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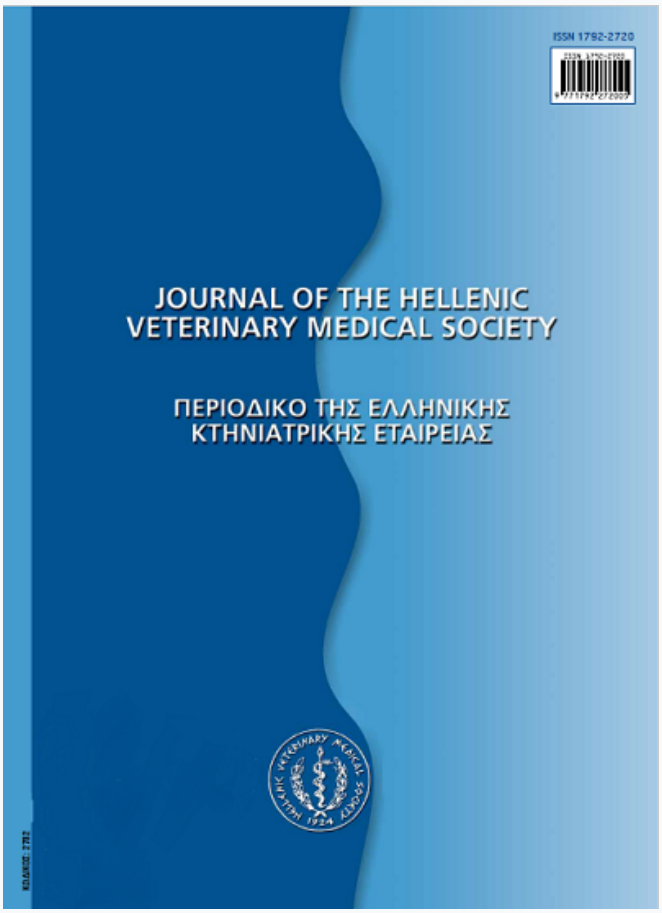

An update on meningoencephalomyelitis of unknown aetiology in dogs

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Review article
Ανασκόπηση

An update on meningoencephalomyelitis of unknown aetiology in dogs

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Νεότερα δεδομένα σχετικά με τη μηνιγγοεγκεφαλομυελίτιδα άγνωστης αιτιολογίας στους σκύλους

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ABSTRACT. Inflammatory diseases of the central nervous system are common causes of neurological dysfunction in the dog and can be grouped into two broad categories; those of infectious and those of unknown aetiology. Meningoencephalomyelitis of unknown aetiology include non-infectious inflammatory central nervous system diseases in which abnormal findings on magnetic resonance imaging and cerebrospinal fluid analysis indicate inflammatory central nervous system disease, but for which histopathological confirmation has not been reached. Meningoencephalomyelitis of unknown aetiology describes a group of non-infectious inflammatory diseases of the central nervous system. These include the granulomatous meningoencephalomyelitis and the necrotising encephalitis, the latter can be further distinguished into two subtypes: necrotising meningoencephalitis and necrotising leucoencephalitis. Steroid-responsive meningitis-arteritis may be also included to this category and, usually, does not present signs of encephalitis or/and myelitis (except in the chronic form) and is easier diagnosed even without histopathological examination. In most cases of meningoencephalomyelitis of unknown aetiology, a presumptive diagnosis can be achieved by the assessment of case presentation, the neurologic signs, cerebrospinal fluid testing, cross-sectional imaging of the central nervous system and appropriate microbiological tests. Definite diagnosis is achieved with histopathological examination. The underlying cause for these diseases is unknown. The clinical signs in meningoencephalomyelitis of unknown aetiology is variable and depends on which area of the central nervous sytem is affected. Meningoencephalomyelitis is acute in onset, progressive in nature and associated with multifocal to diffuse neuroanatomic localization. Extraneural signs are less common and these usually include pyrexia and peripheral neutrophilia. The differential diagnosis for dogs presented for an acute onset of multifocal central nervous system signs includes genetic abnormalities, metabolic disorders, infectious meningoencephalitis, toxin exposure, stroke and neoplasia. The diagnostic approach includes a complete blood count, a comprehensive chemistry panel, urinalysis, survey radiographs of the thorax plus abdominal ultrasound to rule out systematic disease and metastatic neoplasia, computed-tomography or magnetic reso-

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nance imaging, cerebrospinal fluid analysis and microbiological tests. When neoplasia is suspected, computed-tomography-guided brain biopsy may be required for the differentiation. Meningoencephalomyelitis of unknown aetiology responds more or less to immunosuppressive therapies, but the prognosis should be guarded to poor with the exception of steroid-responsive meningitis-arteritis, for which it is good. Treatment protocols are based on prednisolone, but new immunosuppressive agents have now been added in those to control the diseases and they seem to be effective. However, gold standard protocols have yet to be established.

