative or metabolic disorders). A detailed knowledge of the anatomy and physiology of eye movements enables the physician to localize the disturbance to a specific area in the brainstem (midbrain, pons or medulla) or cerebellum (in particular the flocculus). For example, isolated dysfunction of vertical eye movements is due to a midbrain lesion affecting the rostral interstitial nucleus of the medial longitudinal fascicle, with impaired vertical saccades only, the interstitial nucleus of Cajal or the posterior commissure; common causes with an acute onset are an infarction or bleeding in the upper midbrain or in patients with chronic progressive supranuclear palsy (PSP) and Niemann–Pick type C (NP-C). Isolated dysfunction of horizontal saccades is due to a pontine lesion affecting the paramedian pontine reticular formation due, for instance, to brainstem bleeding, glioma or Gaucher disease type 3; an impairment of horizontal and vertical saccades is found in later stages of PSP, NP-C and Gaucher disease type 3. Gaze-evoked nystagmus (GEN) in all directions indicates a cerebellar dysfunction and can have multiple causes such as drugs, in particular antiepileptics, chronic alcohol abuse, neurodegenerative cerebellar disorders or cerebellar ataxias; purely vertical GEN is due to a midbrain lesion, while purely horizontal GEN is due to a pontomedullary lesion. The pathognomonic clinical sign of internuclear ophthalmoplegia is an impaired adduction while testing horizontal saccades on the side of the lesion in the ipsilateral medial longitudinal fascicle. The most common pathological types of central nystagmus are downbeat nystagmus (DBN) and upbeat nystagmus (UBN). DBN is generally due to cerebellar dysfunction affecting the flocculus bilaterally (e.g., due to a neurodegenerative disease). Treatment options exist for a few disorders: miglustat for NP-C and antimyopyridines for DBN and UBN. It is therefore particularly important to identify treatable cases with these conditions.

Keywords Ocular motor · Examination · Neurodegenerative disorder · Diagnosis · Treatment

Introduction

Many patients present with symptoms of blurred vision, reduced visual acuity, 'bouncing images' (oscillopsia) or double vision. Other patients complain of dizziness, vertigo, postural imbalance, tendency to fall or recurrent falls, gait...
disturbances or ataxia. These symptoms may indicate a dysfunction of the ocular motor system [1]. Unfortunately, they are often overlooked simply because patients are not adequately clinically examined, although an impairment of eye movements is important for the differential diagnosis and, in particular, to ascertain whether the brainstem or the cerebellum is affected. Further, the examination of eye movements is of clinical relevance for several disciplines, especially neurology, ophthalmology, pediatrics and neuropsychiatry, internal medicine and otorhinolaryngology. In patients with an acute onset of the above-mentioned symptoms, the most important differential diagnosis is ischemia, bleeding or inflammation of the brainstem; they may also occur in Wernicke encephalopathy. If the symptoms are chronic or chronically progressive, possible causes can include metabolic, neurodegenerative, inherited or inflammatory disorders (multiple sclerosis or encephalitis) or tumors.

To classify the symptoms topographically, anatomically, a systematic clinical bedside examination of the different types of eye movements is mandatory, particularly to distinguish between central and peripheral ocular motor disorders [1, 2] and central and peripheral vestibular disorders [3, 4]. In this context, it is important to note that the bedside examination of eye movements, even without equipment-based additional investigations, is evidently even more sensitive for the diagnosis of acute vestibular syndromes and for differentiating between peripheral and central lesions than magnetic resonance imaging (including diffusion-weighted sequences) [5].

The diagnosis of an acute central disorder requires rapid admission to hospital as this may be caused by brainstem ischemia or bleeding. Clinical experience shows that the examination of patients with ocular motor disturbances presents a particular challenge for many clinicians for three reasons: first, the anatomy and physiology of the ocular motor, vestibular, and cerebellar systems are complex; second, the neurological and neuro-ophthalmological examinations require a systematic approach and an experienced diagnostic perspective; third, the interpretation requires an evaluation of all neuro-otological and neuro-ophtalmological findings within the context of the patient’s history. In addition to a precise topographic anatomical diagnosis of these disorders, one should focus on those forms of central ocular motor disorders and nystagmus that are treatable, such as downbeat nystagmus (DBN), upbeat nystagmus (UBN), Wernicke encephalopathy, Niemann–Pick disease type C (NP-C) and Gaucher disease type 3.

