Hydrocephalus in Animals

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Abstract

Naturally occurring internal hydrocephalus is diagnosed in all kinds of mammals including exotic species as well as in birds. The underlying pathomechanisms are extremely variable and species-specific. In ruminants, teratogenic viruses are the main underlying cause for congenital hydrocephalus. Intrauterine infections do not play a role in equids, and the site of obstruction of CSF flow typically remains undetermined. In birds and large felids, hydrocephalus is usually acquired and often associated with vitamin A deficiency. In dogs and cats, it can be congenital but also associated with impaired skull and vertebral growth. Reduced cranial capacity impairing cerebral compliance and malformations of the craniovertebral junction (atlantoaxial instability, occipito-atlantoaxial overlap syndrome, and "Chiari-like malformation") are the most common causes for an impaired CSF flow and communicating hydrocephalus in a high number of brachycephalic breeds.

With increasing knowledge and the increasing disposition of patient owners, veterinary specialists and researchers enduringly invest in the patient management; ventriculoperitoneal shunting techniques have become a reasonable treatment strategy in dogs.

Introduction

The focus of veterinary profession has shifted significantly over the past 100 years. Paralleling societal development, the role and importance of animals in our society has been continually evolving with dogs, cats, and horses leading the way. Dogs and cats are no longer kept for companionship purely; they have grown into family members, for whom highly specialized state-of-the-art medical care is a matter of course. Especially the relationship of people with their dogs is a unique affectionate bond. Also in large animal medicine, the treatment of the individual animal is gaining more and more interest over of the health of the whole population. The increasing clients' expectations have influenced the level of the service provided. Many diagnostic and therapeutic procedures have been adopted from human medicine or developed independently and are widely available for veterinary use. Along with the establishment of veterinary specialty associations, this provided a stimulus for the development of new diagnostic and therapeutic methods and the pursuit of research to perpetually improve clinical practice in veterinary neurology and neurosurgery.

Despite being a common clinical condition in dogs and cats, the body of scientific evidence and comprehensive experience with internal hydrocephalus used to be limited for a long time. No research group focused on the systematic workup of this condition in animals, and most publications were confined to case reports or

series in the past. Therefore, studies on diagnosis and treatment were heterogeneous and mostly descriptive in nature. Our research group includes scientists and professionals in veterinary diagnostic imaging and neurosurgery with an interest in the pathophysiology and treatment of mammalian brain malformations. Our goal is to understand the pathophysiology of disturbed CNS development including internal hydrocephalus and to develop novel diagnostic tools to aid their diagnosis and treatment.

The scope of internal hydrocephalus in companion animals needs to be differentiated from induced hydrocephalus models in experimental studies. As opposed to experimental animal models, the outcome of clinical cases of internal hydrocephalus is limited to financial restraints, nonstandardized conditions, and ambiguous pathophysiology. Expectedly the treatment success in clinical hydrocephalus lags behind the results of experimental studies, which may be overcome in the future with increasing knowledge about the underlying pathomechanism(s) and the increasing disposition of patient owners, veterinary specialists, and researchers to enduringly invest in the patient management.

Hydrocephalus in Dogs and Cats

Internal hydrocephalus is the most common brain malformation in dogs (Selby et al. 1979; Spaulding and Sharp 1990). Pathological studies documenting changes of the ventricular dimensions and associated clinical signs in canines have been described for almost 100 years (Fankhauser 1959; Dexler 1923). However, the pathomechanism behind the abnormal ventricular distension was largely ignored, and the prognosis was generally assessed as poor. A classification of hydrocephalus was and still is limited to communicating or non-communicating and congenital or acquired forms. From today's clinical perspective and with the experience of the last 10 years, we are aware of the diversity of underlying pathomechanisms, concurrent defects, and clinical presentations. With increasing experience in diagnosis and treatment of hydrocephalus, determination and observation of subgroups that differ in their potential clinical outcome, complication rate, and long-term survival is essential for the future.

Congenital Hydrocephalus in Dogs and Cats

Congenital hydrocephalus is frequently diagnosed in small brachycephalic dog breeds including the Boston terrier, Chihuahua, English bulldog, Maltese, Pug dog, Pekingese, and Yorkshire terrier (Selby et al. 1979; Biel et al. 2013; Shihab et al. 2011; de Stefani et al. 2011). The prevalence of congenital hydrocephalus in cats on the other hand is very low (Nelson et al. 1978; Priester et al. 1970). Despite the existing knowledge of the genetics of hydrocephalus in rodents, knowledge about the genetic and molecular mechanisms that cause canine and feline hydrocephalus is very limited. Some evidence has been found that hydrocephalus in

Siamese cats can be inherited as an autosomal recessive trait (Silson and Robinson 1969), but this has never been investigated adequately. The Chihuahua is the most commonly affected breed, which may also imply genetic factors to play a role in the pathogenesis of hydrocephalus in this breed. It is, however, difficult to assess whether the higher prevalence of hydrocephalus in this breed is determined by a genetic anomaly affecting the central nervous system directly or rather associated with their aberrant head morphology (see achondroplasia). It is likely that analogous to internal hydrocephalus in people, a substantial number of currently unknown etiologies exist in dogs and cats which remain to be determined. The effect of prematurity on the central nervous system of companion animals has never been investigated. The well-documented association of hypoxia and/or intraventricular hemorrhage and the development of hydrocephalus in premature infants has not been demonstrated in dogs and cats yet. The close supervision of gestation and the neonatal period of dogs and cats is not equally established to document a pathophysiological link. However, the impact of prematurity and dystocia, which both are prevalent in small brachycephalic dogs, should be considered to be of similar importance for the development of hydrocephalus in animals.

Aqueductal Stenosis

Aqueductal stenosis, forking, and septum formation have only been anecdotally described in dogs (Fig. 1) (Fankhauser 1959; Sahar et al. 1971; Zeitlinger 1925; Frauchiger and Frankhauser 1957). Aqueductal stenosis is generally assumed to be a result of intrauterine virus infections. Experimental inoculations of parainfluenza and paramyxovirus have shown to be capable of inducing encephalitis in neonatal dogs (Baumgärtner et al. 1982), and the development of aqueductal stenosis and internal hydrocephalus after reconvalescence has been described in puppies (Csiza 1971). The feline *Parvovirus* can produce similar changes in infected cat fetuses (Johnson and Johnson 1968). It is known from these inoculation studies that virus-mediated narrowing of the aqueduct occurs after ependymal cell destruction and subependymal reactive gliosis that produces a stenotic lesion later during the course of the disease. A number of canine viruses have a high affinity to ependymal and leptomeningeal cells, but virus protein or other evidence of viral infection has never been detected directly within the brain parenchyma of dogs with naturally occurring hydrocephalus. The experimental studies have shown, however, that aqueductal stenosis can develop without overt signs of inflammation in the periventricular parenchyma or viral persistence in ependymal cells (Baumgärtner et al. 1982; Johnson and Johnson 1968).

Recent reviews suggested that aqueductal stenosis is often associated with the fusion of the rostral (superior) colliculi (Thomas 2010; Estey 2015; Harrington et al. 1996; Summers et al. 1995). However, there is no substantial evidence to prove this assumption. Fusion of the rostral colliculi could not be identified in a large MRI survey of dogs with ventriculomegaly and hydrocephalus (Biel et al. 2013; Shihab et al. 2011; de Stefani et al. 2011; Ryan et al. 2014).
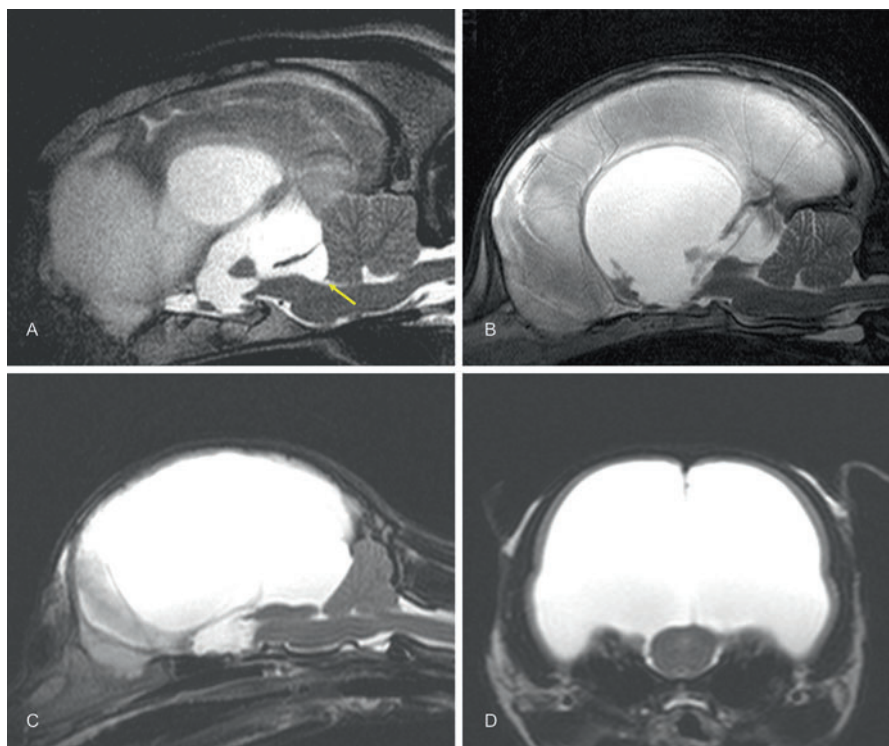
Fig. 1 Sagittal T2-weighted MR images of dogs with a primary (**a**, **b**) and secondary obliteration of the mesencephalic aqueduct. In a Rottweiler, (**a**) a thin septum spans over the caudal end of the aqueduct and bulges toward the cerebellum. In a young French bulldog, (**b**) rostral stenosis of the aqueduct was suspected. In the presence of subtentorial expansion of the hemispheres and supracollicular fluid accumulation, compression from the surrounding tissue is considered rather than primary aqueductal stenosis (**c**, **d**)

Aqueductal stenosis has been found to be associated with primary ciliary dyskinesia in laboratory mice and also in Bernese mountain dogs (Edwards et al. 1992; Banizs et al. 2007; Daniel et al. 1995). Ciliary dyskinesia is a rare inherited disease in dogs characterized by congenitally impaired mucociliary clearance within the respiratory system. Neurologic deficits lag behind the severe respiratory signs, and hydrocephalus is usually an incidental finding in postmortem examinations.

Obstruction of the Interventricular Foramen (Foramen of Monro)

Occlusion of the interventricular foramen is an uncommon cause of hydrocephalus in dogs and cats (Fig. 2a, b). Few cases of this alteration in the CSF pathways have been documented. Pathological studies were able to identify obstruction at the level of the interventricular foramen as a total foraminal atresia or membranous stenosis
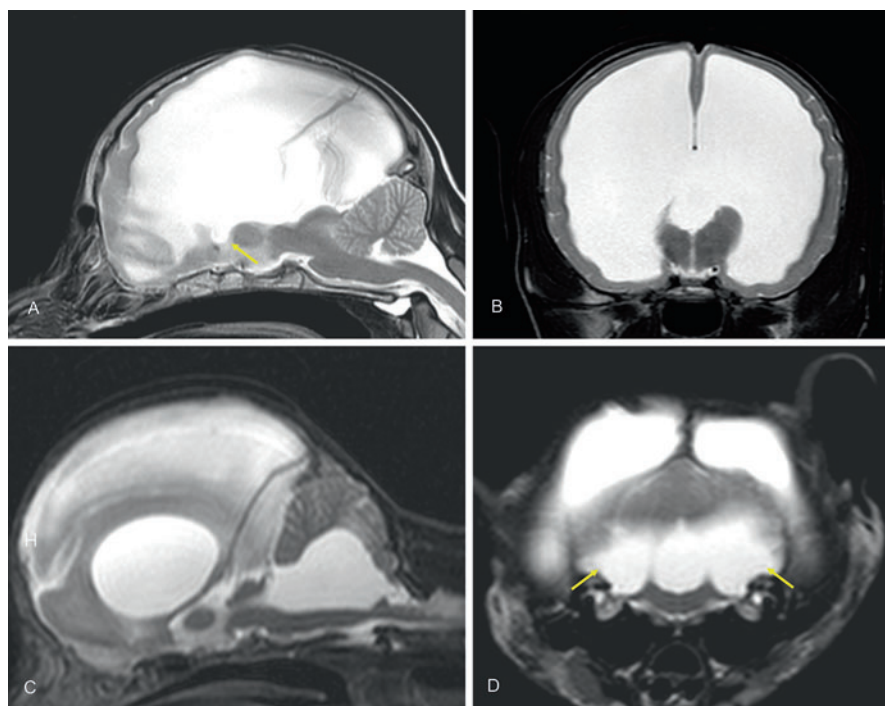
Fig. 2 Sagittal (**a**–**c**) and transverse T2-weighted MR images of dogs with hydrocephalus. In the crossbreed (**a**, **b**), a bulging rounded septum can be visualized that blocks the passage of CSF from the lateral to the third ventricle. In the Chihuahua (**c**, **d**), massive dilation of the fourth ventricle including the fastigial recess indicates impairment of CSF flow through the lateral apertures

by a septum in dogs (Fankhauser 1959; Summers et al. 1995). Indirect indication of a block of CSF flow at this site may be the dilation of the lateral ventricles and normal appearance of the third ventricle. On rare occasions, we were able to identify a thin septum bulging from the interventricular foramen toward the third ventricle on MR images (Fig. 2a). In vivo identification of such delicate structures via MRI certainly depends on image quality and may be detected with increasing frequency in the future owing to the growing number of high-field scanners used in the veterinary field.

Obstruction of the Lateral Apertures

A relative decrease in CSF flow volume through the lateral apertures is usually suspected in the presence of fourth ventricular dilation. Direct visualization of a structural resistance to flow is uncommon, but the lateral extension of T2-hyperintense CSF signal from the lateral apertures beyond the cerebellar peduncles in transverse MR images is suggestive for functional block of flow from the

ventricular system into the subarachnoid space (Fig. 2c, d). We have performed CT-ventriculography through a ventricular catheter in euthanized dogs with fourth ventricular dilation. Contrast agent was found in the cisterna magna immediately after injection. However, the marked density gradient between the contrast within the ventricles and within the cisterna magna suggested incomplete or relative obstruction of the lateral apertures.

Rarely, congenital cystic lesions cause mechanical resistance to CSF flow. Intraventricular arachnoidal pseudocysts are mostly found in the quadrigeminal cistern where they usually don't act as a barrier to CSF flow. An uncommon site of occurrence is the fourth ventricle where they can impede CSF flow (Bazelle et al. 2015). Fourth ventricular choroid plexus cysts are typically incidental, asymptomatic cysts in dogs. Some tend to expand causing symptoms of obstruction at the lateral apertures (Brewer et al. 2010; Galano et al. 2002). Moreover, cystic lesions inside the fourth ventricle are an unusual manifestation of choroid plexus tumors in dogs (Oura et al. 2013).