Keywords: dog, inflammatory diseases, meningoecephalomyelitis, nervous system

ΠΕΡΙΛΗΨΗ. Στη μηνιγγοεγκεφαλομυελίτιδα άγνωστης αιτιολογίας περιλαμβάνονται η κοκκιωματώδης μηνιγγοεγκεφαλίτιδα, η νεκρωτική μηνιγγοεγκεφαλίτιδα και η νεκρωτική λευκοεγκεφαλίτιδα. Καθεμία από τις παραπάνω, μη μικροβιακής αιτιολογίας εγκεφαλοπάθειες έχει διαφορετικά ιστοπαθολογικά ευρήματα. Περαιτέρω, στις εν λόγω νόσους περιλαμβάνεται και η μηνιγγίτιδα-αρτηρίτιδα που ανταποκρίνεται στα γλυκοκορτικοστεροειδή, η οποία όμως συνήθως περιγράφεται χωριστά, επειδή εκδηλώνεται σπάνια με συμπτώματα εγκεφαλίτιδας και/ή μυελίτιδας (εκτός από τη χρόνια μορφή αυτής). Η κλινική διάγνωσή τους μπορεί να γίνει με βάση το ιστορικό, την κλινική εικόνα, τα ευρήματα της ανάλυσης του εγκεφαλονωτιαίου υγρού, τις ειδικές ανοσολογικές εξετάσεις στο αίμα και το εγκεφαλονωτιαίο υγρό και τα ευρήματα των απεικονιστικών εξετάσεων. Μολαταύτα, για οριστική διάγνωση απαιτείται ιστοπαθολογική εξέταση. Η ακριβής αιτιολογία των εν λόγω παθολογικών καταστάσεων παραμένει άγνωστη, πολύ πιθανόν όμως αυτές να είναι ανοσολογικής φύσεως. Η κλινική εικόνα της μηνιγγοεγκεφαλομυελίτιδας άγνωστης αιτιολογίας ποικίλει, εξαρτώμενη από την έκταση της προσβολής του κεντρικού νευρικού συστήματος. Τα συμπτώματα, που εκδηλώνονται απότομα και εξελίσσονται προοδευτικά, συνήθως υποδηλώνουν διάχυτη ή πολυεστιακή εγκεφαλοπάθεια. Στα γενικά συμπτώματα, τα οποία εν γένει δεν παρατηρούνται συχνά, περιλαμβάνονται ο πυρετός και η λευκοκυττάρωση. Η διαφορική διάγνωση περιλαμβάνει τα κληρονομικά, τα μεταβολικά και τα λοιμώδη νοσήματα, τις νευροτοξικώσεις, την ισχαιμική εγκεφαλοπάθεια και τις νεοπλασίες του εγκεφάλου. Η αιτιολογική διάγνωση είναι δύσκολη. Η αρχική εργαστηριακή διερεύνηση αποσκοπεί στον αποκλεισμό των συστηματικών παθήσεων με τη διενέργεια εργαστηριακών (πλήρης αιματολογική και βιοχημική εξέταση του ορού του αίματος, ανάλυση ούρου) και απεικονιστικών (ακτινογραφίες θώρακα και υπερηχογράφημα κοιλίας) εξετάσεων. Η διάγνωση της μηνιγγοεγκεφαλομυελίτιδας άγνωστης αιτιολογίας στηρίζεται στις ειδικές απεικονιστικές εξετάσεις (αξονική και μαγνητική τομογραφία) και στην ανάλυση του εγκεφαλονωτιαίου υγρού. Σε κάποια περιστατικά, μπορεί να γίνει βιοψία από τις αλλοιώσεις με τη βοήθεια ειδικής βελόνης βιοψίας υπό καθοδήγηση αξονικού ή μαγνητικού τομογράφου. Στο αρχικό στάδιο της νόσου, υπάρχει ανταπόκριση στην αγωγή με ανοσοκατασταλτικά φάρμακα, όμως μέχρι σήμερα δεν έχει βρεθεί κάποιο αποτελεσματικό θεραπευτικό σχήμα. Η πρόγνωση είναι συνήθως επιφυλακτική ή και κακή. Εξαίρεση αποτελεί η μηνιγγίτιδα-αρτηρίτιδα που ανταποκρίνεται στα γλυκοκορτικοστεροειδή, της οποίας η πρόγνωση είναι καλή.

Λέξεις ευρετηρίασης: μηνιγκοεγκεφαλίτιδα, νευρικό σύστημα, σκύλος, φλεγμονώδης νόσος

INTRODUCTION

Inflammatory diseases of the central nervous system are common causes of neurological dysfunction in the dog and can be grouped into two broad categories; those of infectious and those of unknown aetiology. Meningoencephalomyelitis of unknown aetiology include non-infectious inflammatory central nervous system diseases in which abnormal findings on magnetic resonance imaging and cerebrospinal fluid analysis indicate inflammatory disease, but for which histopathological confirmation has not been reached.

Meningoencephalomyelitis of unknown aetiology includes the granulomatous meningoencephalomyelitis and the necrotising encephalitis, the latter can be further distinguished into two subtypes: necrotising meningoencephalitis and necrotising leucoencephalitis. Steroid-responsive meningitis-arteritis may be also included to this category. Meningoencephalomyelitis of unknown aetiology usually have acute onset and rapid deterioration of the clinical signs, although, sometimes, they are present with a long-standing clinical course (Le Couteur, 2009).

The underlying causes of meningoencephalomyelitis of unknown aetiology are unknown. Proposed causes include infectious (Schatzberg et al., 2005), auto-immune (Kipar et al., 1998, Matsuki et al., 2009) and neoplastic conditions. Moreover, for some breeds, there may be a genetic component for these disorders (Greer et al., 2008). Numerous attempts have been made to identify infectious agents in affected dogs, but, up to date, these have been unsuccessful. A possible explanation is that these disease processes may be triggered by an infectious agent

that is rapidly eliminated, but which, nevertheless, has initiated a destructive immune response. As a result, treatment protocols applied are based, in principle, on immunosuppressing the animal (Olby, 2010).

GRANULOMATOUS MENINGOENCEPHALOMYELITIS

Granulomatous meningoencephalomyelitis is an inflammatory disease of the central nervous system, which affects mainly dogs and, rarely, cats (Vandevelde et al., 1981; Braund, 1985; Robin et al., 1993). The disorder may account for up to 25% of all central nervous system diseases in dogs (Tipold, 1995). The cause of granulomatous meningoencephalomyelitis is unknown. although it has been suggested that a T cell-mediated delayed-type hypersensitivity can be a possible pathogenetic mechanism for the disease (Kipar et al., 1998). This mechanism would lead to formation of peri-vascular cellular infiltrates of histiocytic cells mixed with lymphocytes, plasma cells and, occasionally other leukocytes, involving the majority of the blood vessels in the white matter (predominantly), as well as the pia matter of the central nervous system (Cordy, 1979). It is also possible that granulomatous meningoencephalomyelitis represents an altered host response to an infectious agent or a genetic disorder (Sutton and Atwell, 1982). It has been also reported that the disease may be triggered by vaccination against canine distemper and rabies (Harris et al., 1988), which lends support to the hypothesis of autoimmune type disease.

Clinical presentation

Most cases of granulomatous meningoencephalomyelitis occur in small breed dogs, more commonly in terrier and toy breeds and in Poodles, although any breed may be affected (Munana, 1996). Most cases of the disease would occur in young- to middle-aged dogs, mean age of animals with the disorder being ~5 years (range: 6 months-12 years). Granulomatous meningoencephalomyelitis occurs in animals of both sexes; however, there appears to be a higher incidence risk for the disease in female dogs (Munana and Luttgen, 1998).