In the first part of this article, the different types of eye movements (along with their topographical-anatomical relevance), how to take a patient history and appropriate examination procedures are presented. The second part deals with the most common forms of central eye movement disorders and nystagmus. Any repetition is intentional as different perspectives based on clinical symptoms and functional anatomy are covered.

### Physiological forms of eye movements

Before we focus on pathological eye movements, we list here the physiological forms: (1) smooth pursuit, where the eye follows a moving target; (2) saccades, where the gaze rapidly jumps from one fixation point to another; (3) vergence eye movements (i.e. movements during which the eyes do not move in parallel but relative to one another); (4) vestibulo-ocular reflex (VOR); the signal triggering eye movements comes from the labyrinth, which keeps the image of the visual surroundings stable on the retina during head movements; (5) optokinetic reflex, which is triggered by moving visual targets and consists of smooth pursuit and saccades; and (6) gaze holding (i.e. the ability to keep the eyes in an eccentric position (see [1, 6]). With the exception of voluntary saccades and vergence/divergence saccades, all the other types of eye movements are reflexive movements. All these different types of eye movements serve to keep the visual target on the macula stable and thus avoid illusory movements (oscillopsia) and blurred vision under different conditions such as fixing a central or peripheral visual target, following a slowly or very quickly moving target, moving the head, or walking and running around.

### Patient history

Depending on the underlying cause, patients with ocular motor disturbances usually report the following symptoms in isolation or in combination: blurred vision, reduced visual acuity, double vision, jumping images (so-called oscillopsia) either while looking straight ahead, right/left or up/down (indicating an underlying nystagmus), or while turning the head or walking (indicating a deficit of the VOR), rotatory vertigo, postural imbalance, tendency to fall or brainstem-related symptoms (e.g., swallowing or speaking difficulties), cerebellar symptoms (e.g., coordination problems of the extremities), or symptoms of the inner ear (e.g., hearing loss or tinnitus).

### Clinical bedside examination of the ocular motor and vestibular system

A combined examination of these systems in patients with the above-mentioned symptoms is always necessary to make a correct anatomical diagnosis. An overview is given in Table 1.
Table 1 Overview of the examination of the ocular motor and the vestibular systems (modified from [3])

<table>
<thead>
<tr>
<th>Type of examination</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspection</td>
<td>Tilt or turn of head/body</td>
</tr>
<tr>
<td>Head/body posture</td>
<td>Palsy</td>
</tr>
<tr>
<td>Position of eyelids</td>
<td>Misalignment in primary position, spontaneous or fixation nystagmus</td>
</tr>
<tr>
<td>Eye position/motility</td>
<td>Horizontal or vertical misalignment</td>
</tr>
<tr>
<td>Position of eyes during straight-ahead gaze</td>
<td></td>
</tr>
<tr>
<td>Cover/uncover test</td>
<td>Determination of range of motility, gaze-evoked nystagmus (GEN), end-position nystagmus</td>
</tr>
<tr>
<td>Examination of eyes in eight positions (binocular and monocular)</td>
<td>GEN; horizontal and vertical, rebound nystagmus</td>
</tr>
<tr>
<td>Gaze-holding function</td>
<td>Smooth or saccadic</td>
</tr>
<tr>
<td>10–40° in the horizontal or 10–20° in the vertical and back to 0°</td>
<td>Latency, velocity, accuracy, conjugacy</td>
</tr>
<tr>
<td>Slow smooth pursuit movements</td>
<td>Inducible, direction, phase (reversal or monocularly diagonal)</td>
</tr>
<tr>
<td>Horizontal and vertical</td>
<td></td>
</tr>
<tr>
<td>Saccades</td>
<td></td>
</tr>
<tr>
<td>Horizontal and vertical when looking around or at targets</td>
<td></td>
</tr>
<tr>
<td>Optokinetic nystagmus (OKN)</td>
<td></td>
</tr>
<tr>
<td>Horizontal and vertical with OKN drum or tape</td>
<td></td>
</tr>
<tr>
<td>Peripheral vestibular function</td>
<td>Unilateral or bilateral peripheral vestibular deficit</td>
</tr>
<tr>
<td>Head-impulse test (for clinical examination of the VOR (Halmagyi–Curthoys test)):</td>
<td></td>
</tr>
<tr>
<td>rapid turning of the head and fixation of a stationary target</td>
<td></td>
</tr>
<tr>
<td>Fixation suppression of the VOR</td>
<td>Impairment of fixation suppression of the VOR</td>
</tr>
<tr>
<td>Turning the head and fixation of a target moving at same speed</td>
<td></td>
</tr>
<tr>
<td>Examination with Frenzel’s glasses</td>
<td>Peripheral vestibular spontaneous nystagmus versus central fixation nystagmus</td>
</tr>
<tr>
<td>Straight-ahead gaze, to the right, to the left, downward and upward</td>
<td>Head-shaking nystagmus</td>
</tr>
</tbody>
</table>