Idiopathic Communicating Hydrocephalus

Very often a specific cause for the hydrocephalus is not obvious. Our experience from the last decades documented normal mesencephalic architecture with patent CSF pathways in most dogs and cats with ventriculomegaly or hydrocephalus. The problem is, though, that physiological dimensions of the canine and feline aqueduct are largely unknown. Brain volume varies dramatically with body weight in dogs, and the relative volume proportions of the CSF pathways to the parenchyma have never been examined. As hydrocephalus is diagnosed in dogs with a body weight between 500 and 50 kg, aqueductal stenosis could be under-recognized.

In our opinion, a reduced cranial capacity and malformations of the craniovertebral junction (atlanto-occipital overlap, atlantoaxial instability; see below) are the likely causes for communicating hydrocephalus in a high number of brachycephalic breeds (Fig. 3). The reduced cranial space compresses dural veins, and the obliteration of the basal cistern reduces the "bagpipe effect" of cerebral arterial perfusion. This in turn leads to direct transmission of arterial pressure waves onto the intraparenchymal vessels increasing the pulsation of the brain itself, which overloads the capacity of the CSF pathways (Orešković and Klarica 2011). The findings of high CSF flow velocities in the mesencephalic aqueduct of dogs with ventriculomegaly and hydrocephalus compared to normal controls support this theory.
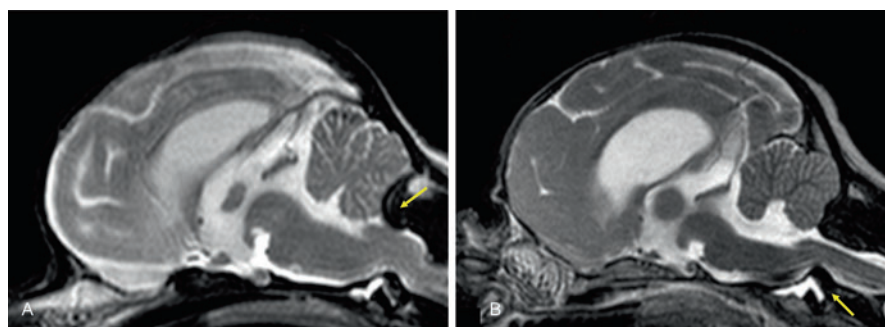
Fig. 3 Sagittal T2-weighted MR images of dog with atlantoaxial instability. In the pug (**a**) invasion of the atlas lamina into the foramen magnum can be seen. In the Boston terrier, (**b**) laxity and moderate dorsal deviation of the dens axis lead to stenosis of the cisterna magna

Clinical Signs in Congenital Hydrocephalus

Morphological Appearance

Hydrocephalic puppies often show a retarded skeletal growth as compared to their littermates. In many cases it can be diagnosed tentatively by assessing the head circumference. Standard charts and references for normal head dimensions in dogs and cats do not exist, and pure morphological diagnosis can be a challenge in some individuals. Especially in juvenile non-brachycephalic animals, macrocephaly becomes less overt. A comparison with littermates can be helpful (Fig. 4a, b). The presence of frontal bossing, hypertelorism, and asymmetry of the bony orbit are more reliable indicators than head circumference alone, especially in cats.

In dog skulls, fontanels are completely closed by 1 month of age. Textbooks often mention that an open rostral (anterior) fontanel after this time indicates internal hydrocephalus, especially in toy breeds such as the Chihuahua, Maltese, and Pomeranian. Other data imply that there is no association between the conditions (Hagedorn et al. 2012). Delayed or absent closure of the calvarial growth centers is rather associated with the miniaturization process in toy breeds.

Neurological Signs

Depending on the time of onset and the progression of intraventricular pressure, there is significant variation in the clinical presentation and severity of clinical signs. Affected puppies may not have any obvious neurological symptoms, especially when they are very young. Clinical signs may be rather unspecific including poor appetite, decreased muscle tone, and respiratory difficulties. Nausea and vomiting may occur. In some young dogs, polyuria and polydipsia have been reported, which

Fig. 4 Doming and deformation of the skull can be difficult to diagnose in young mesocephalic dogs. Comparison of two German shepherd dog littermates shows the difference between hydrocephalic (**a**) and unaffected animal (**b**). Brachycephalic dogs often have a rounded to domed skull, but unaffected (**d**) animals never show frontal bossing (**c**), which is a reliable indicator for hydrocephalus

have been attributed to inadequate vasopressin secretion (SIADH) as a consequence of ventricular expansion into the infundibular recess (Shiel et al. 2009).

Consciousness (Alertness)

As altricial animals, neonatal dogs and cats are completely dependent beings. In the neonatal period, they are almost devoid of senses, and they sleep most of the time, which makes an assessment of proper consciousness difficult. After the neonatal period (>4 weeks), the comparison with littermates is the best indication for any abnormality. However, in large litters, some puppies suffer from uterine malnutrition due to competition with other developing fetuses. This continues after birth in competition for milk. The smallest puppies are therefore prone to hypoglycemia, which can influence the level of alertness. The level of vigilance and the scoring of sleep and arousals as in infants and children are not existent in companion animals. In older animals the change of vigilance is usually overt (Fig. 5a, b).

Fig. 5 The most common signs of hydrocephalus in carnivores are severe sleepiness and obtundation (**a**, **b**). Ventrolateral strabismus (**c**) is common but is also seen in unaffected brachycephalic dog breeds. Severe craniofacial dysmorphia with distortion of the orbits is usually more pronounced in cats (**d**)

Impaired Vision

Puppies are born with sealed eyes to protect the immature optical system, therefore being functionally blind. When they start to open their eyes at about 2 weeks of age, the optic system is still not fully developed. It takes around 2 weeks for their eyelids to open and to take on response to their environment. It will take several more weeks before their visual system matures and their eyesight begins to approach normal conditions. In this maturation period, they are hardly responsive in classical tests of visual function. Later in life, unusual behavior may lead to a suspicion that the vision is disturbed. In older puppies, owners realize that their animals show confusion in new or changed surroundings and are being easily startled. Cats often appear hesitant when walking or may bump into objects and misjudge heights. This may only be noticed when furniture and other objects are moved, because cats possess a tremendous ability to adapt to impaired vision. With increased intracranial pressure, there is always the potential for visual loss secondary to the papilledema. This is, however, rarely observed in dogs and cats with congenital hydrocephalus. The loss of visual pathways in the periventricular white matter and compression of the lateral geniculate body must be considered as the underlying cause for visual impairment, because

the pretectal part of the visual system and visual cortex is usually preserved (Wünschmann and Oglesbee 2001). Clinical examination reveals poor attention to visual stimuli. It is usually tested using the menace response test that produces reflex blinking in response to the rapid approach of the examiner's hand toward the eye of the animal. Absent menace response with normal pupillary light reflexes is indicative for a lesion in the cortical part of the visual system. However, even in hydrocephalic animals with degeneration of almost the entire hemispheres and lack of any reaction to visual stimuli, blindness is often not complete. We have noticed a reaction when viewing moving objects compared to stationary objects. A lot of clinically blind animals show brisk response of changes in light. Although visual processing may occur on lower levels as the optic tectum, the reaction on subtle sounds or vibration can never be excluded.

Ventrolateral Strabismus

Bilateral ventrolateral strabismus ("sun-setting sign") is a common symptom of hydrocephalic dogs and cats. In some individuals, expansion of the cranial cavity causes distortions of the orbits that create all kinds of strabismus (Fig. 5c, d). However, unilaterally or bilaterally divergent strabismus (exotropia) occurs in a large number of brachycephalic breeds, which has been attributed to abnormal insertion of the medial rectus eye muscle. Care must be taken with some breed specialities. Siamese, Birman, and Himalayan cats frequently demonstrate congenital abnormalities of the visual pathways leading to strabismus (isotropic) and pendular nystagmus. Axonal projections from the temporal retina usually do not cross within the optic chiasm but for unknown reasons cross in these cats. This leads to conflicting visual information from both visual fields. The resulting convergent strabismus is interpreted as the result of a compensatory attempt to obtain a better overlap of the visual fields (Marzi 1980).

Behavior

Changes in the animal's behavior, especially affective aggression, are frequently reported in older puppies. The distinction between changes associated to the brain malformation and general behavioral problems can be challenging. Small brachycephalic dogs demonstrate more generalized aggression than large brachycephalic dogs, which can have an individual variation, especially in young males. In this point, a clear differentiation between the origins of behavioral changes can be challenging. Better indicators are simple learned behavior patterns that may get lost or are never learned. Owners often report the inability to become house trained or mention the loss of house training. Some dogs show unaimed vocalization often occurring at inappropriate times of the night or day. Dogs can become shy, fearful, and unable to handle any kind of stress (Thomas 2010).

Seizures

In some animals, owners report epileptic seizure events, which are described as generalized tonic-clonic in all instances (Biel et al. 2013; Shihab et al. 2011; Thomas 2010). In our clinic, we have seen epileptic seizures only in association with additional inflammatory diseases and other concomitant malformations, especially porencephaly, that may remain unrecognized if ventricular distension is diagnosed using ultrasonography or CT. Especially in those dogs, in which seizural activity is the only clinical sign, we consider idiopathic epilepsy or inflammatory brain disease on top of ventricular distension as the more likely cause of epileptic seizures until proven otherwise.

Cerebello-vestibular Signs

Clinical signs are more variable and are dependent on the expansion of different parts of the ventricular system. A dilatation of the fourth ventricle may cause compression of the brainstem and primarily cerebello-vestibular signs. Head tilt, tremor, nystagmus, and hypermetric ataxia on all four limbs may be seen. Reduced postural reactions may be observed in severe brainstem compression (Biel et al. 2013; Shihab et al. 2011; Thomas 2010).

Congenital Brain Malformations Associated with Internal Hydrocephalus

Holoprosencephaly (Arhinencephaly)

Holoprosencephaly is a rare brain anomaly, which may be seen in live-born animals, although it is more common in stillbirths. Most types of separation failure of the two hemispheres known in humans also occur in animals. Lobar holoprosencephaly with complete absence of midline separation, cyclopean, and a proboscis is mostly described in large animals, especially in herbivores grazed on *Veratrum californicum* early in gestation. The teratogenic alkaloids of this plant are capable to inhibit the sonic hedgehog (shh) signal transduction pathway regulating induction of dorsal and ventral prosencephalic separation (Cho et al. 1985; Schulze and Distl 2006; Welchl et al. 2009). Complete fusion of the cerebral hemispheres and a single dilated "lateral" ventricle is accompanied by the absence of olfactory nerves, bulbs, and peduncles, which is why the malformation is often called arhinencephaly. This severe form has also been termed synophthalmia, focusing on the ocular and ignoring the underlying brain defects (Summers et al. 1995; Vandevelde et al. 2012; Williams 2010).

In carnivores, the development of this rare malformation is still poorly understood. Lobar holoprosencephaly has a high prevalence in miniature schnauzers. The dogs have no neurologic dysfunction but a defective central thirst regulation leading

to adipsia and hypernatremia in affected dogs (Sullivan et al. 2003). In other breeds only sporadic cases consistent with abnormalities from the holoprosencephaly spectrum have been reported usually referred to as corpus callosum abnormalities. In some dogs, fusion of the midline structures is very subtle, often confining to the ventral rostro-commissural area resembling septo-optic (or septo-preoptic) holoprosencephaly in humans. Lobar holoprosencephalies frequently occur with interhemispheric cysts (IHC) or hydrocephalus.

Recently, an inherited prosencephalic midline defect has been described in Toyger cats. This new breed was selected phenotypically for its short and rounded ears and a striped coat, which resembles a miniature tiger (Keating et al. 2016). Multiple defects in midline structures are associated with this phenotype, including the corpus callosum, interthalamic adhesion, septum pellucidum, and the hippocampal commissure and fornix as well as ventriculomegaly. Various degrees of abnormal gyral patterns with shallow sulcal depth can be found in mildly affected animals, whereas the more severely affected cats show an almost flat pallium. Enlargement of the olfactory recesses of the lateral ventricles implies increased intraventricular pressure, probably due to secondary aqueductal obliteration by the supracollicular cysts (Keating et al. 2016).

Cortical Migration Disorders

Two main types of cortical migration disorders exist in domestic animals, which are lissencephaly and polymicrogyria. With the exception of rabbits, rodents, and birds, all domestic animals have cortical convolutions. In ungulates, the adult neocortical pattern is fully developed at birth; in dogs and cats, the gyrification is completed 2 weeks postpartum (Schmidt et al. 2012a). Defects in neuronal migration leading to a marked reduction or absence of the convolutional pattern of the cerebral hemispheres have been diagnosed together with ventriculomegaly rather than with hydrocephalus. However, ventricular enlargement can be marked and easily mistaken for clinically relevant ventricular distension. Lissencephaly has been described only rarely. It can occur sporadically in animals due to nongenetic influences but is diagnosed in the Lhasa apso dog with a higher frequency (Greene et al. 1976; Saito et al. 2002; MacKillop 2011). It encompasses a spectrum from complete agyria (absent gyri) to regional pachygyria (Fraser et al. 2016). Lissencephaly can be part of complex brain malformations and may be accompanied by cerebellar hypoplasia or other structural defects (Summers et al. 1995). In cats, lissencephaly has been observed in the Korat cat breed with a higher frequency (Summers et al. 1995) and occasionally in the domestic shorthair cat. Attempts to explore the genetic background were not successful yet (Hermann et al. 2011). Affected pups can survive but tend have serious difficulties and may develop seizures, ataxia, tetraparesis, and serious behavioral issues as they get older. They also often have visual deficits and show aggressive behavior, all of which can be clinical signs of internal hydrocephalus.

Polymicrogyria is breed related as well with preponderance for Standard poodles (Jurney et al. 2009). Changes of ventricular dimensions have not been reported yet.

Dandy-Walker Malformation

Complete or partial agenesis of the cerebellar vermis with cystic dilation of the fourth ventricle and enlargement of the posterior fossa has been described in the dog and other species. In many canine cases, no substantial enlargement of the caudal (posterior) fossa is observed, which has led to the introduction of the term "Dandy-Walker variant." A continuum of developmental abnormalities exists. In some dogs, abnormalities are confined to partial absence of the caudal vermis; in others multiple supratentorial malformations can be found in association with Dandy-Walker malformation (DWM) such as porencephaly, polymicrogyria, corpus callosum agenesis, heterotopia, and also hydrocephalus (Fig. 6) (Schmidt et al. 2008; DeLahunta and Glass 2009).