Clinical signs

Granulomatous meningoencephalomyelitis occurs as an acute-onset, progressive, multifocal neurologic disease that may be fatal if left untreated (Munana et al., 1998; De Lahunta and Glass 2009). Clinically, the disease is characterised by three clinical differing presentations: multifocal, focal, ocular.

The multifocal form is the most common; typically, it has acute onset, with rapidly progressing multifocal neurologic signs over a period of one to eight weeks, involving the cerebrum, the caudal brainstem, the cerebellum or the cervical spinal cord (Cordy, 1979; Braund, 1985; Munana, 1996). Clinical signs, which reflect a multifocal syndrome, as a result of the scattered distribution of the lesions, include incoordination, vestibular or proprioceptive ataxia, cervical hyperesthesia, head tilt, nystagmus, facial and/or trigeminal nerve paralysis, circling, visual deficits, seizures and depression (Braund et al., 1978; Alley et al., 1983; Bateman and Parent, 1999). Occasionally, fever and peripheral neutrophilia would accompany the neurological signs (Cordy, 1979; Sorjonen, 1990).

The focal form of the disease is less common, although focal signs have been reported in up to 50% of cases (Munana and Luttgen, 1998). This form represents a true mass lesion located most often in the cerebral hemispheres, brainstem or spinal cord (De Lahunta and Glass, 2009).

An infrequently reported ocular form of granulomatous meningoencephalomyelitis appears to be related to lesions localized in the optic nerves and optic chiasm and can result in visual impairment and abnormal pupillary reflexes. A hyperaemic and oedematous optic disk may be seen in ophthalmic examination; vessels can be seen to be dilated, whilst focal haemorrhage may be present. Dogs with the ocular form of the diseases may also, concurrently, show or develop the multifocal form (Braund, 1985; De Lahunta A and Glass, 1995).

Generally, it has been reported that 50% of the dogs with granulomatous meningoencephalomyelitis have forebrain-type symptoms and 50% have both forebrain-type and brainstem-type symptoms. In addition, dogs with acute form of the disease show often signs of central vestibular syndrome (Le Couteur, 2009). Cervical spinal pain is also common in patients with more often and it can sometimes preexist in combination with spinal cord signs.

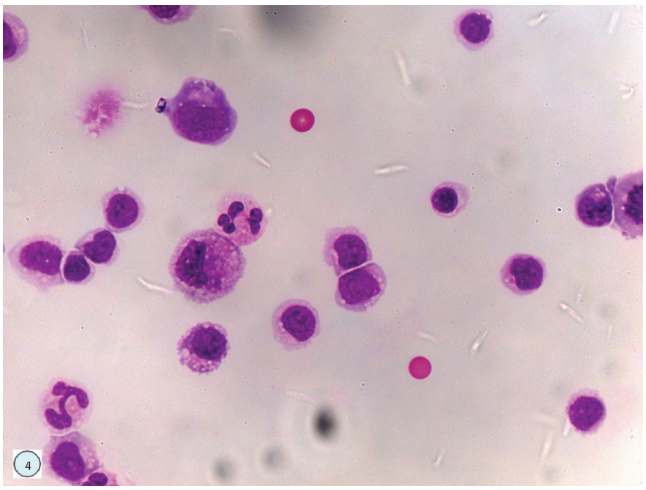

Fig. 1. Predominance of lymphocytes in cerebrospinal fluid sample from a dog with granulomatous meningoencephalomyelitis (modified Wright-Giemsa, ×60 objective).

Diagnosis

A tentative diagnosis may be suggested by the medical history, the clinical presentation, the results of clinical examination, the examination of cerebrospinal fluid and the findings from neuroimaging (magnetic resonance imaging, computed-tomography). Definitive diagnosis is based on the histopathological findings in lesional central nervous system tissue, which can be collected by computed-tomography-guided brain biopsy or other neurosurgical techniques (craniotomy or laminectomy) (Le Couteur, 2009).

In most dogs, results of examination of cerebrospinal fluid indicate mild to pronounced pleocytosis, ranging from 50 to 900 leucocytes μL^{-1}. Mononuclear cells, mainly lymphocytes (60%-90%) and monocytes (10%-20%) can also be present (Fig. 1). While neutrophils typically comprise from 1%-20% of leucocytes the cerebrospinal fluid, they may be the predominant cell type on rare occasions. Protein concentration is usually mildly or moderately increased, ranging from 40 to 400 mg dL^{-1} (Russo, 1979; Demierre et al., 2001).

The most common magnetic resonance imaging findings for the multifocal form include multiple hyperintensities on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences scattered throughout the central nevous system white matter. These lesions typically assume an infiltrative appearance and have irregular margins. Lesions visible in magnetic resonance imaging often are distributed throughout both gray and white matter. The lesions display a variable intensity on T1-weighted images and variable degrees of contrast enhancement (Fig. 2). Meningeal enhancement is uncommon (Cherubini et al., 2006). The focal form may be indentified on magnetic resonance imaging or computed-tomography as a non-specific single space-occupying mass lesion (Speciale et al., 1992). In the optic form, optic nerves may be iso-intense on T2-weighted images and may enhance on T1-weighted image with contrast medium; the optic chiasm also may appear enlarged (Kitagawa et al.; 2009).

Computed-tomography may reveal evidence of brain inflammation, although it is not as sensitive as magnetic resonance imaging in delineating the parenchymal and meningeal lesions. Both focal and multifocal forms may be associated with contrast enhancement on computed-tomography and a mass effect may be observed by displacement of the surrounding brain tissue. The multifocal form is characterized by presence of multiple poorly defined, enhancing lesions of the parenchyma and meninges (Plummer et al., 1992).

Differential diagnosis

The differential diagnosis includes infectious meningoencephalomyelitis (including canine distemper encephalomyelitis, toxoplasmosis, neosporosis and cryptococcosis) and brain tumours.