*GEN* gaze-evoked nystagmus, *OKN* optokinetic nystagmus, *VOR* vestibulo–ocular reflex

Head tilt

An abnormal position of the head toward the right or left shoulder is observed particularly in patients with paresis of the oblique eye muscles (e.g., palsy of the trochlear nerve or the superior oblique muscle, in which the head is turned to the non-affected side to lessen diplopia), or in those with an ocular tilt reaction (OTR) due to a tonus imbalance of the VOR in the roll plane [7, 8]. In the OTR the head is tilted to the side of the lower eye. A tilting of the head to the side of the lesion indicates either an acute unilateral peripheral vestibular lesion or an acute unilateral central lesion in the medulla oblongata (e.g., in Wallenberg’s syndrome) [9]. A head tilt to the contralateral side occurs in pontomesencephalic lesions [10, 11].

Examination of the eye position during straight-ahead gaze with the cover tests

When examining the patient, attention should be paid to the primary position of the eyes when the patient looks straight ahead, when one eye is covered or when each eye is covered alternately (alternating cover test), that is parallel position or horizontal or vertical misalignment. These tests allow diagnosis of latent or manifest strabismus. The prerequisite for all cover tests is the presence of foveal fixation.

The one-eye cover test

In the one-eye cover test heterotropia (i.e., manifest strabismus) can be observed in the uncovered eye; the latter moves when the other eye is covered (Fig. 1). Heterotropia is defined as a misalignment of the visual axes, even during binocular fixation. First, the patient is asked to fixate either a near target (at a distance of 30–40 cm) or one 5–6 m away. Then the examiner covers one eye and looks for correction movements of the now uncovered eye. If the uncovered eye moves: (a) from the inside outward, esotropia is present; (b) from the outside inward, exotropia; (c) from above downward, hypertropia and; (d) from below upward, hypotropia. The other eye is then examined. An
acute vertical divergence (so-called skew deviation; one eye is higher than the other) indicates a central lesion of graviceptive pathways as part of the so-called OTR.

The one-eye cover/uncover test.

The one-eye cover/uncover test is used to prove the presence of heterophoria (i.e. latent strabismus) (Fig. 1). This is a misalignment of the eye axes when a target is fixated with one eye only. It is important to perform the above-mentioned cover part of the test before the cover/uncover part to first exclude heterotropia. First, one eye is covered for about 10 s, then uncovered; the possible corrective movements of the previously covered eye are observed. If it moves: (a) outward, esophoria is present; (b) inward, exophoria; (c) downward, hyperphoria; and (d) upward, hypophoria.

The alternating cover test

This test is also useful to determine the maximum misalignment of the eye axes in both a tropia as well as a phoria. The alternating cover test is also helpful when establishing a vertical divergence/skew deviation (in the context of an OTR), i.e. a vertical misalignment of the eyes that cannot be explained by an ocular muscle palsy or damage to a peripheral nerve. In contrast to trochlear nerve palsy or superior oblique muscle palsy, in skew deviation as a component of the OTR the vertical misalignment changes little or not at all during different directions of gaze [12].