Strong evidence for an autosomal recessive inheritance of DWM has been found in Boston terriers (Noureddine et al. 2004), Chow Chows (Knecht et al. 1979) and Eurasian dogs. A very low-density lipoprotein receptor (VLDLR) gene mutation was recently identified in the latter breed, which normally is part of the reelin pathway modulating neuroblast migration in the cerebellum (Gerber et al. 2015).

Clinical signs of cerebellar dysfunction are noted early on in DWM. After getting ambulatory affected dogs display nonprogressive ataxia, nystagmus, occasional head tremors, and absence of the bilateral menace reaction beyond 10–12 weeks of age. Interestingly, some dogs with structural abnormalities are clinically unremarkable except for subtle problems of balance. Epileptic seizures may occur later in life in some dogs. The allocation of a seizure focus to a definite structural abnormality is difficult.

In dogs with massive enlargement of the fourth ventricle, compression of the brainstem can cause tetraparesis. Shunting of the fourth ventricle can improve clinical status in these dogs. Internal hydrocephalus in combination with signs of abnormal cerebellar function is often not treated due to unfavorable long-term prognosis.

Hydrocephalus Associated with Cranio-cervical Malformations

Chiari-Like Malformation in Dogs

In a couple of small toy-breed dogs, structural changes of the skull and the central nervous system have been described resembling pathological findings of the human Chiari malformation type 1 (CM1). Features noted include deviation and sometimes herniation of the cerebellum into the foramen magnum with consecutive development of syringomyelia (Fig. 7a). The clinical symptoms of affected dogs also showed striking analogy to symptoms of humans affected by this condition, which
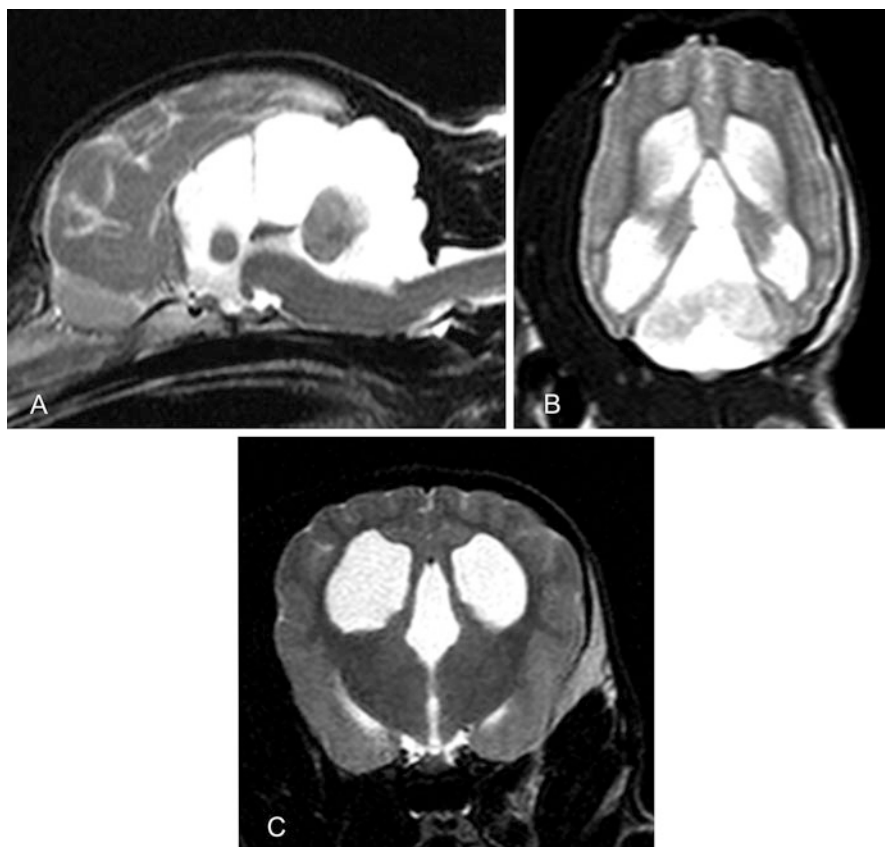
Fig. 6 Lateral, dorsal, and transversal T2-weighted MR image of a Eurasian dog with Dandy-Walker malformation. The cerebellar vermis is completely absent and the hemispheres reduced in size. There is cystic enlargement of the caudal fossa and rostral elevation of the osseous tentorium. There is supracollicular fluid accumulation (quadrigeminal cyst) that compresses the occipital lobes and bilateral hydrocephalus

is why the disease was referred to as the "canine form of CM." Veterinary researchers agreed upon the use of the term Chiari-like malformation (CLM) to describe the malformation found in the dog.

As in humans, herniation of the cerebellum into the foramen magnum was proposed to alter CSF flow by attenuation of the subarachnoid space leading to turbulent CSF flow and jets and eventually to SM (Driver et al. 2013). The obstruction of cerebrospinal fluid (CSF) flow at the foramen magnum could be proven for the CKCS using phase-contrast cine magnetic resonance imaging (MRI). Turbulent CSF flow patterns and increased CSF flow velocity were shown to be related to the presence and severity of syringomyelia. The pathogenesis of CM/SM in the dog has been under evaluation and discussion for decades. In the ongoing search for the underlying etiology of cerebellar herniation, two main hypotheses have been

Fig. 7 Sagittal T2-weighted MR images of Cavalier King Charles spaniels with Chiari-like malformation. There is a herniation of the cerebellar vermis through the foramen magnum and se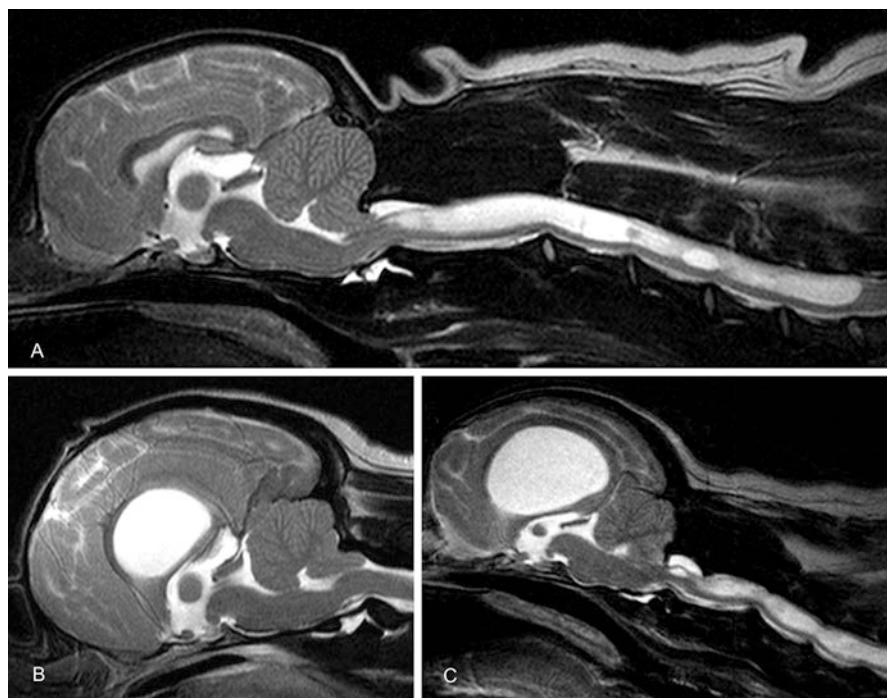vere syringomyelia (**a**, **c**). The blockage of the CSF flow from the caudal fossa into the cisterna magna is impaired. Interestingly some dogs develop both hydrocephalus and syringomyelia, others only one of the malformations. The third ventricle is usually not dilated in the dogs

proposed (Driver et al. 2013). Next to a suspected enlargement of the cerebellum, the main hypothesis focuses on abnormal skull development. In analogy to human patients, hypoplasia of the basioccipital bone and a consecutive reduction in the volume of the caudal cranial fossa have been suggested. Volume overload of the caudal skull compartment and deviation of the cerebellum into the foramen magnum are assumed a consequence. However, independent studies were not able to demonstrate a difference in caudal cranial fossa volume in CKCS compared to other dog breeds (Cross et al. 2009; Schmidt et al. 2009). Hypoplasia of the occipital bone in relation to the whole skull volume could also not be confirmed (Schmidt et al. 2012b), but a reduced length and depth of the basioccipital bone were found in CKCSs with SM (Carrera et al. 2009). This is in conformity with the finding that the growth centers of the basicranium (spheno-occipital synchondrosis) undergo premature closure in CKCSs in comparison to mesocephalic and other brachycephalic dog breeds (Schmidt et al. 2013). Overall, not the volume of the skull compartments but the relative length of the cranial base seems to be the consistent finding in dogs and humans with SM. Laxity of the cranio-cervical junction with subluxation and

"basal invagination" has been proposed to contribute to the constriction of the spinal canal, with further compromise of the CSF flow.

Some but not all dogs with CLM and SM do also have an internal hydrocephalus. Interestingly, some of these dogs only show increased volume of the lateral ventricles with normal dimensions of the third and fourth ventricles. It is unclear which factor influences the additional distension of the compartments and why not all parts of the ventricular system develop pre-stenotic dilation (Fig. 7b, c).

Cerebellar Herniation, Syringomyelia, and Hydrocephalus in Large Felids

In captive large felids, especially in the lion and the cheetah, cerebellar herniation, syringomyelia, and hydrocephalus can be a consequence of vitamin A deficiency. The diet of captive large felids usually consists of red meat and bones, which is different from wild animals. Although the feeding of whole carcasses to captive felids may be the natural strategy, it is usually not the most practical method of feeding in zoos and other research centers. This practice has resulted in nutritional deficiencies, especially vitamin A deficiency, even when vitamins are supplemented. Vitamin A plays an important role in cell division, cell differentiation, and the maintenance of differentiated cells in a number of tissues including the differentiation of osteoplastic cells. A severe impact on balanced bone growth associated with osseous hypertrophy in young growing felids has been observed (Fig. 8). The imbalanced growth mainly affects the cranial bones, especially the occipital bones and the osseous tentorium, which can result in severe constrictive compression of the cerebellum with consecutive herniation through the foramen magnum. The affected animals develop syringomyelia and non-communicating internal hydrocephalus. Clinical signs are characterized by medullary compression and upper motor neuron paresis of all four limbs with extensor spasticity of limb and neck muscles. Nystagmus may result from cerebellar compression. Obtundation occurs rather from medullary compression than from ventricular distension.

Therapeutic trials involve high doses of vitamin A and surgical decompression of the foramen magnum in individual cases. If supplemented (2000 IU/kg weekly for 4 weeks, (Hartley et al. 2005) early on and damage to the nervous tissue is not too advanced yet, the osseous hypertrophy can be reversed, and affected animals show marked improvement of clinical signs (De Risio et al. 2010; Kaiser et al. 2014; Beckmann et al. 2013).

Canine Occipito-atlantoaxial Overlapping Syndrome

One of the common morphological changes associated with miniaturization and brachycephaly in toy-breed dogs is misalignment of the cranio-cervical junction. The occipito-atlantoaxial overlapping syndrome describes the cranio-dorsal displacement of the atlas toward or through the foramen magnum and rostral
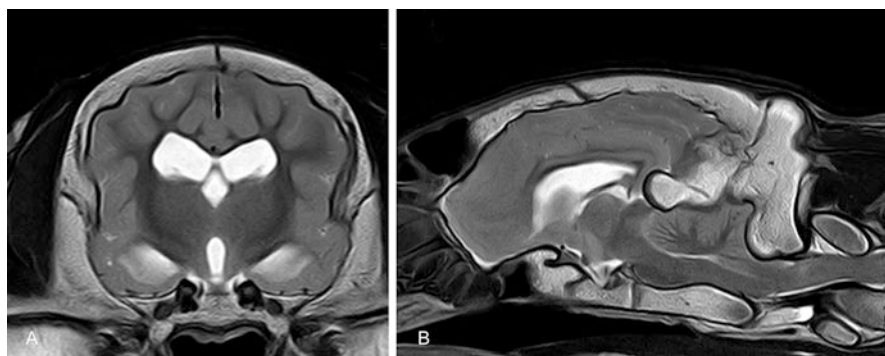
Fig. 8 Two-month-old tiger cub with severe bony hyperostosis due to vitamin A deficiency. The osseous tentorium and the occipital bones press the cerebellum ventrally. The lateral ventricles are only beginning to expand in this early phase of the disease. (Image courtesy of PD Dr. med. vet. (habil.) Marcin Wrzosek, University of Wroclaw)

invagination with cranial and dorsal displacement of the dens axis. The morphological changes in these dogs are similar to those found in the human disorder basilar invagination. Both conditions lead to dorsal elevation of the caudal aspect of the medulla oblongata and cranial aspect of the cervical spinal cord, as well as compression of the cerebellomedullary cistern, and variable indentation of the cerebellum (Cerda-Gonzalez et al. 2016; Loughin and Marino 2016). An abnormally short and flat dorsal arch of the atlas and a short cranial base have been identified as important structural differences between affected and unaffected dogs (Ondreka et al. 2015). Both changes allow for upward displacement of vertebral elements into the foramen magnum. This in turn leads to static or dynamic stenosis of the cerebellomedullary cistern with obstruction of CSF pathways and flow between the cranial cavity and spinal canal, which results in faulty craniospinal flow dynamics. Hydrocephalus and/or syringomyelia may also be seen because of direct mechanical blockage of normal CSF flow. Affected dogs can develop cervical pain and ataxia of variable degree. In some animals occipito-atlantoaxial overlapping is an incidental finding.