Differentiation from canine distemper encephalomyelitis can be based on vaccination history and the presence of systemic (respiratory, gastrointestinal) signs, although sometimes vaccinated dogs may also be affected (Braund, 1980). Differentiation from toxoplasmosis and neosporosis can be based on information from history, clinical presentation, clinical pathology findings (non-regenerative anaemia, increase of blood neutrophils concentration, lymphocytosis, eosinophilia and increased serum alanine transaminase, aspartate aminotransferase, kreatinine cinase activity, especially in dogs with acute liver and/or muscle necrosis) (Dubey and Lappin, 1998) and measurement of serum IgG and IgM; IgM indicate active infection by the above protozoa, hence its measurement is preferable to that of IgG (Bjorkman and Uggla, 1999). PCR could also aid as it detects

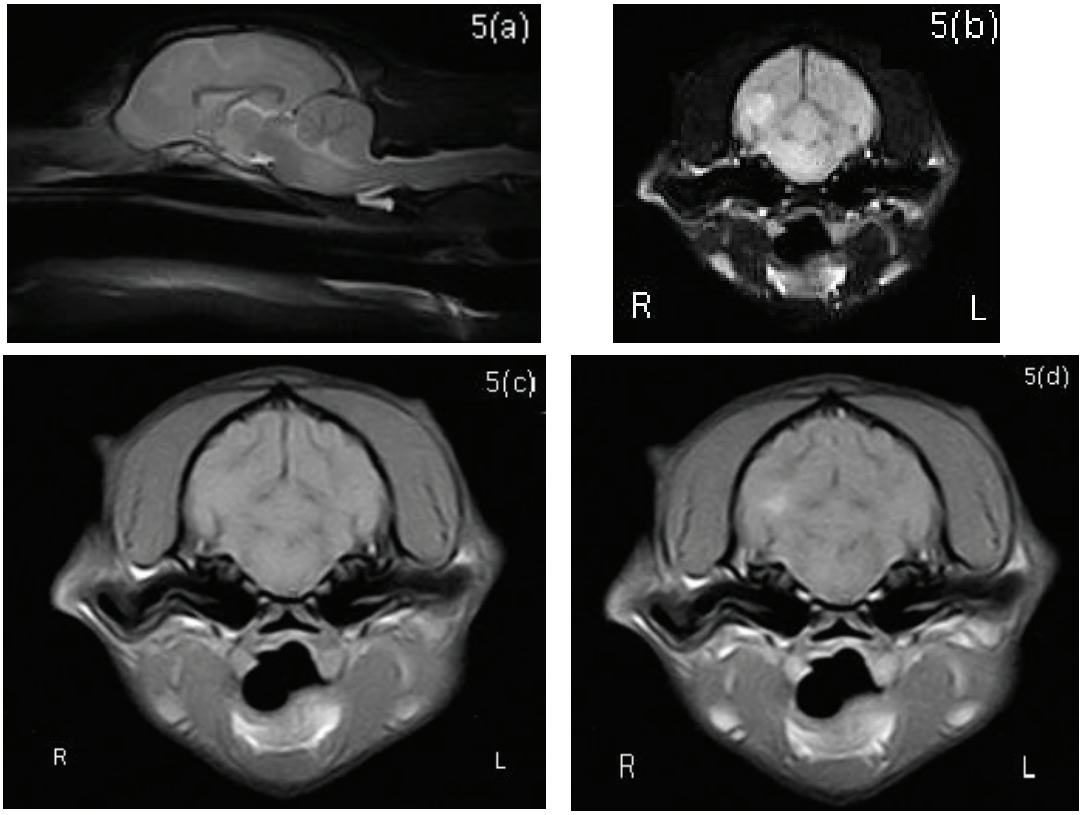

Fig. 2. Magnetic resonance imaging findings in multifocal granulomatous meningoencephalomyelitis: (a) sagittal, T2-weighted MR image at the level of midline, with focal hyper-intense area in the brainstem extending from pons cranially to medulla oblongata caudally; (b) transverse, fluid-attenuated inversion recovery MR image at the level of the pons, with hyper-intensity of previously described brainstem lesion and hyper-intense lesion in the caudal right occipital lobe, reflecting focal inflammation and oedema; (c) transverse T1W pre-contrast MR image at the same level as (b), with extremely mild hyper-intensity of the right occipital lobe lesion involving the grey and white matter, whilst the brainstem lesion is iso-intense to the surrounding tissue and cannot be visualized; (d) transverse T1W post-contrast MR image at the same level as (b), with the occipital lobe lesion enhancing and the brainstem lesion not enhancing (figure generously provided by Dr Nicolas Rousset from the Queen's Veterinary School Hospital of the University of Cambridge).

protozoal DNA and is highly sensitive (Spencer et al., 2000). Cryptococcosis is rare and, apart from the neurological signs, it is accompanied with other symptoms, e.g., nasal and ocular discharge and submandibular lymph node enlargement. Moreover, as in toxoplasmosis/neosporosis, serological testing and PCR will aid in the diagnosis. In addition to this, the demonstration of organisms on smears taken from the discharge and in cultures from it will differentiate between the two diseases (Berthelin et al., 1994). Finally, brain tumours can be differentiated from granulomatous meningoencephalomyelitis mainly by the magnetic resonance imaging findings, although this may prove difficult in some cases. As a result, histologic examination of the lesions may be inevitable.

Prognosis

Prognosis of granulomatous meningoencephalomyelitis is poor without aggressive immunosuppression. Immunosuppressive treatment, mainly corticosteroids, is believed to markedly improve the clinical outcome (Coates et al., 2007). Most of the affected dogs succumb to the disorder or are euthanised within a few weeks to months after diagnosis, despite the treatment. Dogs with granulomatous meningoencephalomyelitis have been reported to survive longer (3-6 months or even more) than those with the multifocal form, which die within a few days to weeks (median interval from diagnosis to death: 8 days). Dogs with focal forebrain-type signs had significantly longer survival times (>1 year) than dogs with signs indicating localisation in other areas of the central nervous system (2 months) (Munana and Luttgen, 1998).