Clinical examination with Frenzel’s glasses or a Fresnel-based device

The magnifying lenses (+16 diopters) with light inside, on the one hand, prevent visual fixation, which typically suppresses a peripheral vestibular spontaneous nystagmus, and on the other, facilitate the observation of the patient’s eye movements (Fig. 2). The examination should include peripheral vestibular spontaneous nystagmus, head-shaking nystagmus (for this test the patient is instructed to turn their head quickly to the right and to the left about 20 times; then the eye movements are observed), positioning and positional nystagmus, as well as hyperventilation-induced nystagmus. Spontaneous nystagmus indicates a tonus imbalance of the VOR. If it is caused by a peripheral vestibular lesion, as in vestibular neuritis, the nystagmus is typically dampened by visual fixation, whereas central fixation nystagmus is not suppressed by fixation or may become even worse. Head-shaking nystagmus is due to a latent asymmetry of the so-called velocity storage of the VOR, which can be due to peripheral and central vestibular disorders. In a peripheral vestibular deficit, the head-shaking nystagmus heats toward the ear with intact labyrinthine function. So-called cross-coupling can occur in central cerebellar disorders: the horizontal head-shaking maneuver induces vertical nystagmus (see [1]).

Examination of the eye position in the nine eye positions

The position of the eyes should be examined when the patient is looking straight ahead in the eight eccentric
positions to look for: (a) a range of eye movements and thereby positional deficits of one eye (e.g., in cases of paresis of the ocular muscle with a misalignment of the axes of the eyes) or both eyes (e.g., in progressive supranuclear gaze palsy (PSP)); (b) gaze-evoked nystagmus (GEN; i.e. disorders of the gaze-holding function, described below); and (c) nystagmus, whether its intensity changes depending on the direction of gaze (e.g., in DBN an increase in intensity when looking to the right, left and downward, or in peripheral vestibular spontaneous nystagmus an increase when looking in the direction of the quick phase and a decrease when looking in the opposite direction (‘Alexander’s law’).

The examination can be performed with a small object for fixation or a small rod-shaped flashlight (Fig. 3). Using a small rod-shaped flashlight has the advantage that the corneal reflex images can be observed and thus ocular misalignments can easily be detected. It should be noted that it is important to observe the corneal reflex images from the direction of the illumination and to ensure that the patient attentively fixates the object. In the primary position one should first look for misalignment of the axes of the eyes and periodic eye movements, especially spontaneous nystagmus or so-called saccadic oscillations/intrusions. A nystagmus can be horizontal rotatory (typical for an acute vestibular neuritis), vertical downward or upward (DBN and UBN), or purely torsional. One should look for suppression of the nystagmus by visual fixation [typical for peripheral vestibular spontaneous nystagmus (see below)] or only slight suppression during fixation (or even an increase) of the intensity of the fixation (typical for central fixation nystagmus). Infantile/congenital nystagmus beats horizontally as a rule at various frequencies and amplitudes and increases during fixation.

Impaired visual fixation includes square-wave jerks (small saccades of 0.5°-5° with an inter-saccadic interval) which cause the eyes to oscillate around the primary position and are observed in progressive supranuclear palsy (PSP) or certain cerebellar syndromes. Other forms are ocular flutter (intermittent rapid bursts of horizontal oscillations without an inter-saccadic interval) or opsoclonus (combined horizontal, vertical and torsional oscillations also without an inter-saccadic interval) [13] which are not distinct forms of nystagmus but are so-called saccadic oscillations/intrusions. They occur in various disorders, for example, brainstem encephalitis, tumors of the brainstem or cerebellum, intoxication, or most often in paraneoplastic syndromes.

Examination for a gaze-holding deficit: GEN

The distinction between GEN (Fig. 3) and so-called endpoint nystagmus is a widespread clinical problem. Many healthy subjects have physiological end-point nystagmus during maximal eccentric gaze. End-point nystagmus is pathological if it lasts for longer than 20 s (sustained endpoint nystagmus), is notably asymmetrical, and/or is accompanied by other ocular motor disturbances [14].