Hydrocephalus Associated with Coronal Craniosynostosis in Persian Cats

Ventricular enlargement and clinically relevant internal hydrocephalus have been described with increased frequency in the modern Persian cats. Starting from the middle of the twentieth century, American breeders reinforced phenotypic traits leading to a rather stocky short body along with a rounded head, shorter face, and short tree-trunk legs. This show line of the Persian breed has been called the "peke face" describing the triangular midface due to the extremely shortened, repositioned nose that is aligned with the eyes. "Peke-faced" Persians present a high incidence of internal hydrocephalus. The traditional "doll-faced" Persian has a nose of regular
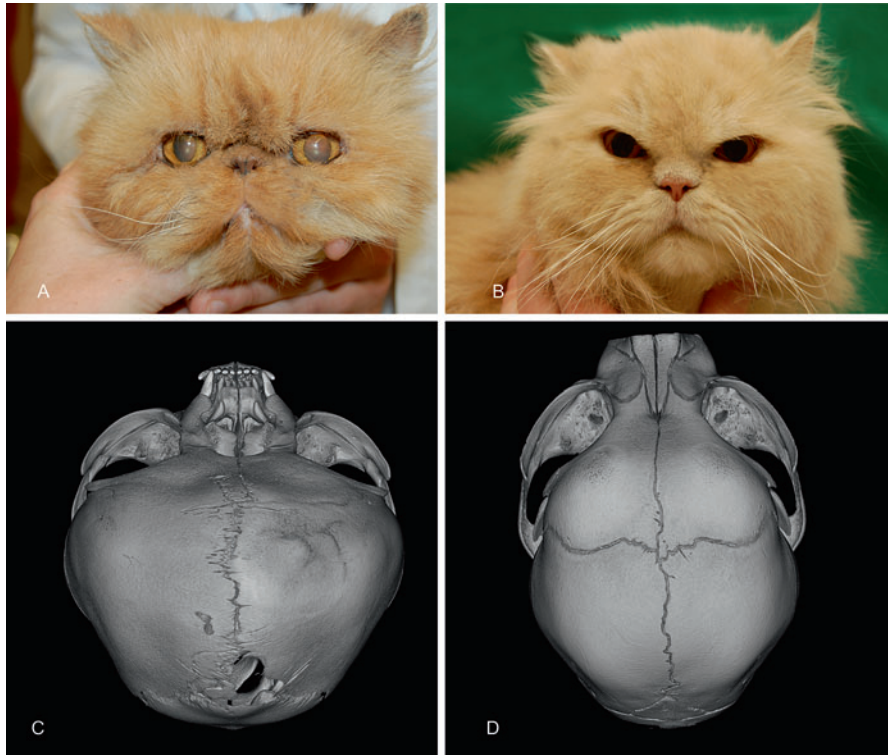
Fig. 9 Persian cats with different craniofacial morphologies. The new show type of this breed accentuates the very short nose that is set back behind the eyes (**a** "peke-face type"). In the traditional Persian, the reduction of the facial bones is less pronounced (**b** "doll-face type"). The brachycephalic morphology of the cranium is due to a premature closure of the coronal suture in these cats

length that is in proportion with the rest of the skull. Hydrocephalus is not seen in this phenotype (Fig. 9a, b).

Premature closure of the coronal suture in comparison to mesocephalic kittens of the same age has been found in these cats (Fig. 9c, d) (Schmidt et al. 2014a). Disruption of normal skull growth is also associated with midface hypoplasia, which is the desired morphology in this breed, as well as large skull bone defects, malocclusion, reduced cranial capacity, and communicating hydrocephalus of different degree, which resembles the Crouzon syndrome in people. In some cats, ventricular distension occurs at young age with a fatal course. The kittens are severely ataxic or unable to rise and severely obtunded and die around 4 weeks of age. In others, development of internal hydrocephalus is rather chronic, with a normal life expectancy and only subtle clinical signs such as visual impairment, deafness, and a certain "clumsiness" which the owners often realize only after diagnosis (Fig. 10).
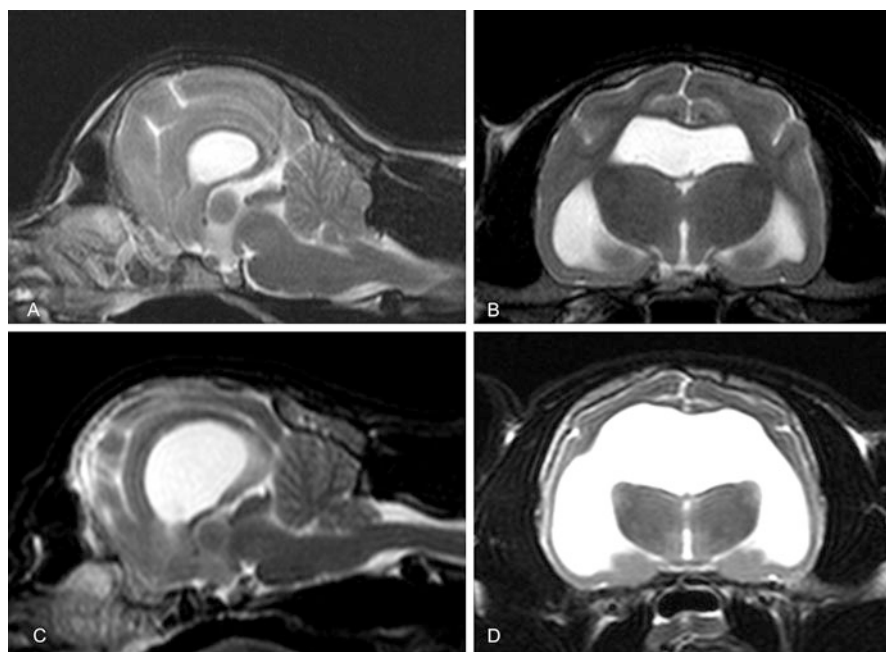
Fig. 10 Sagittal and transversal T2-weighted MR images of Persian cats with a severely disturbed skull development due to premature closure of the coronal sutures. There seems to be a phenotypical spectrum of the growth disturbance. Late premature closure (**a**) usually leads to ventriculomegaly without overt clinical signs, whereas early (**b**) closure causes severe reduction of the cranial capacity, cerebellar herniation, and massive ventricular distension

Frontonasal Dysplasia in Burmese Cats (Maxillonasal Hypoplasia)

Frontonasal dysplasia and the underlying defect in the ALX1 gene have recently been examined in the Burmese cat (Lyons et al. 2016). The defect was originally described as maxillonasal hypoplasia (Zook et al. 1983). It occurred after the creation of a contemporary style of the cat's phenotype aiming at a more rounded head shape. Unfortunately, the matings produced lethal facial defects in 25% of the homozygous offspring. Agenesis of the nose ridge and upper lip and duplication of the maxillary processes are seen. Ocular degenerations and meningoencephaloceles are observed. Frontonasal dysplasia may also include holoprosencephaly malformations of low severity such as absence or deformity of the corpus callosum and occasional hydrocephalus. In the heterozygous littermates, the effects of the gene variant are less pronounced creating the preferred head morphology.

Acquired Hydrocephalus in Dogs and Cats

Canine Ventriculomegaly

Enlarged ventricles are a common finding in adult brachycephalic dog breeds and have been referred to as "ventriculomegaly" to demarcate this finding from relevant internal hydrocephalus. Dogs with mere ventriculomegaly are considered to be asymptomatic and are not thought to have associated increased intraventricular pressure. As most brachycephalic dogs are small toy breeds, it has been suggested that ventricular size follows negative allometric growth principles – the smaller the dog, the larger the ventricles. The term "constitutional hydrocephalus" has been used to describe the common association of large ventricles with short stature in brachycephalic dogs.

However, morphological studies have shown that dogs with ventriculomegaly have reduced cerebral white matter volumes (Schmidt et al. 2015). A predetermined relationship exists between white and gray matter mass in the brain of mammals. Hence, this white matter atrophy cannot be interpreted a physiological state. It should rather be considered as a form of arrested hydrocephalus due to up to now undetermined disturbances in CSF dynamics. MRI-perfusion studies in dogs with ventriculomegaly have revealed reduced cerebral blood flow, which substantiates the hypothesis that ventriculomegaly is due to active distension of the ventricles. One possible cause of impaired CSF flow could be the obstruction of the foramen magnum as found in dogs with morphological changes in the cranio-cervical junction (occipito-atlantoaxial malformation, Chiari-like malformation).

The association of ventriculomegaly with neurological deficits in dogs has been rejected. This lack of clinical signs as a consequence of ventricular enlargement may initially be striking. However, locomotion, urinary, and other functions are not only controlled on the cerebral level in dogs. Cognitive brain function cannot be assessed, at least not in a clinical setting, and the actual status of canine cognitive abilities cannot be determined with absolute certainty. Detailed behavioral studies of the impact of white matter loss on the full functional integration of the nervous system are necessary to clarify whether mere ventriculomegaly alone should be considered an indication for CSF shunting procedures in dogs already. Clinical or experimental evidence of cognitive impairment or intermittently high CSF pressure waves would render naturally occurring ventriculomegaly in dogs an interesting animal model for human normal pressure hydrocephalus.

Detection of ventriculomegaly as an incidental finding is of particular importance in inflammatory/infectious brain disease, which may encompass ventricular enlargement without other specific imaging findings. Hence, in these specific cases, the ventricular dilation may be misdiagnosed as relevant internal hydrocephalus and interpreted to be the cause of clinical signs in dogs that actually are affected by inflammatory/infectious disorders.
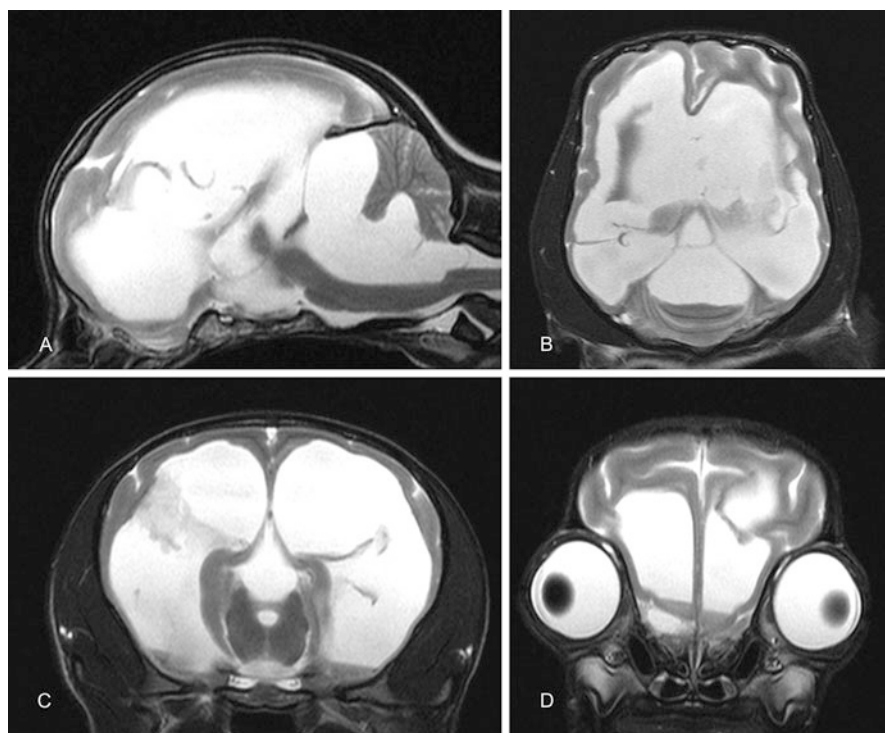
Fig. 11 Sagittal, dorsal, and transversal T2-weighted MR images of a Jack Russel terrier with hydrocephalus suspected to be due to bacterial encephalitis. There are multifocal perivascular cavitations and widespread tissue destruction around the lateral ventricles. CSF examination was unremarkable in the dog

Hydrocephalus After Bacterial Encephalitis

Bacterial meningitis or meningoencephalitis is rare in dogs and usually rapidly disseminates leading to serious illness and death (Radaelli and Platt 2002). Hydrocephalus can be associated with "subclinical" periventricular bacterial encephalitis in dogs (Cammermayer et al. 1961; Higgins et al. 1977; Cantile et al. 1997). The sparse literature pertaining to this underlying cause of hydrocephalus is primarily based upon necropsy findings. The hallmark of this form of hydrocephalus is the formation of multifocal to diffuse subependymal diverticula, periventricular cavities, and malacia (Fig. 11). Perivascular accumulation of neutrophils suggests a primary bacterial infection. In some dogs *Staphylococcus* spp. have been isolated from the parenchyma although the CSF examination was unremarkable. The clinical signs are comparable to congenital hydrocephalus with the difference that the puppies are normal at birth and clinical signs deteriorate rapidly.

Canine Idiopathic Meningitides

Interestingly ventricular enlargement is not seen in association with noninfectious meningitis. Steroid-responsive meningitis-arteritis (SRMA) is a systemic immune-mediated disorder characterized by inflammatory cell invasion of the leptomeninges and the meningeal arteries that is typically responsive to corticosteroids. Elevated concentrations of immunoglobulin A are present both in the serum and cerebrospinal fluid of affected dogs. This is a feature shared with human Kawasaki syndrome. In the chronic form of SRMA, meningeal fibrosis secondary to the inflammatory lesions can compromise the CSF flow and rarely causes hydrocephalus (Summers et al. 1995; Tipold and Jaggy 1994).

Fungal Granulomatous Ependymitis

Mycoses of the central nervous system are rare in companion animals and confined to endemic areas. The most common agents are *Aspergillus*, *Candida*, and *Cryptococcus* species (Vandevelde et al. 2012). Cerebral infections can develop from systemic mycoses or from invasion through the nasal cavity and cribriform plate, leading to pyogranulomatous leptomeningitis and later to a generalized granulomatous encephalitis (Greene and Prescott 2012). In some animals ependymal inflammation without any sign of parenchymal invasion occurs leading to multiple subependymal granulomas. In others a chronic diffuse leptomeningitis develops. Both forms may disturb CSF flow and absorption (Robson and Smith 2011). Signs of ventricular distension precede signs caused by generalized encephalitis that arise in the later stage of the disease.

Acquired Hydrocephalus in Cats

Post-inflammatory Hydrocephalus After Feline Coronavirus Infection

The feline coronavirus (FeCV) creates a fatal immune-mediated disease known as feline infectious peritonitis (FIP). The ubiquitous virus replicates in enterocytes but this enteric infection is rarely fatal. The virus can pass the enteric border into the blood and is rapidly cleared in most instances. However, for not precisely determined reasons, some of these viruses mutate (Vennema et al. 1998). This mutation leads to the ability to invade and replicate in macrophages causing a violent multisystemic inflammatory reaction. This reaction can have two forms, granulomatous or effusive. In granulomatous FIP there is no inflammatory exudation into the body cavities which is a classical clinical sign in the effusive form. The granulomatous form involves the central nervous system. The virus causes a cellular inflammatory reaction with inflammatory cells forming small granulomas around CNS arteries and venules. This periventricular vasculitis leads to exudation of a cell- and protein-rich
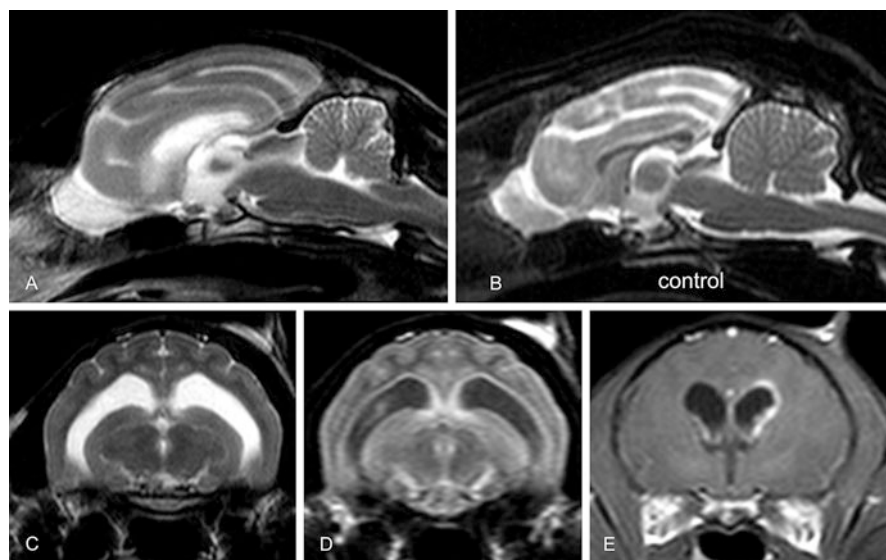
Fig. 12 Classical MRI features of a cat with ependymitis and ventricular distension due to infection with feline coronavirus (**a**, **c**–**d**) (neural form of feline infectious peritonitis, FIP). Distension of the lateral and third ventricles is mild. Deformation of the interthalamic adhesion suggests increased intraventricular pressure. Transversal T2-weighted images (**c**) do not reveal periventricular hyperintensities that become obvious in FLAIR (**d**). Strong contrast enhancement proves ependymitis (**e**). CSF examination and determination of coronavirus protein using PCR from CSF result in the diagnosis of coronavirus encephalitis

fluid and periventricular reactive astrocytosis. Hydrocephalus, secondary to disease of the choroid and ependyma, has been well documented (Hayashi et al. 1980; Krum 1975; Foley et al. 1997).