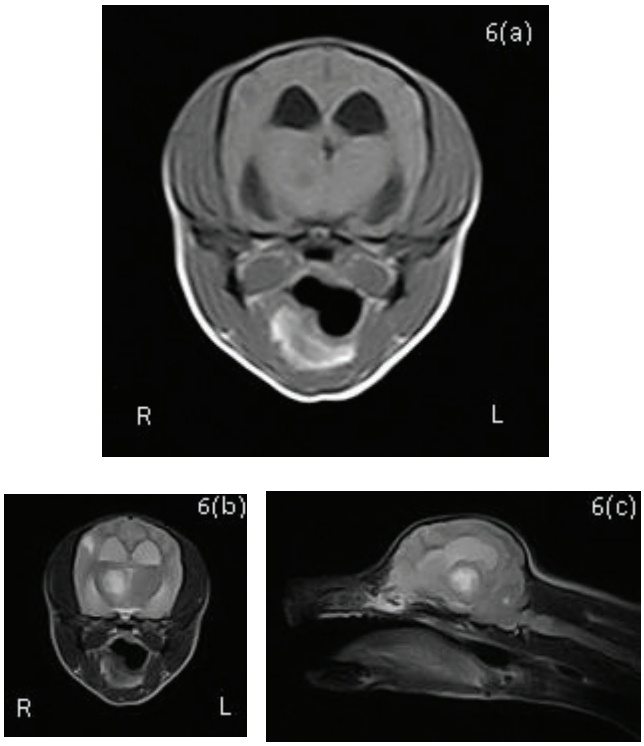

Fig. 3. Magnetic resonance imaging findings in necrotising encephalopathy: (a) transverse, T1-weighted MR image at the level of thalamus and cerebral hemispheres, with hypo-intense lesion involving the grey/white matter peripherally in the right parietal lobe and a further hypo-intense lesion identified in the right thalamus with a mass effect and midline shift towards the left; (b) transverse, T2-weighted MR image at the same level as (a), with hyper-intensity of the previously (a) described lesions; (c) right parasagittal, T2-weighted MR image, with focal hyper-intensity of the right thalamus (figure generously provided by Dr Nicolas Rousset from the Queen's Veterinary School Hospital of the University of Cambridge).

NECROTISING ENCEPHALITIS

There are two distinct subtypes of necrotising encephalitis: necrotising meningoencephalitis and necrotizing leucoencephalitis. Both have similar clinical presentation and histopathologic features, as they cause bilateral, asymmetric cerebral necrosis. Necrotising meningoencephalitis commonly affects the cerebral hemispheres and subcortical white matter, with profound inflammation extending from the leptomeninges through the cerebral cortex into the corona radiata (De Lahunta and Glass, 1995). On the other hand, necrotising leucoencephalitis is relatively sparing of the cerebral cortex and meninges, predominately affecting perivascular cerebral white matter, including the *centrum semiovale*, the thalamocortical fibres, the internal capsule, the thalamus and, sometimes, the brainstem (Le Couteur, 2009).

The aetiopathogenesis for these disorders is not yet fully understood. It is believed that a combination of genetic, infectious (mainly *Canine Herpesvirus-1*) and environmental factors trigger the onset of necrotising encephalitis through the immune mediated responses (Percy et al., 1970; Whitley and Gnann, 2002). As far as necrotising meningoencephalitis is concerned, it has been suggested that auto-antibodies against astrocytes and glial cells (anti-astrocytic and glial fibrillary acid protein antibodies) may be responsible for the disease, based on their presence in the cerebrospinal fluid of affected dogs. However, similar antibody levels occur in the cerebrospinal fluid of dogs with granulomatous meningoencephalomyelitis or brain tumours, even in a few clinically normal dogs (Shibuya et al., 2007).

Clinical presentation

Necrotising encephalitis is breed-specific. Breeds affected include Pugs, Maltese, Chihuahuas, Yorkshire Terriers, Pekingese, West Highland White Terriers, Boston terriers, Japanese Spitz, Miniature Pinschers, French Bulldogs, Lhasa Apso and Shih-Tzu (Cordy et al., 1989; Coates, 2011). Necrotising meningoencephalitis affects more often Pugs and Maltese and necrotising leucoencephalitis Yorkshire Terriers and French Bulldogs (Coates, 2011).

Most cases of necrotising meningoencephalitis occur in young dogs. Age of dogs at onset of clinical signs range from 6 months to 7 years, with mean age being 2.5 years (Cordy and Holliday, 1989). Necrotising leucoencephalitis occurs in animals aged 4 months to 10 years, with the mean age being 4.5 years (Kuwamura et al., 2002). Female animals are more frequently affected than males (Coates, 2011).

Clinical signs

Dogs with necrotising encephalitis commonly manifest cerebrothalamic-type signs, because of the localisation of the lesions in the prosencephalon. In necrotising leucoencephalitis, mid-to-caudal brainstem-type signs may also occur, due to additional lesions in that area of the brain. The clinical signs progress rapidly; most commonly, they include seizures, depression, circling, vestibulocerebellar-type signs, visual deficits, ultimately leading to death (Coates, 2011). Generally, the signs vary and depend

on the brain area that has been affected (De Lahunta and Glass, 2009). Cervical spinal pain is a common symptom that occurs, because of the localization of the lesions in the meninges and/or the forebrain (Munana, 1996).

Diagnosis

A tentative diagnosis of the NE may be suggested by the history, the clinical presentation, the results of clinical examination, the results of cerebrospinal fluid analysis and the neuroimaging findings (magnetic resonance imaging, computed-tomography). Definitive diagnosis is based on the histological examination of the lesions. Cerebrospinal fluid analysis, as in granulomatous meningoencephalomyelitis, reveals increased protein content and mononuclear (usually lymphocytic) pleocytosis. Magnetic resonance imaging lesions associated with necrotising meningoencephalitis include asymmetric, multifocal prosencephalic-type lesions affecting the gray and white matter that appear hyper-intense on T2-weighted images and iso-intense to slightly hypointense on T1-weighted images, with slight contrast enhancement. Loss of gray/white matter demarcation may be noticed (Fig. 3). In necrotising leucoencephalitis, multiple, asymmetric bilateral prosencephalic lesions appear mainly in the subcortical white matter. The lesions are hyper-intense on T2-weighted and fluid-attenuated inversion recovery images and hypo-intense or iso-intense on T1-weighted images, with variable contrast enhancement (von Praun et al., 2006; Young et al., 2009). Computed-tomography scan may also contribute to the diagnosis. In the acute, mainly, stages of necrotising encephalitis, focal hypodense lesions in the prosencephalon may be revealed, which may or may not be enhanced with contrast (Thomas, 1998).

Differential Diagnosis

Differential diagnosis includes neoplastic, infectious and immune-mediated disorders of the central nervous system.

Prognosis

Prognosis should be guarded and depends on severity of clinical signs and distribution of lesions in the central nervous system. Median interval from diagnosis to death has been estimated to 93 days (Coates, 2011).

