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Dropped head syndrome in mitochondriopathy

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Abstract In a 63-year-old, 165-cm-tall woman with a history of repeated tick bites, dilative cardiomyopathy, osteoporosis, progressive head ptosis with neck stiffness and cervical pain developed. The family history was positive for thyroid dysfunction and neuromuscular disorders. Neurological examination revealed prominent forward head drop, weak anteflexion and retroflexion, nuchal rigidity, weakness of the shoulder girdle, cog-wheel rigidity, and tetraspasticity. The lactate stress test was abnormal. Electromyograms of various muscles were myogenic. Muscle biopsy showed non-specific myogenic ab-

normalities and generally weak staining for cytochrome oxidase. Mitochondriopathy with multi-organ involvement was suspected. The response to anti-Parkinson medication was poor. In conclusion, dropped head syndrome (DHS) may be due to multi-organ mitochondriopathy, manifesting as Parkinsonism, tetraspasticity, dilative cardiomyopathy, osteoporosis, short stature, and myopathy. Anti-Parkinson medication is of limited effect.

Keywords Mitochondriopathy · Neck muscles · Myopathy · Anterocollis

Introduction

The dropped head syndrome (DHS), characterised by severe neck extensor weakness with marked anterior curvature or angulation of the cervical spine, is a heterogeneous condition, attributable to various neuromuscular and non-neuromuscular causes (Table 1) [7, 24, 28, 40, 41, 44]. DHS has been frequently described to be associated with Parkinson's syndrome [2, 17, 27, 33]. In a single case, DHS was also associated with borreliosis [7]. The association of DHS, Parkinson's disease, myopathy, borreliosis and dilated cardiomyopathy, as in the following case, has not been reported.

Case report

The patient is a 63-year-old, HIV-negative woman (165 cm tall, 55.7 kg) with a history of repeated tick bites with a frequency of up to 30 per year since childhood. She had a hysterectomy in 1987,

chronic constipation, arterial hypertension detected in 1997, and a questionable myocarditis with anginal chest pain, dyspnoea and leg oedema after pneumonia in 1997. The patient's mother was of short stature, and had a history of "meningitis" and struma. One brother of the propositus had died from "poliomyelitis" at age 18 years. In one of her grandnieces "spinal muscular atrophy" was diagnosed in early childhood. Several family members had hyperthyroidism and arterial hypertension.

In January 2001, the patient showed a decline in performance, clumsiness of the left hand, exertional dyspnoea and tremor. A specialist for internal medicine suspected heart failure and Parkinsonism. Cardiological examination in February 2001 revealed left bundle branch block, dilatation of the left atrium and left ventricle, mitral insufficiency, and reduced systolic function. Coronary angiography in August 2001 was normal. Thus, dilated cardiomyopathy was diagnosed and enalapril and hydro-chlorothiazide were given with success. To prevent the patient from thromboembolic events, therapy with phenprocoumon was initiated. Additionally, bisoprolol was prescribed.

From March 2001 the patient developed vertigo and gait disturbance. Clinical neurological examination in April 2001 revealed propulsive posture, akinesia with reduced arm swing, and marked hypomimia. A CT scan of the brain disclosed a small non-enhancing, parasagittal, hypodense lesion in the pons. Parkinson's disease was diagnosed. Levodopa/carbidopa and pramipexol were pre-

Table 1 Conditions associated with head ptosis [40, 44]

Diagnosis	NP	Reference
Myopathy		
INEM	20	[15, 20, 23, 24, 25, 31, 32, 33, 36, 40, 41, 45]
Myasthenia gravis	5	[25, 36]
Polymyositis	3	[15, 20, 25]
Focal myositis	2	[4, 7]
Inclusion body myositis	2	[18, 30]
Mitochondriopathy	2	[2, 5, 40]
Carnitine deficiency	2	[22]
Nemaline myopathy	at least 2	[11, 29, 35]
FSH	1	[23, 34]
Dermatomyositis	1	[23, 25]
Nonspecific congenital myopathy	1	[39]
Myotonic dystrophy type 1	1	[23]
Myotonic dystrophy type 2	at least 1	[12]
Acid maltase deficiency	at least 1	[43]
Hypokalaemic myopathy	1	[8]
Hypothyroid myopathy	1	[3]
Hyperparathyroidism	at least 1	[6]
Neuropathy		
ALS	ng	[25, 36]
Post-polio syndrome	at least 1	[10]
CIDP	1	[16]
Guillain-Barre syndrome	ng	[42]
Borreliosis	1	[7, 40]
Non-neuromuscular		
Parkinson syndrome	18	[2, 17, 21, 27, 33, 46]
MSA	3	[9, 26, 38]
Elastic tissue loss	at least 1	[1]
Malignancy	1	[28]
Cushing syndrome	ng	[40]
Diffuse Lewy body disease	at least 1	[37]