The clinical signs are not specific for the disease. The broad spectrum of clinical signs reflects the fact that any part of the CNS may be involved. Abnormal mental status and behavior, cranial nerve deficits, central vestibular signs, ataxia, and tetraparesis have all been described in the veterinary medical literature. Out of our experience, feline congenital hydrocephalus is not associated with seizures. If young kittens show ventricular distension, the occurrence of seizures should raise the suspicion of an underlying inflammatory disease.

MRI findings are usually very characteristic (Fig. 12). The inflammation of the periventricular tissue creates hyperintense signals of the periventricular tissue, which is best seen in FLAIR sequences. Incomplete suppression of the CSF in FLAIR indicates elevated protein levels in the CSF. The same findings can be seen in the subarachnoid space. Ependymal and meningeal enhancement of the lateral ventricles is a common finding on post-contrast images. The choroid plexus can appear prominent and thickened, and the mesencephalic aqueduct may be completely obliterated. Moderate to severe enlargement of the ventricular system is seen. Unfortunately, not all cats with CNS FIP infections create detectable MRI findings

indicative for inflammation, and even CSF examination does not show increased cell counts and elevated protein levels. Dilation of the ventricular system can be the only finding, and then idiopathic hydrocephalus may be diagnosed erroneously.

Although FIP can affect cats of any age, it is most commonly diagnosed in sexually intact purebreds such as Abyssinians, Bengals, Birmans, and British shorthair <4 years of age from multiple-cat homes. If hydrocephalus is diagnosed in cats with this clinical profile, FIP should be considered an underlying cause, especially when seizures are part of the clinical presentation. Serologic titers do not discriminate between the mutated and the ubiquitous unmutated coronavirus because they are antigenically indistinguishable. RT-PCR is recommended to identify FIP coronavirus in CSF. Due to the poor prognosis for long-term survival, CSF drainage is not recommended.

Tumor Associated Hydrocephalus

Meningiomas

Meningioma is the most commonly reported brain tumor in dogs and cats (Troxel et al. 2003). Canine and feline meningiomas are mainly located at the region of the cerebral convexities, but as a special characteristic in the cat, meningiomas can arise from the tela choroidea within the ventricular system, in particular associated with the third ventricle (Troxel et al. 2003). In this location, they often block CSF flow, and the first symptoms of this tumor can be due to rapid ventricular distension (Nafe 1990). Location of the meningioma ventral to the brainstem or in the cerebellopontine angle can block CSF pathways. Radiation therapy is currently the therapy of choice for these tumors owing to the limited surgical accessibility. Ventriculoperitoneal shunting is recommended to improve clinical status in these animals until the tumor mass is sufficiently reduced to restore patency of the ventricular outflow.

Choroid Plexus Tumors

Tumors arising from the intraventricular choroid plexus can be associated with internal hydrocephalus in dogs and cats. They account for approximately 10% of all primary intracranial tumors in dogs. Three histological subtypes according to the human WHO classification system as either Grade I CP papillomas, Grade II atypical CP papillomas, or Grade III CP carcinomas have been determined in dogs (Westworth et al. 2008). Breed predisposition has not been previously recognized, but one study found golden retrievers to be 3.7 times more likely to be diagnosed with CPT. Distension of the ventricular system with periventricular edema consistent with high intraventricular pressure occurs in the majority of dogs with CPTs. The most common location is in the fourth ventricle. Prolonged survival using primary
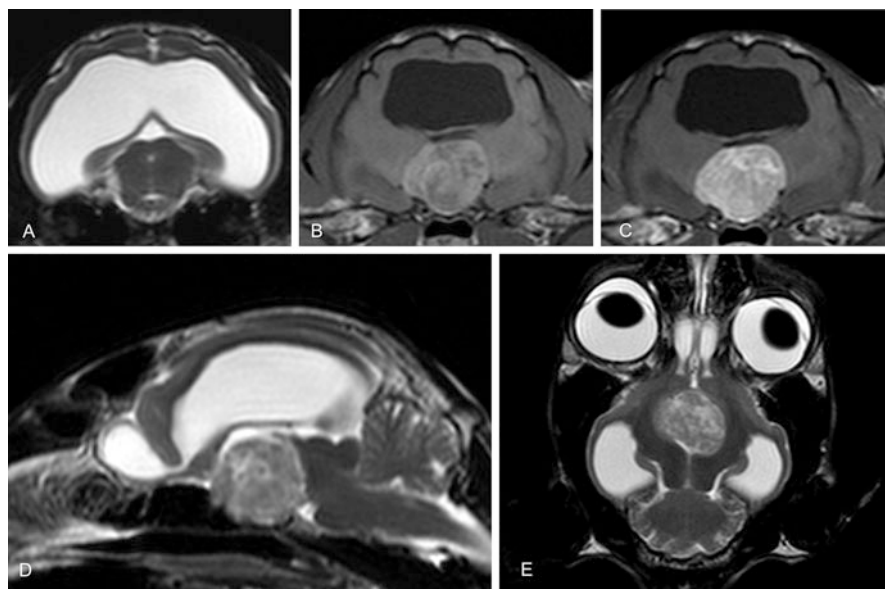
Fig. 13 Transverse (**a**), sagittal (**d**), and dorsal (**e**) T2-weighted MR images as well as T1-weighted images pre- (**b**) and post-contrast administration of a cat with a large macroadenoma of the pituitary gland. The tumor blocks the mesencephalic aqueduct leading to accumulation of the CSF and distension of the lateral ventricles

radiation therapy has been suggested (Bley et al. 2005; Spugnini et al. 2000), which may be combined with CSF drainage.

Middle Fossa Tumors (Sella Tumors)

Middle fossa tumors in animals include pituitary adenomas, meningiomas, lymphomas, germinomas and craniopharyngiomas, which can all expand dorsally exerting a mass effect on the adjacent di- and mesencephalon and may therefore block CSF pathways. Most of these tumors exhibit slow growth and therefore may expand far beyond the sella without overt clinical signs (Fig. 13). Suprasellar macroadenomas are the most common sellar tumors in dogs and cats. Because pituitary imaging is not routinely performed in animals with pituitary-dependent hyperadrenocorticism, the true incidence may be higher than reported. In cats, pituitary-dependent hypercortisolism (PDH) is usually associated with diabetes mellitus, and the most frequent clinical signs are polyuria, polydipsia, and polyphagia rather than neurologic deficits. Acromegaly, due to growth hormone hypersecretion, is another possible clinical presentation of pituitary adenoma in cats. If the tumor starts compressing the thalamus, the most common neurologic sign is stupor. Dogs and cats may present behavioral abnormalities (disorientation, compulsive gait) and bilateral pretectal blindness suggesting compression and disruption of the optic chiasm and optic

nerves. Due to the slow adenomatous growth, VP shunting is a reasonable therapeutic option to decrease intracranial pressure in affected animals.

Medulloblastoma

Primitive neuroectodermal tumors arising in the cerebellum are extremely rare in dogs and cats. They are thought to arise from the cerebellar external germinal layer, often located in the midline vermis. From here they can invade the cerebellar hemispheres and also expand into the fourth ventricle, where they may pose restriction to CSF flow. They have a predilection for young animals and have never been diagnosed in an adult animal (Summers et al. 1995).

Diagnosis of Internal Hydrocephalus

Imaging data complement the information obtained by the morphological phenotype and neurological examination. Given the highly variable cranial morphology depending on age and breed in dogs and cats, the choice of the appropriate imaging techniques depends on the sensitivity and specificity of the method for a particular age group, availability, cost, risk, and of course experience in its use.

Radiography

The radiographic examination of the skull in puppies can only give an indication of pathological growth of the cranium and is usually not helpful to obtain a definitive diagnosis. The persistence of coronal sutures and suture separation with large cranial defects has been suggested to be a sign of pathological brain expansion in the past. This is a common misconception as persistent fontanels are simply a common finding in toy breeds especially in the Chihuahua and not associated with hydrocephalus. Lacking gyral impressions in the calvarial bone on radiographs are not a pathological finding either as the skull bones can be very thin in toy breeds. Radiographs of the skull alone are usually not helpful for definitive diagnosis. Pneumo- or contrast ventriculography had been used in the past to demonstrate ventriculomegaly but is obsolete owing to the potential of adverse side effects and the widespread availability of more accurate methods that pose a lower risk to the patient.

Ultrasonography

The essential part of the evaluation of neonatal animals with suspected hydrocephalus is to assess ventricular size and to detect or exclude other malformations that influence treatment and prognosis. Ultrasonography is a safe, minimally invasive

modality to image the ventricular system. A transcranial approach can be performed in conscious animals, which is crucial for the examination of neonatal patients. An open fontanel provides an acoustic window for ultrasound waves and allows visualization of the lateral and third ventricles even in skeletally mature patients. With gentle handling and bending of the head, the caudal (posterior) cranial fossa, brainstem, and cerebellum can be examined through the foramen magnum. In our experience congenital hydrocephalus has already caused severe reduction of the cerebral parenchyma at the time of the diagnosis. Ventriculomegaly is not found in normal puppies. Hence, ultrasonography can be used as an easy screening test to confirm or rule out hydrocephalus in neonatal puppies. The most important differential diagnosis is hydranencephaly, which cannot be clearly distinguished from severe hydrocephalus (Hudson et al. 1998).

Doppler Ultrasonography

Doppler ultrasound is used to measure basilar artery blood flow and to determine cerebral arterial resistive indices (RI) (Seo et al. 2005). Studies of experimentally induced hydrocephalus in cats have shown that the increased intraventricular pressure leads to a reduction of 22% in the blood flow into the brain (Hochwald et al. 1975). The RI is assumed to be an indirect measure of intracranial pressure. RI of the basilar artery has been found to correlate with clinical signs in hydrocephalic dogs (Saito et al. 2003). Decreasing RI after therapy was able to correctly predict an improvement in the clinical status. Doppler ultrasonography may be useful to monitor treatment response of patients with intracranial hypertension noninvasively.

Tomographical Imaging

There is no study that compares the sensitivity and specificity between CT and MRI, but we consider magnetic resonance imaging as the method of choice for the assessment of hydrocephalus in animals. It allows assessment of the whole brain especially cortical morphology to exclude polymicrogyria, macrogyria, and myelination status and, most importantly, improves the detection of inflammatory diseases.

The diagnosis of hydrocephalus may be difficult to establish, particularly in small brachycephalic dog breeds that tend to have relatively larger ventricles in comparison to mesaticephalic dogs (see ventriculomegaly). The identification of clinically relevant ventricular distension is extremely substantial for the correct causal indication of CSF shunting. We have seen a number of dogs with neurological signs, which had been referred to our hospital for ventriculoperitoneal shunting, in which a diagnosis of internal hydrocephalus was made based on the finding of ventricular enlargement alone. CSF examination, however, often revealed idiopathic encephalitis, which primarily requires medical treatment. Inflammatory brain disease may easily be overlooked, and large ventricles can easily be misinterpreted as the

underlying cause for present neurological signs in those dogs. Detailed morphological abnormalities indicative of increased IVP beyond ventricular dilation can be identified by means of MRI, which help to distinguish between the two entities. We were able to identify morphological differences between hydrocephalus and ventriculomegaly, which are useful in the differentiation of these two entities (Troxel et al. 2003). In high intraventricular pressure, the lateral ventricles often extend into the olfactory peduncles and bulbs, which is not a normal finding in carnivores. Care must be taken in ungulates, where the olfactory recess is physiologically widely open. Periventricular edema is the most useful indicator of overpressure but is unfortunately not present in all patients with clinical manifestation of internal hydrocephalus.

Dilation of the third ventricle has been shown to indicate a high pressure gradient between the ventricle and the ventral subarachnoid spaces (interpeduncular cistern and hypophyseal cistern). The two thalami are connected in the midline in companion animals. Structural changes of the interthalamic adhesion can be used as an obvious indicator for pressure changes in the third ventricle. These changes can of course not be seen in obstruction of the interventricular foramen (Hecht and Adams 2010).

Changes in the appearance of the corpus callosum have been documented. Structural changes due to high intraventricular pressure include stretching and upward displacement of the body of the corpus callosum and concurrent downward depression of the fornix. Demyelination of the callosal axons has been suggested to be the underlying cause of increased compliance of the commissural fibers, leading to the upward bowing of the corpus callosum with increased pressure (Laubner et al. 2015).

Ventricular distension occurs in association with a couple of other malformations, especially with cortical migration disorders and porencephaly. If one of these malformations is present, there usually is no overpressure within the dilated ventricular system. Clinical signs are rather due to the other malformations and unlikely to resolve after shunting.

Differential Diagnoses

The diagnosis should never be based on MRI findings only but also on patient signalment, history, and exclusion of other paralleling conditions. Ventriculomegaly is often erroneously diagnosed as hydrocephalus, and the actual underlying cause of presenting clinical signs is missed. Hepatic encephalopathy due to portosystemic shunting is very common in toy-breed dogs and can present with very similar clinical signs and should be ruled out before the introduction of general anesthesia (CBC, biochemistry panel, bile acids, blood ammonia). Idiopathic inflammatory brain disease is also common in brachycephalic dogs. The suspicion should be raised especially when epileptic seizures are a presenting clinical sign. CSF examination completes the clinical workup for internal hydrocephalus.