STEROID-RESPONSIVE MENINGITIS-ARTERITIS

Steroid-responsive meningitis-arteritis is a debilitating inflammatory disease of the canine central nervous system. Pathogenesis of the disease is unclear, but it has been proposed that it may be triggered by environmental factors, which activate an immune-mediated reaction (Tipold et al., 1995). Specifically, it has been suggested that a Th2 immune response is responsible for the disease. In that, activated T cells produce large amounts of interleukin-4 (IL-4), which stimulates B cells to produce large amounts of immunoglobulin A. That infiltrates into the meningeal vessels (mainly in the cervical area) causing vasculitis and meningitis (Schwartz et al., 2011). Increased concentration of immunoglobulin A in blood and cerebrospinal fluid (Tipold and Jaggy, 1994; Tipold et al., 1995), remission of clinical signs after the administration of immunosuppressive doses of steroids (Meric et al., 1985) and absence of identifiable infectious organisms (Harcourt, 1978; Poncelet and Balligand, 1993; Tipold and Jaggy, 1994) lend support to this hypothesis.

Moreover, it has also been suggested that repeated vaccinations against various pathogens may cause the disease by sensitizing the dog to those antigens. This may account for increased incidence of the disease in young animals (Le Couteur, 2009).

Steroid-responsive meningitis-arteritis may sometimes occur in combination with immune-mediated polyarthritis, identified as ‘polyarthritis-meningitis syndrome’.

Clinical presentation

Steroid responsive meningitis-arteritis usually affects medium to large breeds of dogs. Specific breeds with an increased risk for developing the disease are the Beagles, the Boxers, the Weimaraners, the Bernese Mountain Dogs and the Nova Scotia Duck-Tolling Retrievers. The disease occurs mainly in dogs younger than 2 years, although it has been reported in dogs as old as 7 years (Tipold and Jaggy, 1994; Coates, 2011).

Webb et al. (2002) described that ~30% of dogs with immune-mediated polyarthritis had associated spinal pain; subsequently 50% of those were diagnosed with steroid responsive meningitis-arteritis. Dogs with ‘polyarthritis-meningitis syndrome’ expe-

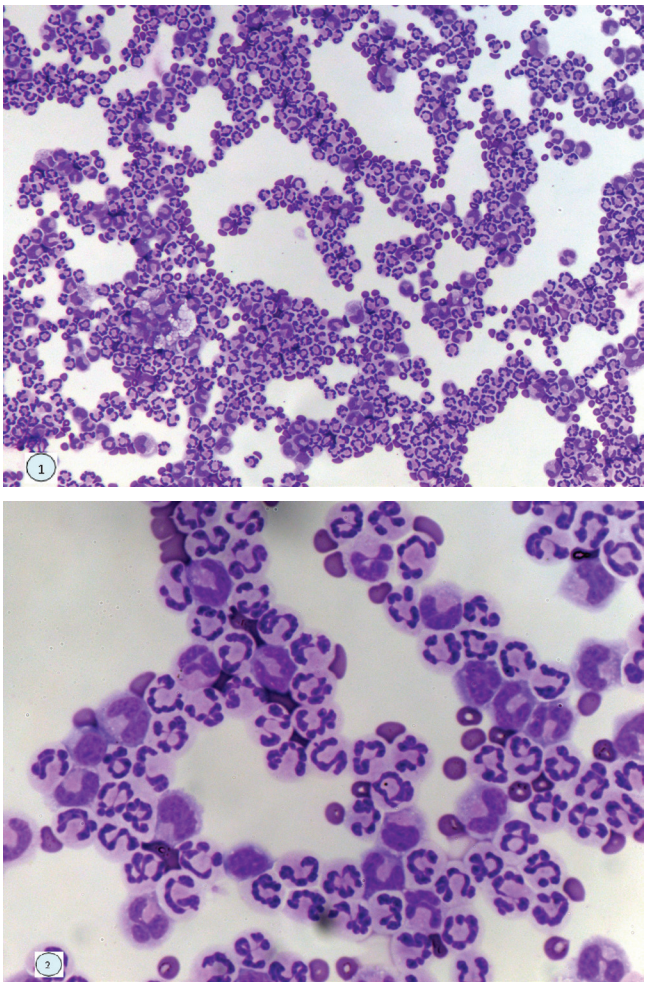

Fig. 4. Smear of cerebrospinal fluid sample from a dog with steroid responsive meningitis-arteritis, with predominance of neutrophils, of which a large number has with hyper-segmented nuclei, and a smaller number of macrophages (modified Wright-Giemsa, (a) ×20 objective, (b) ×40 objective).

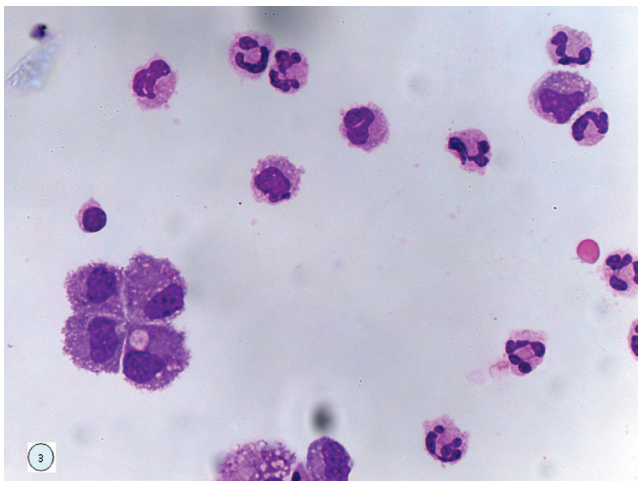

Fig. 5. Smear of cerebrospinal fluid sample from a dog with long-standing form of steroid responsive meningitis-arteritis, with predominance of macrophages and scarce macrophages (modified Wright-Giemsa, ×60 objective).

rience spinal pain, possibly due to both meningeal and intervertebral joint inflammation (Webb et al., 2002).