GEN often allows a topographic anatomical diagnosis: (a) GEN in all directions occurs in cerebellar disorders, particularly impaired function of the flocculus/paraflocculus, and above all in neurodegenerative diseases, but can also be caused by drugs such as anticonvulsants, benzodiazepines or alcohol; (b) purely horizontal GEN can indicate a structural lesion in the area of the brainstem [nucleus prepositus hypoglossi, vestibular nuclei, and cerebellum (flocculus/paraflocculus)]—the neural integrator for horizontal gaze-holding function; (c) purely vertical GEN is observed in midbrain lesions involving the interstitial nucleus of Cajal (INC)—the neural integrator for vertical gaze-holding function; (d) dissociated horizontal GEN (greater in the abducting than the adducting eye) in combination with an adduction deficit is the sign of internuclear ophthalmoplegia (INO) due to a defect of the medial longitudinal fascicle (MLF), ipsilateral to the adduction deficit; (e) DBN usually increases when looking down, and especially to the side, most likely due to an additional gaze-holding deficit [15], so that the nystagmus beats diagonally downward in the sideward gaze (the cause of DBN is generally bilaterally impaired function of the flocculus/paraflocculus; (f) patients with GEN also often show a rebound nystagmus. To examine for so-called rebound
nystagmus, the patient should gaze for at least 60 s to one side and then return the eyes to the primary position. This can cause a transient nystagmus to appear with slow phases in the direction of the previous eye position. Rebound nystagmus generally indicates damage to the flocculus/paraflocculus or cerebellar pathways.

Clinical examination of smooth pursuit eye movements

The generation of smooth pursuit eye movements, which keep the image of an object stable on the fovea, involves diverse supra- and infratentorial structures: the visual cortex, medial temporal area, medial superior temporal area (MST), fronto eye fields (FEF), dorsolateral pontine nuclei, cerebellum (flocculus), and vestibular and ocular motor nuclei. These eye movements are influenced by alertness, a number of drugs and age. The patient is asked to track visually an object moving slowly in horizontal and vertical directions (10–20°/s) while keeping the head stationary. It is important that the subject is able to fixate the target. Corrective (catch-up or back-up) saccades are looked for; they indicate a smooth pursuit gain (ratio of eye movement velocity and gaze target velocity) that is too low or too high: a saccadic smooth pursuit in all directions indicates an impaired function of the flocculus/paraflocculus [e.g., in spinocerebellar ataxias, drug poisoning (anticonvulsants, benzodiazepines), or alcohol abuse]. However, marked asymmetries of smooth pursuit indicate a structural lesion. If the smooth pursuit is saccadic to the left, this indicates a left-sided lesion of the flocculus/paraflocculus.

Clinical examination of saccades

First, it is necessary to observe spontaneous saccades, for instance, when taking patient history and when triggered by visual or auditory stimuli. The patient is then asked to glance back and forth between two horizontal and two vertical targets (Fig. 4). The velocity, accuracy and the conjugacy of the saccades should be noted: (a) normal individuals can immediately reach the target with a single fast movement or one small corrective saccade; (b) slowing of saccades in all directions—often accompanied by hypometric saccades—occurs, for example, in neurodegenerative disorders or with intoxication (and with medication, particularly anticonvulsants and benzodiazepines); (c) isolated slowing of horizontal saccades is observed in pontine brainstem lesions due to a dysfunction of the ipsilateral paramedian pontine reticular formation (PPRF); this can be caused by ischemia, bleeding, pontine gliomas but also in Gaucher disease type 3, the later stages of NP-C and PSP; (d) isolated slowing of vertical saccades indicates a midbrain lesion in which the rostral interstitial medial longitudinal fascicle (rMLF) is involved, as in ischemic or neurodegenerative diseases, especially progressive supranuclear palsy or inherited disorders such as NP-C (in the latter, typically first downward and then downward and upward because there is a double innervation for upward saccades from the rMLF [16] —a bilateral lesion of the INC impairs the range of all types of vertical eye movements and is accompanied by a vertical GEN, and a lesion of the posterior commissure (PC) also impairs all types of vertical eye movements and is associated with a convergence-retraction nystagmus (see [1])); (e) hypermetric
saccades, which can be identified by a corrective saccade back to the object, indicate lesions of the cerebellum (especially the vermis) or the cerebellar pathways. Patients with Wallenberg’s syndrome make hypermetric saccades toward the side of the lesion and hypometric saccades toward the opposite side due to a dysfunction of the inferior cerebellar peduncle (conversely, defects of the superior cerebellar peduncle lead to contralateral hypermetric saccades); (f) a slowing of the adducting saccade ipsilateral to a lesion of the MLF is pathognomonic for INO; (g) delayed initiation of saccades is most often due to supratentorial cortical dysfunction affecting the frontal or parietal eye field (e.g., Balint’s syndrome) and is called oculomotor apraxia. Nowadays, the velocity of saccades can be quantified in clinical routine by video-oculography (Fig. 5), which also allows the detection of mild to moderate slowing of saccades that could be the first clinical sign of PSP, NP-C or Gaucher disease type 3.