Treatment Principles

Medical Therapy

Medical treatment to lower intraventricular hypertension aims to reduce CSF production by using diuretics (furosemide) and proton pump inhibitors (omeprazole). It is still proposed as a reasonable treatment option in a number of textbooks. The carbonic anhydrase inhibitor acetazolamide is traditionally recommended as medical treatment option as well (Thomas 2010; Estey 2015; Harrington et al. 1996). These treatment strategies need to be reconsidered. Recently, it has been found that the ventricular volume and the clinical signs of dogs with internal hydrocephalus were not changed sufficiently using acetazolamide 10 mg/kg TID (Kolecka et al. 2015). Similarly, in a long-term study in dogs, the H^+-K^+ inhibitor omeprazole (10 mg/kg SID) was also not able to significantly decrease CSF production in dogs (Girod et al. 2016). This is in contrast to former experimental studies, which have shown that these agents can reduce CSF production significantly. However, their efficacy was never evaluated over a longer study period. Adaptive processes such as increased production of osmogenic ions from the ependyma and choroid plexus or the upregulation of an acetazolamide-resistant isozyme might be an explanation for the lack of treatment success. Reduction of CSF production and intraventricular pressure has been demonstrated after administration of all of the aforementioned drugs as a short-term effect. The use for temporary palliation of clinical signs (12–48 h) might therefore be reasonable.

Surgical Therapy

Currently, placement of a ventriculoperitoneal shunt in dogs and cats with internal hydrocephalus is the most reasonable treatment option. Due to the connection of the two thalami, third ventriculostomy is not feasible in carnivores. There is no specialized shunt system for animals, and most veterinary neurosurgeons use different pediatric shunts with ball valves and various opening pressures (Biel et al. 2013; Shihab et al. 2011; de Stefani et al. 2011; Filgueiras Rda et al. 2009).

Systematic investigations considering the intraventricular pressure changes in hydrocephalic animals are hardly available. Physiological intracranial pressure is 14 ± 3 cm H_2O in dogs (Vullo et al. 1998; Bagley et al. 1995) and 13 ± 1 cm H_2O in cats. In hydrocephalic animals, pressures around 40 cm H_2O have been measured (Vullo et al. 1998). Individual variation in pressure attributed to different size and age of animals and the need for higher valve resistance in upright positions require further investigation.

The difference in intraventricular pressures between lying and standing positions is probably not as pronounced in dogs and cats as in humans. Despite having no substantial evidence, we consider that CSF tends to drain faster when a dog or cat is standing. We therefore use a gravitational valve with an opening pressure of 9 in lying position and 19 in standing position.

Prognosis

Overall the success rate for dogs treated with shunting ranges between 72% and 90% (Biel et al. 2013; Shihab et al. 2011; de Stefani et al. 2011). However, these clinical studies analyze nonuniform groups of dogs including congenital hydrocephalus with severely reduced cerebral parenchyma and adult animals with obviously acquired hydrocephalus with neoplastic or infectious origin.

Two major factors influence the survival, which are postoperative overdrainage and shunt obstruction. Early complications are usually seen within weeks after the surgical intervention. Despite the use of valve systems, the most refractory problem of CSF shunt diversion has been overdrainage whose consequences occur usually 3–4 days after implantation, especially in congenital hydrocephalus. This can result in the devastating complication of subdural hematoma requiring rapid intervention or complete collapse of the hemispheres, which results in euthanasia (Fig. 14). An important intermediate postoperative complication is obstruction of the intraventricular catheter. Clinical evaluation of animals is not helpful because they do not clearly show signs of headaches or visual impairment. Changes of their clinical status appear rather instantaneously. We try to control proper shunt function to the greatest possible extent by daily CSF examinations at inpatient care by tapping of subcutaneous flushing reservoirs. Until now we could not identify a threshold level, but continuous increase of CSF protein within the 1st week after surgery is a significant indicator in expecting shunt obstruction. At recheck after 3 months, CSF can often not be sampled from the shunt system. This may be found in animals with shunt obstruction but also in animals with complete restoration of the cerebral parenchyma that now completely surrounds the ventricular catheter. Recheck MRI is therefore mandatory to determine the underlying cause and appropriate therapeutic approach. Economic constraints often limit surgical revision.

Infection of the ventricular or peritoneal catheter, with subsequent signs of raised intracranial pressure, is only rarely observed (Platt et al. 2012).

The main reason for the euthanasia in the intermediate postoperative period (>12–15 months) is the absence of improvement of clinical signs after surgery. According to our studies, blindness is the only true clinical sign that may persist after successful VP shunting and full restoration of the brain parenchyma. Epileptic seizures are not typically a sign of hydrocephalus unless the ventricular dilation is associated with other disorders or defects. Other or multiple pathologies should always be considered in seizuring animals. The incidence of postoperative epilepsy emerging from the anatomical site of shunt insertion is low (Biel et al. 2013).

Isolated Fourth Ventricle

The situation in which the fourth ventricle no longer communicates with the third ventricle as well as the basal cisterns is often seen after implantation of a shunt into the lateral ventricles in adult large mesocephalic dogs. Although the shunt system is properly draining CSF from the lateral ventricles, the fourth ventricle may remain
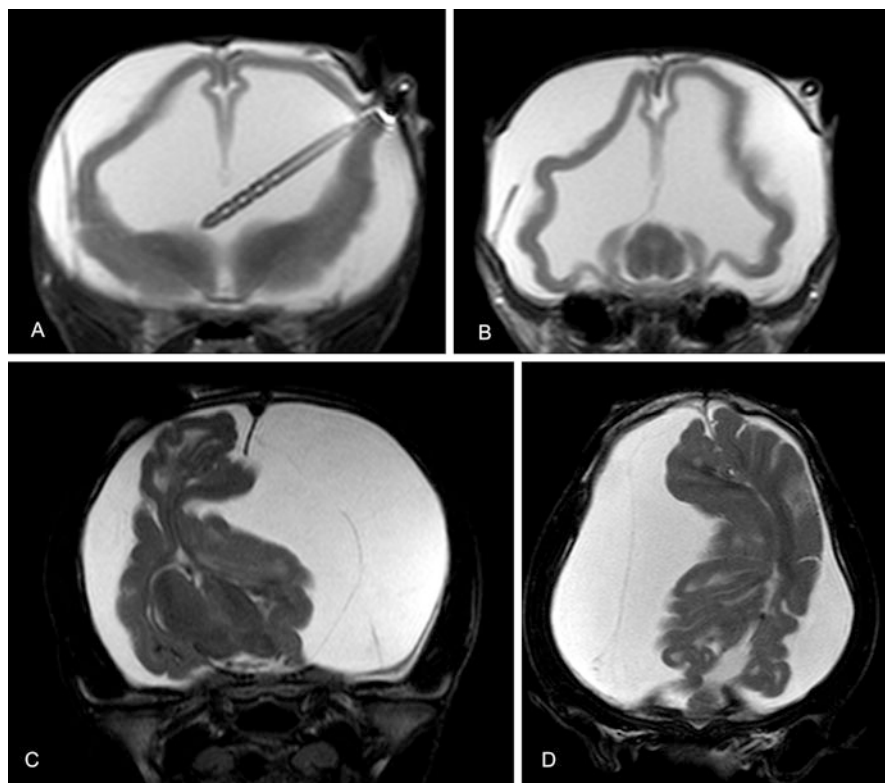
Fig. 14 Postoperative control MRI of a domestic shorthair cat (**a**, **b**) and a crossbreed dog (**c**, **d**) with partial and total collapse of the ventricles after VP shunting

expanded with associated brainstem and cerebellar dysfunction. Veterinary literature does not suggest any particular management strategy yet. Fourth ventricle-peritoneal shunting is an option. Because of concomitant syringomyelia, we often treat isolated ventricles with suboccipital craniectomy and excision of the caudal medullary velum. Direct microsurgical approaches as aqueduct canalization need to be evaluated in the future.

Hydrocephalus in Birds

The cerebral ventricular system, as well as the production and circulation of CSF in birds, is comparable to that in mammals. The only structural characteristic of the avian ventricular system is a side branch of the mesencephalic aqueduct (mesencephalic recess) that extends bilaterally into large lateral protrusions of the mesencephalic tectum, the so-called optic lobes (Mestres and Rascher 1994).

Congenital Hydrocephalus

Congenital forms of hydrocephalus have been sporadically diagnosed in poultry. In turkeys, hydrocephalus has been linked to an autosomal recessive semilethal gene, leading also to malformed beaks and absence of the terminal digits. In chickens, it has been diagnosed in association with intrauterine *Parvovirus* infections, but this was rather suitable with encephaloclastic ventricular enlargement (Marusak et al. 2010).

Definitive diagnosis of internal hydrocephalus has been so far only documented in psittacines with the African gray parrot being mainly affected (Keller et al. 2011; Wack et al. 1989; Orosz 1997; Fleming et al. 2003; Johnston et al. 2006). Congenital hydrocephalus has not been described. The animals develop clinical signs as adults suggesting an acquired form of the malformation. In most birds, dilatation of the subarachnoid space over the cerebral convexities has been described implying a defect in CSF absorption at the arachnoid granulations. Histopathological examination of the parrots shows extensive proliferative changes of the arachnoid membranes that may be sufficient to inhibit the function of the arachnoid granulations, diminishing CSF resorption. In most of these birds, other findings such as hyperkeratotic lesions in the epidermis indicate vitamin A deficiency that can be a consequence of pure seed diets (Brue 1994; Roudybush 1996).

Clinical Signs

Although it has been stated that the neurological examination in bird does not differ from mammals, they possess extensive species-specific characteristics of their central nervous system that cannot be found in mammals. Centers for control of their bipedal walk totally differ from those of the wings during flight. Alertness and mental responsiveness in solitary birds can be totally different from birds living in a flock, etc. These differences pose a challenge to comprehensive clinical neurological workup.

Unspecific findings such as progressive anorexia and weight loss and poor feathering have been described. Obtundation, decreased vocalization, and impaired responsiveness to external stimuli seem to be consistent presenting signs. Ataxia of the pelvic limbs and difficulty walking have been described as well as loss of proprioception in both feet.

Visual deficits including lack of pupillary light reflex and menace response can also be associated with internal hydrocephalus.

Diagnosis

CT and MR imaging have been used to diagnose hydrocephalus in birds. Given the small dimensions of the ventricles, even mild distensions should be considered abnormal, especially when the periparenchymal subarachnoid space is also dilated
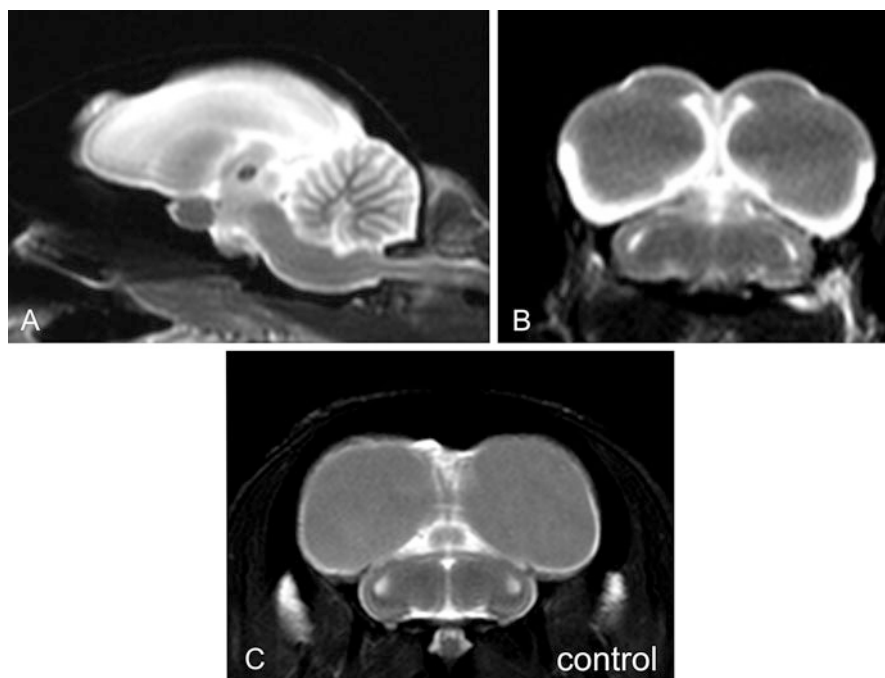
Fig. 15 Sagittal (**a**) and dorsal (**b**) T2-weighted images of a gray parrot with internal hydrocephalus compared to a normal control (**c**)

and dilatation of the third ventricle and ventricle of the mesencephalic tectum is seen (Fig. 15). Birds with internal hydrocephalus have bilateral disease. Unilateral ventricular enlargement without dilation and absence of other distended ventricles should be regarded hydrocephalus ex vacuo, as it can occur after cerebrovascular disease and other forms of encephalomalacia (Keller et al. 2011)

Therapy

VPS has not been used in avian patients yet. The small size of the birds and the limited time under general anesthesia make the use of commercially available shunt systems difficult. Medical options aiming reduction of CSF production are not evaluated in birds just as VP shunting. If medical history suggests hypovitaminosis A, a clinical trial with vitamin supplementation might be an option.

Hydrocephalus in Ungulates

Internal hydrocephalus has been described in many ungulate species, most commonly in cattle and sheep. However, only a limited number of investigations have systematically studied the prevalence, diagnostic, and treatment of hydrocephalus in large animals. Detailed knowledge on neurological diseases is generally limited in large animal practitioners as they only face them sporadically and hydrocephalus was, for decades, mainly a clinical diagnosis based on the obvious cranial deformity in large animal medicine.

As the exposure to teratogenic viruses during fetal development can cause cerebral malformations including hydrocephalus, pathological examinations of hydrocephalic large animals were mostly confined to the exclusion of contagious epizootic diseases as they have a high economic impact (Givens and Marley 2008). The pathophysiology and structural CNS changes underlying hydrocephalus beyond these infectious diseases were rather neglected.

Hydrocephalus in Horses

Congenital Hydrocephalus in Horses

Congenital hydrocephalus is an infrequent brain malformation in horses compared to other ungulates. The prevalence has been estimated to be around 0.6 affected foals per 1000 births (Crowe and Swerczek 1985) occurring sporadically in all breeds. Unlike in ruminants teratogenic viruses have not been identified in horses as the underlying cause for hydrocephalus (Givens and Marley 2008). Developmental defects of the CSF pathways are hardly characterized. Fusion of rostral colliculi and stenosis of the mesencephalic aqueduct have been described in foals (Ferris et al. 2011), but the site of obstruction of CSF flow typically remains undetermined (Carbery 1979).

Clinical Signs

Because of its precocious nature, the equine newborn is neurologically well developed at birth. Within its first hour of life, the newborn foal makes the first attempts to stand, and although the gait may be uncontrolled, the foal is capable of trotting and galloping within a day (Knottenbelt et al. 2004). Principally any aberration from this gradual increase in activity, alertness, and normal behavior in young foals may imply neurological problems. Clinical signs can vary in severity and are not specific for hydrocephalus. A range of nonspecific signs is described, including altered mentation, poor bonding with the dam, and many more. Although doming of the skull is obvious in most foals, some can appear physically normal. Signs of forebrain dysfunction can be head pressing, compulsive walking, and obtundation. Involvement of the brainstem is indicated by strabismus or limb ataxia and weakness.