Clinical signs

Dogs are presented with cervical spinal hyperaesthesia (in over 90% of affected dogs), most commonly occurring with low head carriage and arched back (Tipold and Jaggy, 1994). Other clinical signs that may be present from time to time include reluctance to move, stiff gait, pain on mouth opening, muscle rigidity and anorexia. Cervical spinal pain may be coupled by thoracolumbar pain, although, in some cases, only the latter is present (Le Couteur, 2009). Pyrexia and neutrophilic leucocytosis with a left shift occurs in approximately two-thirds of affected dogs (Coates, 2011). Clinical signs may have an acute onset and progressive (acute form) or with a waxing and waning course over a period of weeks or months (chronic form) (Le Couteur, 2009). Dogs developing the acute form that remain untreated may self-limit the clinical signs within 12 to 18 months (Penderis, 2008) or develop resistance to the disease with ageing (Scott-Moncrieff et al., 1992). Alternatively, they may develop the chronic form, where, apart from meningitis, myelitis or encephalitis are also present (Tipold and Jaggy, 1994; Wrzosek et al., 2009). Therefore, in the chronic form, neurological signs (e.g., ataxia, paresis) may occur (Tipold, 2000). Lastly, it has been reported that inflammation may spread from meninges to the cerebral hemispheres, which would potentially be fatal for the animal (Wrzosek et al., 2009).

Diagnosis

Diagnosis is based on history, clinical presentation, findings of clinical examination, cerebrospinal fluid analysis and supported by haematological and biochemical findings. Cerebrospinal fluid analysis is characterized by increased total nucleated cell count (reference range: <5-8 leucocytes μL^{-1} for cerebellomedullary cistern collection) (Di Terlizzi and Platt, 2006; Bathen-Noethen et al., 2008). A predominance of neutrophils in the absence of bacteria is recorded in animals with acute form of the disease (Fig. 4). However, as the disease progresses, a mixed pleocytosis is present with macrophages, lymphocytes and monocytes (Fig. 5). In association with this inflammatory response, an increase in the

cerebrospinal fluid total protein concentration can also be expected (reference range: <250 mg L^{-1} for cerebellomedullary cistern collection) (Di Terlizzi and Platt, 2006; Tipold, 2000). The cerebrospinal fluid total protein concentration in the chronic form may be within normal limits or slightly elevated (Tipold, 2000). Cerebrospinal fluid changes appear sensitive to immunosuppressive doses of steroid administration and will be suppressed if the patient has received treatment prior to cerebrospinal fluid sampling, although further investigation would be required to evaluate whether any particular cell lines are affected preferentially (Lowrie et al., 2008).

Haematological findings may demonstrate evidence of a leucocytosis with left shift (Hayes et al., 1989). Serum biochemistry results may reveal a mild hypoalbuminaemia due to the inflammatory reaction, as albumin is a negative acute phase protein (Cerón et al., 2005). Hyperglobulinaemia has also been reported; increased concentrations of IgA are likely responsible for this (Tipold and Jaggy, 1994; Tipold et al., 1995).

In both the acute and chronic forms of the disease, IgA concentrations are increased in blood and cerebrospinal fluid. Though the increase in IgA in the cerebrospinal fluid is a common feature of many central nervous system diseases, the significant increase in serum concentrations is more characteristic, as in other central nervous system diseases concentrations may be normal or slightly increased (Tipold and Jaggy, 1994; Tipold et al., 1995). Therefore, IgA measurements can be useful for differentiation of steroid-responsive meningitis-arteritis from other neurological disorders. This can be especially helpful in the chronic form, which is not easily distinguished in terms of clinical presentation from other similar diseases. Specificity of the test varies from 88% (Tipold and Jaggy, 1994) to 100% (Tipold et al., 1995). As part of the differential diagnosis process, one should be aware that increased serum IgA may also be present in animals with lymphoma, myeloma or histiocytosis (Tipold, 2000).

Evaluation of acute phase proteins can also be useful for diagnosing the disease. Acute phase proteins, e.g. C-reactive protein, blood concentrations are increased, as in other inflammatory diseases, and may lead to early diagnosis of steroid-responsive meningitis-arteritis (Lowrie et al., 2009).

Finally, computed-tomography imaging may help localize changes in the central nervous system and support monitoring of the efficacy of treatment (Tipold, 2000).

Differential diagnosis

Spinal pain may be caused by any condition affecting muscles, vertebrae, facetal joints, nerve roots and meninges. The most common causes of spinal pain in a young adult dog include discospondylitis, cervical instability (cervical spomdylopathy, atlanto-axial subluxation), intervertebral disk extrusion or protrusion pinching nerve root or meninges, trauma (fracture), and occasionally bacterial meningitis and vertebral or meningeal neoplasia.

A neutral lateral cervical radiograph should always be considered in any dog presenting with cervical pain, before manipulation of the atlantoaxial joint is performed due to the possibility of instability within this region. Preferably, radiographs should be taken with the animal in a conscious state, if such instability is suspected. Radiography may also reveal evidence of disconspondylitis, i.e. radiopaque irregular proliferative lesions located at the vertebral end plates (sclerosis) with associated lysis or evidence of disc disease. In case the initial radiographic evaluation does not reveal any abnormality, then specific diagnostic imaging procedures can be performed (myelography, magnetic resonance imaging).

Once these procedures have been performed to rule out instability, then it is safe to proceed with collecting a cerebrospinal fluid sample from the cerebromedullary cistern. Neutrophilic or mixed pleocytosis in the cerebrospinal fluid can be caused by a variety of conditions, such as protozoal and bacterial diseases. Therefore, in the presence of inflammatory cerebrospinal fluid disease, other causes should be excluded by appropriate testing, for example cerebrospinal fluid PCR testing for neosporosis. The differentiation of steroid-responsive meningitis-arteritis from bacterial meningitis is challenging; the latter is uncommon in dogs and can be diagnosed by culture of cerebrospinal fluid samples and the identification of microorganisms in direct observation of smears prepared from the sample (Meric et al., 1985; Tipold, 1995; Radaelli and Platt, 2002). Cerebrospinal fluid bacterial culture has a low sensitivity; thus, it may be vital to proceed to the more sensitive blood cultures (Radaelli and Platt, 2002).

Other potential causes of inflammatory brain

disease include granulomatous meningoencephalomyelitis and necrotising encephalitis. These diseases can be confused with the chronic form of steroid-responsive meningitis-arteritis, when neurological deficits are present. However, these diseases cause brain dysfunction in addition to myelopathy, while in the chronic form of steroid-responsive meningitis-arteritis more often spinal syndrome occurs with no brain involvement. In such cases with brain involvement, the information from the history (i.e., progress from acute steroid-responsive meningitis-arteritis) may be helpful in differentiation. Advanced imaging studies are recommended to evaluate brain involvement in the disease.