Vergence test and convergence reaction

Vergence is tested by moving a target from a distance of about 50 cm toward the patient’s eyes or the patient looks back and forth between a distant and a near target. Looking at a nearby target causes vergence, accommodation and miosis (i.e., the convergence reaction). Neurons that are important for the convergence reaction are in the area of the mesencephalic reticular formation and the oculomotor nucleus. This explains why the convergence reaction is disturbed in rostral midbrain lesions and tumors of the pineal region and thalamus, and why abnormalities of vertical gaze are often associated with these defects. In certain neurodegenerative disorders such as PSP, convergence is also often impaired.

Inborn defects of the convergence reaction also occur in some forms of strabismus. Convergence-retraction nystagmus can be provoked by inducing upward saccades or by looking at a moving optokinetic drum with its stripes going downward. Instead of vertical saccades, rapid convergent eye movements that are associated with retractions of the eyeball occur. The cause is damage to the posterior commissure or, in rare cases, a bilateral disorder of the rostral interstitial nucleus of medial longitudinal fasciculus (rMLF). A spasm of the near reflex is a voluntary convergence accompanied by pupillary constriction. The latter is an important clinical sign for the diagnosis. Occasionally, spasm of the near reflex is psychogenic; it can mimic bilateral abducens palsy.

Examination with the optokinetic drum

The examination of eye movements with the optokinetic drum allows combined testing of smooth pursuit movements and saccades in horizontal and vertical directions (Fig. 6). It is especially helpful with uncooperative or drowsy patients and with children. Intact horizontal and vertical optokinetic nystagmus probably indicates intact function of the midbrain and the pons. One should look for: asymmetries (e.g., between right and left (indicates a unilateral cortical or pontine lesion); vertical worse than horizontal (indicative of a vertical supranuclear gaze palsy due to a mesencephalic lesion); dissociations of the two eyes (a sign of diminished adduction in INO); and reversal of pursuit (indicates congenital nystagmus).

The head impulse test: examination of the horizontal vestibulo-ocular reflex (VOR)

The most common bedside test of the examination of the VOR is the head impulse test, which examines the VOR at a high frequency [17]. To test the horizontal VOR the examiner holds the patient’s head between both hands, asks him to fixate a target in front of his eyes, and very rapidly turns the patient’s head horizontally approximately 20–30°.
to the right and then to the left [18]. This is the most important bedside test for VOR function. In a healthy subject this rotation of the head causes rapid, compensatory eye movements in the opposite direction with the same angular velocity as the head movements, so that the eye position in space remains the same. In this way the target also remains stable on the retina. For instance, in unilateral right-sided labyrinthine failure the eyes move during head rotations with the head to the right, and the patient has to perform a so-called re-fixation saccade to the left to fixate the target again. This is the clinical sign of a deficit of the VOR (in the high frequency range) to the right. If the findings of the bedside test are unclear, the use of a video-based head-impulse test is indicated; this allows the gain of the VOR to be quantified [19].

Testing visual fixation suppression of the VOR

Before testing the visual fixation suppression of the VOR, the examiner must be sure that the VOR is intact (see above). The patient is then asked to fixate a target in front of his eyes while turning his head as uniformly as possible with the same angular velocity as the target in front of the eyes, first horizontally and then vertically, back and forth at moderate speed. The examiner should watch for corrective saccades, which indicate a disorder of the visual fixation suppression of the VOR. If the visual fixation suppression of the VOR is intact, the eye position relative to the head position does not change, but if it is not intact (which is indicated by small corrective saccades and as a rule occurs with smooth pursuit abnormalities, as these two functions use the same neural pathways) this typically indicates lesions of the cerebellum (flocculus or paraflocculus) or of cerebellar pathways [20]. Drugs, particularly anticonvulsants, sedatives and alcohol can also impair visual fixation suppression of the VOR because of their effects on the cerebellum. It is important to note that, in the case of a concomitant bilateral vestibulopathy, visual fixation suppression looks normal because the VOR is not working.