Ventrolateral strabismus and the variable development of menace responses are common abnormalities in hydrocephalic horses.

Genetic Hydrocephalus in Friesian Horses

The Frisian horse is a breed originating from a province of the Netherlands. Since the Frisian horse population has been closed for outside breeding, it has developed a limited genetic diversity and a high rate of inbreeding over the last decades. The prevalence of hydrocephalus has been reported to be higher in this horse breed. The degree of macrocephaly in affected animals is severe, and foals are often stillborn or are fetotomized at birth to facilitate parturition.

Pathological examinations reveal absent or partially fused rostral colliculi. In addition, the jugular foramen is stenotic compared with healthy foals, which leads to intracranial venous hypertension. Both structural changes can contribute to CSF accumulation in the lateral ventricles. A pressure gradient between subarachnoid spaces and the venous sinus is necessary to ensure CSF drainage, which declines in venous hypertension.

The genetic background for these structural changes was discovered recently. The mode of inheritance of hydrocephalus in Frisian horses appears to be autosomal recessive. A nonsense mutation in B3GALNT2 was discovered. This gene is involved in protein glycosylation. Dystroglycan is a highly glycosylated component of the muscle dystrophin-glycoprotein complex. The gene defect leads to muscular dystrophy (dystrophy-dystroglycanopathy). Dystroglycanopathies are clinically heterogeneous disorders and are often associated with central nervous system pathology and also with hydrocephalus in humans (Stevens et al. 2013; Hedberg et al. 2014). Signs of muscular dystrophy are usually not noticed because affected foals are often stillborn and dystrophy is therefore not observed clinically.

Acquired Hydrocephalus in Horses

"Dummkoller" (Sleepy Staggers)

In the imperial times, a clinical entity called "Dummkoller" challenged veterinarians all over the German-speaking countries. It was first described in Prussia (Rolwes 1823) as a devastating noninfectious brain disease that rendered thousands of military horses unusable in the next 150 years.

The German term "Dummkoller" is a mere description of a chronic behavioral change in horses that has been associated with a dilatation of the lateral cerebral ventricles. Dummkoller horses show signs of immobility, sleepiness, dysphagia, and generalized ataxia ("sleepy staggers"). Pathological examinations of Dexler (1899) and later of Fankhauser (Frauchiger and Frankhauser 1957) identified a chronic swelling and edema in the brain in affected horses. They described that this swelling leads to an increase of brain volume, which in turn causes a subtentorial herniation of
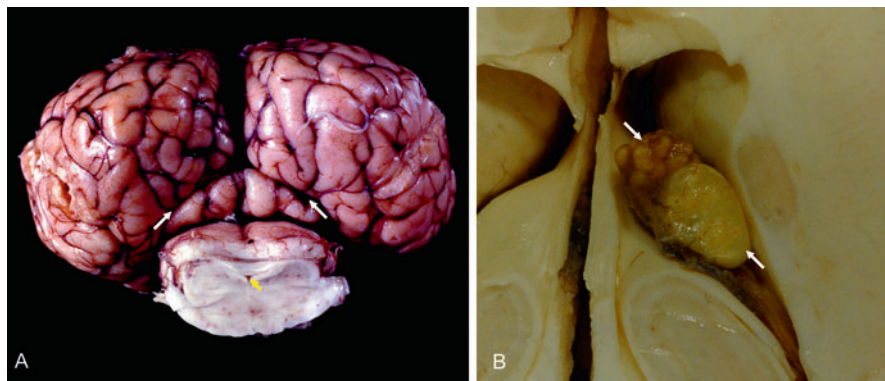
Fig. 16 Formalin-fixed specimens of horse brains. (**a**) Shows the caudal aspect of the brain with a deep fissure in the occipital lobe due to infratentorial herniation of the forebrain ("Druckwulst," white arrow). The herniation causes compression of the mesencephalic aqueduct (yellow arrow) and secondary hydrocephalus. (**b**) Shows the dorsal view into the lateral ventricles after removal of the dorsal hemisphere. A cholesterol granuloma has developed in the plexus of the lateral ventricle caudal to the interventricular foramen, which usually are incidental findings. In some animals these tend to expand leading to blockage of the interventricular foramen. (Images with courtesy of the Institute of Veterinary Pathology, University of Giessen)

the occipital lobe and thus a compression of the mesencephalic aqueduct (Fig. 16a). The large ossified tentorium in horses has been suggested to be a predisposing factor for the herniation (Dexler 1899). Even after the decline of the cerebral swelling, the occipital lobe remains trapped under the osseous tentorium sustaining the obliteration of the aqueduct.

Many underlying causes for the chronic swelling have been suggested, and in fact, subtentorial herniation of the occipital lobe occurs in a plethora of intoxications, infections, and also trauma in equine patients. Dummkoller has fallen into oblivion before systematic histological examinations of affected brains could be performed.

Cholesterol Granuloma

Tumors occurring in parts of the brain within or near the ventricles can obstruct the flow of CSF. One of the most common space-occupying lesions, which block the exit of CSF from the ventricles to the cisterns in horses, are cholesterol granulomas, also called cholesteatomas. These are common nonneoplastic masses in the choroid plexus of mature and aged horses (>15 years). They are usually benign with minimal destruction of adjacent brain tissue (Fig. 16b). Occasionally, they attain large size and block the intraventricular foramen (Monro's foramen) leading to enlargement of the lateral cerebral ventricles. Secondary hydrocephalus and increase of intraventricular pressure lead to signs of obtundation, compulsive circling, ataxia blindness, and seizures.

The masses are composed of cholesterol crystals embedded in granulation tissue implying a foreign body-type inflammatory response to cholesterol in the interstitium of the choroid plexus. A chronic intermittent congestion with extravasation of blood and cholesterol into the choroid plexus was suggested as the origin of the cholesterol. An association between hyperlipidemia and the development of cholesterol granulomas of the choroid plexus could be demonstrated in other animals (Muenchau and Laas 1997; Vanschandevijl et al. 2008) but has not been shown in horses, yet.

CT (Sladky et al. 2000) and MRI (Maulet et al. 2008) have been used to diagnose granulomas. On MRI, they appear as oval to lobulated intraventricular masses with mixed signal intensity. On T2 and FLAIR sequences, they predominantly show isointense signal to white matter and multiple hypointense areas and iso- to hypo-intense signal intensity in T1. The masses typically present moderate uniform contrast enhancement.

Interventional neurosurgical therapy is hardly established in equine medicine, and therapy is limited to anti-inflammatory agents that can be used to reduce parenchymal edema and alleviate neurologic signs temporarily.

Congenital Hydrocephalus in Ruminants (Bovine and Ovine Species)

Exposure to teratogenic viruses is a common source of hydrocephalus in ruminants. A number of intrauterine viral infections have been reported to cause hydrocephalus in ruminants. Bovine viral diarrhea virus is a member of the family *Flaviviridae* causing high economical losses associated with reproductive failure in ruminants all over the world. The bluetongue virus is an *Orbivirus*, which has recently expanded its range in Europe. It most commonly occurs in sheep. Cattle develop clinical signs rather sporadically but act as an important virus reservoir. Schmallenberg virus is a member of the genus *Orthobunyavirus* that was recently discovered as a novel pathogen in ruminants in northwestern Europe. Virus uptake during gestation leads to transplacental infection of the fetus and to a spectrum of lesions in the fetal central nervous system. Corresponding to the virus strain, the distribution of the virus in the central nervous system, and the fetal age at the time of infection, remarkable variations can occur. Infection during early gestational stages, before immunocompetence of the fetus, results in severe dysplastic lesions of the brain and spinal cord. Hydrocephalus usually occurs after infection in the second third of gestation of cattle and sheep. However, the nature of the lesions associated with most of the viruses is indicative for encephaloclastic defects, which are consistent with hydrocephalus ex vacuo. In some fetuses edema of the white matter, disruption of the ependymal lining, and periventricular proliferation of neuroglial fibers were found in association with BVDV suggesting high intraventricular pressure and true hydrocephalus (Maxie and Youssef 2007; Zachary 2007; LeCouteur and Withrow 2007). An updated review of virus-induced defects of the CNS in cattle was published by Agerholm (Agerholm et al. 2015).

Reports of congenital hydrocephalus unrelated to infectious agents in cattle are sparse and usually put more emphasis on the dystocia attributable to the cranial enlargement. In some of these animals, fused rostral colliculi of the corpora quadrigemina leading to aqueductal obliteration were the underlying cause of the ventricular enlargement.

Genetic Hydrocephalus in Ruminants

In the first decades of the twentieth century, several reports about detrimental bovine malformation syndromes have been published. The newborns of certain cattle breeds (Hereford, Charolais, Ayrshire, Dexter, Shorthorn, Holstein, Jersey) have been frequently affected by combinations of skeletal, facial, and intracranial abnormalities including hydrocephalus. The genetic determination was based on the high prevalence of the malformation in certain breeding lines. Extensive use of well-documented artificial insemination in dairy cattle enabled researchers to identify carrier bulls and to determine a genetic basis and the possible mode of inheritance. However, pathological examinations of the brain and other tissues were rudimentary, and the exact pathogenesis has never been identified.

The presence of hydrocephalus-associated defects such as microphthalmia, retinal dysplasia, and muscle dystrophy as well as infertility that are reported in Shorthorn cattle displays similarities to the human Walker-Warburg syndrome (Greene and Leipold 1974; Leipold et al. 1971). Hydrocephalus accompanied by decreased development of the maxillae and nasal bones, cleft palate, and kyphosis has been reported in Jersey and Dexter calves that may be similar to other human genetically determined craniofacial abnormalities.

Arthrogryposis multiplex commonly referred to as "Curly Calf Syndrome" has been reported in Angus cattle. Affected calves are usually stillborn. Hydrocephalus and hydranencephaly have been observed in association with fixed joints in all limbs, lateral deviation of the facial bones (Kampylognathia), and rotational deviation of the cervical, thoracic, and lumbar vertebral column. This malformation has also been observed in sheep (Whittington et al. 1988).

The uptake of teratogenic plant toxins during gestation was also found to cause congenital arthrogryposis and associated malformations in ruminants. Experimental feeding of spotted hemlock (*Conium maculatum*), lupins (*Lupinus*), and shrub tobacco (*Nicotiana glauca*) to bearing cows produced a dose-dependent spectrum of abnormalities (Keeler 1973; Keeler et al. 1980, 1981).

Recently, a genetic mutation has been isolated in Angus and Angus-influenced cattle leading to "neuropathic hydrocephalus." Affected calves have an extremely large cranium, with almost no brain or spinal cord tissue (Kaiser 2009). Although it has been referred to as hydrocephalus, it obviously is a severe encephaloclastic defect of yet unknown origin.

Clinical Signs

Intrauterine development of hydrocephalus in ruminants is often accompanied by massive expansion of the cranium leading to dystocia. Affected animals are often born premature, are stillborn, or die shortly after birth. Animals with a mild degree of ventricular distension can appear normal.

Clinical signs in calves that survive hydrocephalus include weakness, obtundation, weak suckle reflex, droopy head and ears, head tremor, muscular fasciculations, blindness, ventrolateral strabismus, nystagmus, tongue flaccidity, dysphonia, limb spasticity, hyperreflexia, seizures, recumbency, retention of food material in the oral cavity, conscious proprioceptive deficits, and coma (Mayhew 1989; Gilman 1956).

Acquired Internal Hydrocephalus in Ruminants

Bacterial Meningo-ventriculitis

Neonatal calves have a very underdeveloped immune system and are dependent on their dam to provide initial passive immunity through colostrum. Insufficient passive transfer of immunoglobulins often leads to septicemia after neonatal infections through diarrhea and/or pneumonia. The invading bacteria (*E. coli*, *Salmonella*, *Streptococcus*, *Mycoplasma*) may cause focal infections, such as in growth plates, joints, and also the meninges (Seimiya et al. 1992). The fibrinopurulent inflammation of the meninges interferes with CSF absorption (Fecteau et al. 2009), and the inflammation of the subependymal parenchyma leads to obstruction of CSF flow (Fig. 17).

Clinical Signs

The clinical signs of bacterial meningitis depend on the stage of infection. Initially, affected calves are obtunded and the body temperature is rising. Soon they show increased nervousness and an exaggerated responsiveness to external stimuli. Rigidity of the neck is a sign of cervical pain. Classically they stand with the head bent back with the eyes looking upward in a "stargazing" posture (opisthotonus). In the later stage, reduced consciousness due to ventricular distension is the main clinical sign (Green and Smith 1992).

Chiari Malformation in Ungulates

Cerebellar deviation into or herniation through the foramen magnum associated with syringomyelia has been diagnosed in cattle and sheep. Unlike in the dog, all types of the malformation spectrum can be found in calves. Classically the caudal parts of the
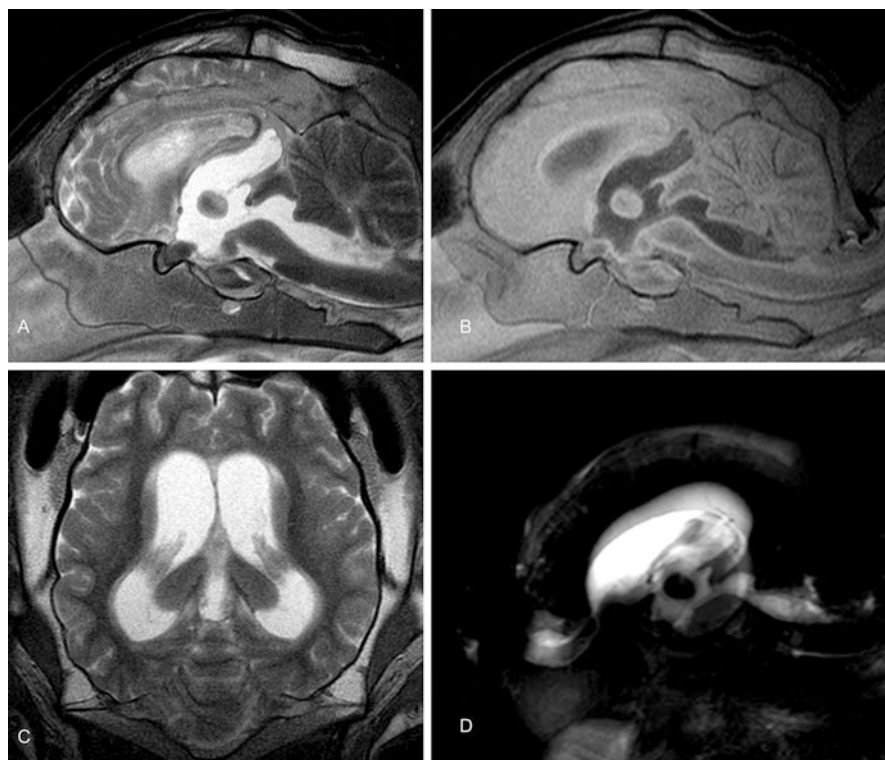
Fig. 17 Sagittal and dorsal T2-weighted image as well as a FLAIR sequence and a myelo-MALF-MIP sequence of a calf with meningo-ventriculitis. There is distension of all ventricles with hyperintensities in the periventricular white matter and medulla of the cerebellum. There is dilation of the cerebellar sulci that also show a hyperintense signal. This signal remains hyperintense in FLAIR suggesting leptomeningitis. The periventricular hyperintensity is consistent with ependymitis. *E. coli* bacteria were isolated from the CSF and from the meninges and brain parenchyma after euthanasia