Prognosis

Prognosis is guarded to good. In acute form and with appropriate treatment, prognosis is excellent. In contrast, in the chronic form with symptoms of myelitis and/or encephalitis, the prognosis is guarded and fatality ranges from 5% to 100% (Tipold and Jaggy, 1994; Cizinauskas et al., 2000).

THERAPEUTIC APPROACH FOR MENINGOENCEPHALOMYELITIS OF UNKNOWN AETIOLOGY

Management of granulomatous meningoencephalomyelitis and necrotising encephalitis

The cornerstone of management of granulomatous meningoencephalomyelitis and necrotising encephalitis is immunosuppressive treatment, mainly with corticosteroids. Depending on the severity of signs and whether or not there is the suspicion for infectious diseases, the clinician may initially administer anti-inflammatory dosages of steroids (prednisolone at 0.5-1.0 mg kg^{-1} bw, per os or intravenously, once daily) and wait for the results of serological examination and PCR. If the results do not provide evidence for an infectious disease or if index of suspicion for meningoencephalomyelitis of unknown aetiology is very high from the beginning (e.g., dog of Pug breed with magnetic resonance imaging lesions consistent with necrotising meningoencephalitis), then the clinician can start the immunosuppressive therapy directly and gradually reduce the dose to the minimum that adequately controls the disease (Schatzberg, 2010). A proposed prednisolone protocol (Schatzberg, 2010) which can be followed is as below:

- 1.5 mg kg^{-1} bw, per os or intravenously, *bid* for 3 weeks,
- 1.0 mg kg^{-1} bw, per os or intravenously, *bid* for 6 weeks,
- 0.5 mg kg^{-1} bw, per os or intravenously, *bid* for 3 weeks,
- 0.5 mg kg^{-1} bw, per os or intravenously, *sid* for 3 weeks,
- 0.5 mg kg^{-1} bw, per os or intravenously, every two days indefinitely; the dose may be reduced to 0.25 mg kg^{-1} bw, per os or intravenously, every two days at a later stage.

Response to corticosteroids is variable and may be temporary, altough dogs often show a good initial response to steroid monotherapy. A median survival time of 36 days (range: 2-1200 days) after corticosteroid treatment in 26 dogs with meningoencephalomyelitis of unknown aetiology has been reported (Granger et al., 2010). Steroid monotherapy may adequately control the clinical signs, but it has been proved to be insufficient for some patients. In addition, long-term, high dose corticosteroid therapy may cause side-effects, including polyuria/polydipsia, polyphagia, weight gain, hepatotoxicity, gastrointestinal ulceration, pancreatitis and iatrogenic hyperadrenocorticism. For the above reasons, it is essential either to combine steroids with one or more immunomodulatory drugs or less often to use the latter as a monotherapy. Cytosine arabinoside, procarbazine, cyclosporine, lomustine, leflunomide and mycophenolate mofetil, all have been reported as additional and effective therapies. However, more clinical trials are needed to confirm their efficacy in controlling meningoencephalomyelitis of unknown aetiology (Schatzberg, 2010).

It is also advisable to use gastroprotectants in combination with the steroid therapy. Therefore, dogs should concurrently receive sucralfate (1-2 g per animal, per os, *tid*), ranitidine (2 mg kg^{-1} bw, per os, *bid*) or famotidine (0.5-1 mg kg^{-1} bw, per os, *sid*) (Lowrie, 2011).

Management of steroid responsive meningitis-arteritis

Initially, immunosuppressive doses of steroids

(prednizolone) can be used, these being gradually reduced within a period of months to the minimum dose that can control the disease. Approximately 50% of dogs with steroid responsive meningitis-arteritis relapse after discontinuation of treatment (Le Couteur, 2009). Furthermore, in dogs not treated appropriately, chronic form of the disease develops (Tipold, 2000). For this reason, it is important that treatment should last at least six months, in order to reduce possibility of disease relapse (Le Couteur, 2009).

Another treatment protocol can be based on administration of prednisolone (4 mg kg^{-1} bw, per os or intravenously, *sid*) initially, followed, after 2 days by a reduction in the dose to 2 mg kg^{-1} bw for one to two weeks, followed by a further reduction to 1 mg kg^{-1} bw for another 2 weeks. At that point and then every 4 to 6 weeks, the dog is re-examined clinically and an evaluation of cerebrospinal fluid and a haematological examination are performed. When clinical and laboratory findings are normal, the dose can be gradually reduced to half that of the preceding regime, until a dose rate of 0.5 mg kg^{-1} bw per os every 48 or 72 hours is attained. Treatment is stopped 6 months after clinical and laboratory findings are normal. If clinical neurologic examination reveals abnormalities in the presence of normal cerebrospinal fluid examination results, then it would be advisable to increase again the dose of prednisolone or to combine it with another immunomodulatory drug (Tipold and Jaggy 1994, Cizinauskas et al. 2000). A good suggestion would be azathioprine (1.5 mg kg^{-1} bw, per os, every 48 hours) which may be used in combination with steroids (e.g., alternating each drug every other day) (Tipold, 2000).

If the diagnosis is uncertain and there is suspicion of infectious (possibly bacterial) meningitis, then an antibiotic which can penetrate the blood-brain barrier should be administered. Such antibiotics are clindamycin (12.5-25 mg kg^{-1} bw, per os, *bid*) and trimethoprim/sulphonamides combination. The use of antibiotics should be stopped when the cerebrospinal fluid culture yields no more microorganisms (Friedland and McCracken, 1994).

During treatment, IgA concentrations in blood and cerebrospinal fluid remain increased despite regression of clinical signs (Tipold, 2000). In addition to this, measurement of acute phase protein concentration in blood is useful for evaluation of the response to the treatment. During treatment, almost concentrations of all acute phase protein decrease significantly compared to their initial values. In contrast, acute phase protein concentrations in cerebrospinal fluid are less reliable markers for evaluation of the response of steroid responsive meningitis-arteritis to the treatment (Lowrie et al., 2009).

CONCLUDING REMARKS

Meningoencephalomyelitis of unknown aetiology includes diseases of the central nervous system, with an immune mediated background and distinct neuropathological findings. Treatment is based on administration of immunosuppressive drugs. In addition to prednisolone, immunosuppressive drugs appear to have a beneficial effect in management of the diseases, improving their overall prognosis. In the future, effective treatments will possibly be established after elucidation of the pathogenesis of these diseases.

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CONFLICT OF INTEREST STATEMENT

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence the content of the paper.

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