Ocular motor disturbances

Topographically and anatomically, ocular motor disturbances can be classified as either peripheral or central. Peripheral forms affect the six outer and/or two inner ocular muscles or the oculomotor nerve, trochlear nerve or abduccens nerve. Patients with peripheral ocular motor disturbances often complain of diplopia, which intensifies in the direction of the paretic muscle/nerve. Peripheral ocular motor disturbances usually affect one eye only (important exceptions include myasthenia gravis, chronic progressive, external ophthalmoplegia).

Central forms usually affect both eyes. These are manifestations of functional impairments of the brainstem (Fig. 7), cerebellum, or (rarely) other higher level centers. Patients with central ocular motor disturbances may report unclear or blurred vision. If the ocular motor disturbance is slowly progressive, such as in PSP, cerebellar degeneration or NP-C, it may remain undetected for a long time. Usually, the extent of the subjective impairments also depends on how acutely the impairments develop.

Central ocular motor disturbances can be classified as follows:

- **Fascicular lesions**—defects of the short part of the individual ocular muscle nerves within the brainstem. These are very rare; at first glance they look like unilateral peripheral lesions, but are accompanied by central ocular motor disturbances.
- **Nuclear lesions**—defects of the oculomotor nucleus (because of the anatomical proximity, almost always both nuclei are affected), the trochlear nucleus, or the abduccens nucleus.
Supranuclear lesions—due to defects of ocular motor pathway systems or supranuclear nuclei (Table 2a). Supranuclear ocular motor disturbances usually impair the movement of both eyes, for example, in the form of gaze palsy, slowed saccades, saccadic pursuit, or a gaze-holding defect, because the structures that are higher level to the cerebral nerve nuclei are affected. Often, such ocular motor disturbances are associated with other neurological deficits, so that the ‘overlap’ of the neurological findings allows location of the level of the lesion in the brainstem region as well as the side.

Cerebellar impairments—lead to impaired smooth pursuit, gaze-holding function, or saccades (Table 2b).

Topographical anatomy

Only a few brainstem centers, which have clearly allocated functions, are important for triggering and controlling eye movements (Fig. 6; Table 2a). This makes their pathological anatomy easy to understand. The following simple clinical rule applies: horizontal eye movements are generated and controlled in the pontine region, whereas vertical and torsional eye movements originate in the midbrain.

Midbrain centers

The center for vertical saccades is the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), and the center for vertical gaze-holding function (the vertical and torsional neural integrator) is the interstitial nucleus of Cajal (INC). It is important to note that a normal floccular function is also required for gaze holding. Clinically, this means that an isolated vertical saccadic paresis or isolated vertical gaze deviation nystagmus would suggest a midbrain lesion.

Pontine and pontomedullary centers

The center for horizontal saccades is the paramedian pontine reticular formation (PPRF); clinically this means that isolated horizontal saccadic palsy indicates a pontine lesion, and a unilateral PPRF lesion will result in saccadic disturbances on the side of the lesion. The center for the horizontal gaze-holding function is the nucleus prepositus hypoglossi together with the vestibular nuclei and the vestibulocerebellum (the horizontal neuronal integrator). Purely horizontal GEN originates from a pontine lesion.

Cerebellar centers

Cerebellar lesions are often accompanied by easily clinically identifiable ocular motor disturbances. For example, defects of the flocculus/paraflocculus are characterized by saccadic pursuit, DBN, and impairments of the visual fixation suppression of the VOR (Table 2b). Lesions of the ocular motor vermis (Lobulus VII) and the fastigial nucleus lead to saccadic dysmetria, whereas nodulus/uvula lesions

\[ \text{riMLF lesion: vertical saccadic paresis} \]
\[ \text{INC lesion: vertical gaze deviation nystagmus} \]
\[ \text{CP lesion: convergence retraction nystagmus} \]
\[ \text{MLF lesion: internuclear ophthalmoplegia} \]
\[ \text{PPRF lesion: horizontal saccadic paresis (ipsiversive)} \]
\[ \text{NPH lesion: horizontal gaze deviation nystagmus} \]
\[ \text{Bilateral floccular lesion or pontomedullar lesion: downbeat nystagmus} \]
\[ \text{Medullary or pontomesencephalic lesion: upbeat nystagmus} \]