cerebellum and brainstem tissue herniate into the foramen magnum. In some calves the cerebellum may be partially absent or hypoplastic which is consistent with Chiari malformation type II. This form is usually accompanied with downward displacement of the occipital lobe through an enlarged foramen magnum. The type II malformation usually is accompanied by vertebral malformations, spina bifida, and meningomyelocele. The majority of these animals present with occlusive internal hydrocephalus, which is caused by compression of the mesencephalon (Cho and Leipold 1977; Madarame et al. 1991). Chiari malformation type 1 is diagnosed sporadically, when syringomyelia causes ataxia or tetraparesis in calves. We have seen mild deviation of the cerebellum in association with increased bone thickness, which has been attributed to hypovitaminosis A in a growing calf (Fig. 18) (Washburn and Streeter 2004).
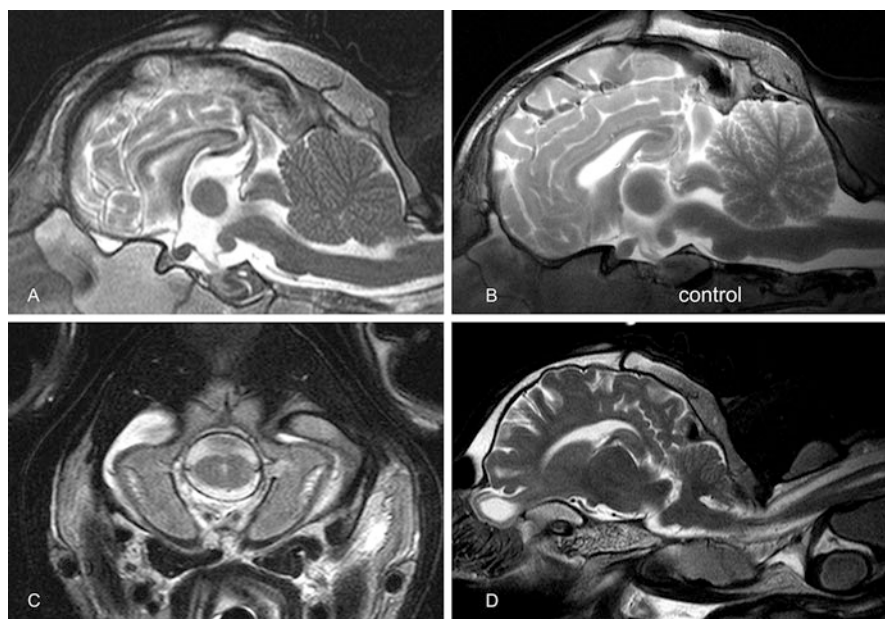
Fig. 18 Sagittal (**a**, **d**) and transversal (**c**) T2-weighted MR images of 8-week-old Simmenthal calf, compared to a normal control animal (**b**). The calf shows mild hypertrophy of the occipital and parietal bones. As bovine species lack an osseous tentorium, the cerebellum is mildly rostrally shifted and not bilaterally compressed. The caudal aspect of the vermis is deviated into the small foramen magnum. Syringomyelia has developed in the cervical spinal cord at the level of the axis. The findings are consistent with those seen in human Chiari malformation

Dandy-Walker in Ruminants

The combination of defects that include an aplastic or hypoplastic cerebellar vermis, occasional hydrocephalus, and other rostrotentorial malformations has been reported in calves and lambs (Mayhew 1989; Buck et al. 2009). A more detailed classification into true Dandy-Walker and Dandy-Walker variant can be difficult in pathological examinations. Both bovine and ovine species lack an osseous tentorium that could help to diagnose enlargement of the caudal fossa postmortem. Cystic dilation of the fourth ventricle would require MR or CT imaging, which is rarely performed (Buck et al. 2009). The underlying cause of Dandy-Walker malformation is unknown in calves; however, it has been reported as a possible genetic defect in British Suffolk sheep (Jeffrey et al. 1990; Pritchard et al. 1994). Even if hydrocephalus is present, clinical signs are consistent with cerebellar dysfunction in both species with Dandy-Walker malformation (tremor, wide-based stance, nystagmus, hypermetria).

Disorders of Cartilage Growth (Achondroplasia, Chondrodysplasia)

In the history of animal husbandry, the morphology of animals was often modified systematically for special functions. Reduction in body size is a common feature of domestication and was desired in a number of species. Toy variants of dogs have been bred for nobility as lap dogs as a luxury item with little apparent purpose but a refined and pleasant "personality." Miniature horses were bred for children or were used in coalmines as draft animals. Small cows were bred for economic advantages over large cows as they have less disorders of their digestive system and generally require significantly less health care. In other breeding lines, the reduced size was a side effect of selection for other traits. As desired or undesired effect, variations in genes responsible for pituitary gland hormones, thyroid gland hormones, hormone production and/or recognition, metabolism, cartilage development, and bone growth plate development have co-occurred. One of these defects is chondrodysplasia, which is a collective term for a large group of pleomorphic, heterogeneous diseases affecting cartilage and thereby bone growth.

Growth of the basicranium follows the same principles of enchondral ossification as the long appendicular bones. Hence, reduction in bone growth is often related to a diminished longitudinal skull growth. As the brain needs space to develop, the skull expands laterally. The cranial base promotes growth of the facial bones, which also may be severely reduced in chondrodysplastic animals. Both aberrant growth patterns result in the brachycephalic phenotype.

Canine Brachycephaly

Some small toy-breed dogs (miniature pinscher, toy poodle, English toy terrier) appear to be miniaturized but proportioned versions of larger breeds. Modification of the IGF1 gene is a major determinant of small size in dogs (Isgaard et al. 1988). However, the skeletal characteristics of brachycephalic dogs cannot be totally explained by IGF1 deficits. Control of postnatal general skeletal and craniofacial growth involves complex interactions of genes, nutrients, and hormones; one of those is the pituitary growth hormone – GH (Wilson and Foster 1992; Rubenstein and Federman 1989). In the appendicular skeleton, the growth hormone (GH) among others regulates the proliferation and differentiation of growth plate chondrocytes, via stimulation of local mediators such as insulin-like growth factor-1 (IGF-1) or fibroblast growth factor-2 (FGF-2) (Isaaksson Isaksson et al. 1991). It is known that growth hormone increases cartilage formation by acting both directly and indirectly on chondrocytes in the appendicular skeleton and the cranial base synchondroses (Konfino et al. 1975). The lack of growth hormone also results in well-proportioned miniature dogs (ateliotic dwarfism). Most of the toy breeds are ateliotic dwarfs: Chihuahuas, Boston terriers, Italian greyhounds, Maltese, miniature pinschers, miniature spaniels, Pomeranians, toy poodles, Yorkshire terriers, etc. (Stockard 1941). The external morphology of the dog head was categorized into three types: animals

with long slender skulls and prominent noses, a large external sagittal crest, and a narrow zygomatic arch were characterized as dolichocephalic (e.g., borzoi dog), while dogs with a round head without a sagittal crest and with a braincase longer than the facial bones were classified as brachycephalic (Pug dog, French bulldog, Pekingese, etc.) and the intermediate type is called mesocephalic (German shepherd dog, Labrador retriever, etc.). Although we have accepted the brachycephalic phenotypes as a breed characteristic, we have to consider that some of these features are representations of a pathologic skeletal development. These breeds show chondrodystrophic changes in their skeletal growth. Radiographic studies have shown that the spheno-occipital synchondrosis undergoes a premature closure in brachycephalic dogs (Schmidt et al. 2008). The resulting shortening of the cranial base determines the restricted growth of the braincase and the facial bones in these animals. One effect of restricted longitudinal growth is a compensatory widening of the skull as a whole and of the skull base, which influences the volume of skull base foramina. A stenosis of the jugular foramen has been found in the brachycephalic Cavalier King Charles spaniels. This stenosis and a consecutive vascular compromise in the foramen may contribute to venous hypertension and increased intraventricular and intracranial pressure.

The restriction of cranial growth in small dog breeds also leads to a generally decreased cranial capacity in relation to the brain parenchyma (Schmidt et al. 2014b). The caudal fossa and especially the basal cisterns are severely constricted with fatal consequences for intracranial compliance and intraventricular pulse pressures. A large part of brachycephalic dogs present ventriculomegaly and hydrocephalus, which is undoubtedly associated with this head morphology. The reduction of longitudinal growth of the skull base is seen in many species with brachycephaly (Fig. 19).

Chondrodysplasia in Ungulates

Horses

Miniature horses have the proportions and other characteristics that make them phenotypically "horses," not ponies. Some breeding lineages focused on selection for extremely diminutive size. Disproportionate dwarf horses emerged from these matings, most of which have significant health issues. Different gene variants associated with the expression of the cartilage core protein aggrecan were identified in miniature horses. The *D1* deletion is lethal in the homozygous form or in combination with other defects. The mutation *D2* causes an unwanted disproportionate dwarfism with a large head and domed frontal bone, enlarged eyes and orbit with a low and severely shortened nasal bone with detruded muzzle, and prognathism of varying severity. These horses can also develop ventriculomegaly and hydrocephalus (Eberth 2013).
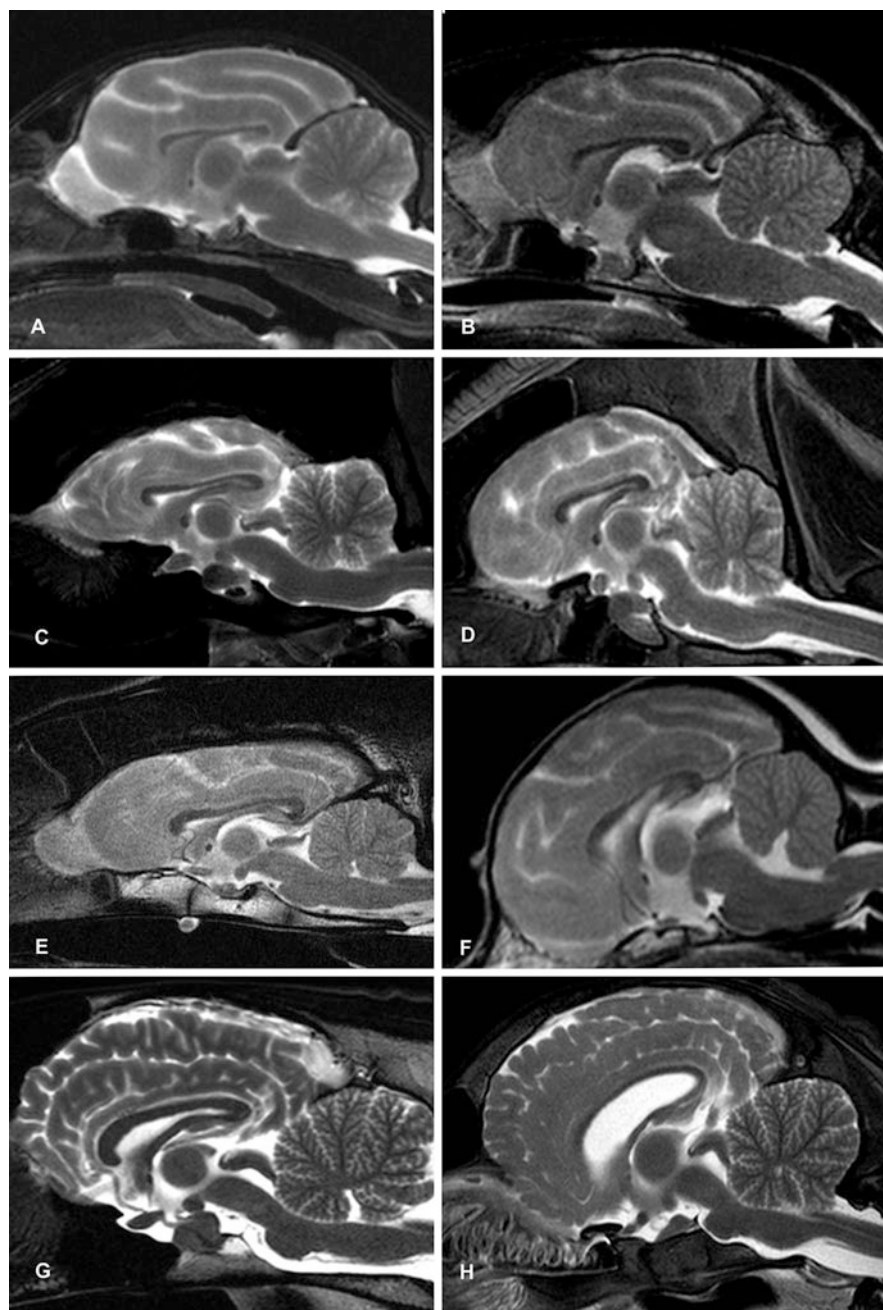
Fig. 19 Midsagittal T2-weighted MR images of a cat (**a**), pig (**c**), dog (**e**), and horse (**g**) with normal head morphology in comparison to brachycephalic breeds (**b** Persian cat, **d** potbellied pig, **f** Chihuahua, and **h** mini Shetland pony). The brachycephalic animals have a shortened skull base and a reduced cranial capacity. The olfactory bulbs are rather ventrally orientated, and the corpus callosum rather has an upright position

Ruminants

In cattle, disproportionate dwarfism has been reported in different breeds such as Angus, Dexter, Holstein, Hereford, Jersey, and Shorthorn. Scientific work in Dexter cattle also revealed multiple different mutations within the gene encoding aggrecan. The Dexter cow presents a type of dwarfism with characteristic short legs, which is caused by two different mutations in the aggrecan gene (Cavanagh et al. 2007). The homozygous dwarf phenotype of chondrodysplasia in the Dexter is similar to the type *D1/D1* seen in the miniature horse. Calves with the homozygote effective gene are aborted with short deformed limbs and scoliosis of the vertebral column. The skull is also abnormal with foreshortening of the facial bones and arrested development of the nasal bones and maxilla with protruding tongue and cleft palate (bulldog calf). Whereas all bones of the skull base are fused at birth, the cranial sutures are wide open. This form of chondrodysplasia is frequently associated with hydrocephalus.

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