INEM Isolated neck extensor myopathy; *NP* number of patients; *CIDP* chronic inflammatory demyelinating polyneuropathy; *FSH* facio scapulo humeral muscular dystrophy; *ALS* amyotrophic lateral sclerosis; *MSA* multi system atrophy; *ng* not given. Causes of DHS may be also classified according to its prevalence as either common or rare [29], according to whether the cause is known or not, as primary or secondary, or according to whether the cause is a neuromuscular or a non-neuromuscular disorder

scribed without effect, pramipexol was replaced by pergolide after 4 weeks. After 1 day, the patient herself discontinued the new combination because of nausea and vomiting. An MRI scan of the brain in August 2001 revealed numerous, glial spots, subcortically distributed over the entire hemispheres and a lacuna in the pons. Due to worsening Parkinson symptoms, including freezing episodes and a β -CIT SPECT showing incipient degeneration of nigrostriatal neurons with right-sided predominance in August 2001, levodopa/carbidopa and cabergoline were started. After 4 weeks, cabergoline was replaced by amantadine because of severe leg oedema. Since December 2001, gait disturbance progressed and there was vertigo when changing to the upright position. Since January 2002, she additionally developed progressive head ptosis with neck stiffness and cervical pain.

Fig. 1 Dropped head in the described patient under L-DOPA and ropinirol in April 2002 **Fig. 2** Needle EMG of the right brachial biceps muscle shows short duration, low amplitude motor unit action potentials with a mean duration of 9.4 ms. The interference pattern was dense with an amplitude of 1.5 mV

Clinical neurological examination in February 2002 revealed a weak and monotonous voice, an exaggerated masseter reflex, prominent forward head drop with inability to lift the chin off the chest, weak antelexion and retroflexion of the head (MRC grade 3–4), nuchal rigidity, weakness of the shoulder girdle muscles (MRC grade 4), cogwheel rigidity of the upper limbs, bradydiadochokinesia, resting and postural tremor, exaggerated biceps and

patellar tendon reflexes on the left side, and positive upper motor neuron signs bilaterally (Fig. 1). The patient walked slowly, taking short steps and had no arm swing. The neck could be passively extended. Blood pressure was 130/70 mmHg. The Schallong test was abnormal. The ECG showed sinus rhythm, left anterior hemiblock, tall S-waves in V2 and tall R waves in V6. Blood chemical investigations revealed slight hyperbilirubinaemia of 1.4 mg/dl (normal: <1.00 mg/dl). Serum creatine kinase and acetylcholine-receptor antibodies were normal. The lactate stress test was abnormal [13]. CSF investigations were positive for IgG antibodies against *Borrelia burgdorferi*. Carotid ultrasonography was normal. An MRI scan of the brain in October 2002 revealed subcortical non-specific spots of demyelination and periventricular demyelination. Plain radiography of the cervical spine revealed abnormal ante flexion, osteochondrosis, spondylosis, spondylarthrosis, and osteoporosis. An MRI scan of the cervical spine showed osteochondrosis exclusively. On IBZM-SPECT, degeneration of the nigro-striatal neurons was suspected. The MIBG SPECT was normal, suggesting multi-system atrophy rather than Parkinson's disease. Repetitive nerve stimulation was normal. Electromyograms of the right sternocleidomastoid, right deltoid, right brachial biceps and right anterior tibial muscles were myogenic (Fig. 2). Electromyography of the right semispinalis capitis muscles revealed multiple short duration potentials. There was no abnormal signal alteration in the cervical paraspinal muscles or atrophy on cervical MRI. Muscle biopsy from the right deltoid muscle showed non-specific myogenic abnormalities. Muscle biopsy from the right semispinalis muscle revealed marked fibre-size variability, angulated and atrophic fibres, and sporadically, accumulations of nuclei. The histochemical staining for cytochrome oxydase was generally weak. Mitochondriopathy with multi-organ involvement was suspected. Therapy in October 2002 comprised L-DOPA, entacapon, ropinirol, metoprolol, clopidogrel, ventafaxin, enalapril, hydrochlorothiazide, esomeprazol, alendrone acid, and furosemide. A trial with corticosteroids over 8 weeks and injection of botulinum toxin into the sternocleidomastoidei, and right platysma, galenus medialis, splenius capitis, trapezius and levator scapulae muscles was ineffective.

Discussion

DHS is either due to severe weakness of the neck extensors or increased tone of the head flexors [44]. If there is additional weakness of the periscapular, shoulder girdle and thoracic muscles, or even more extensive distribution, the condition is called dropped head plus syndrome [2]. In contrast to other spinal disorders, DHS is not fixed and can be corrected by passive head extension or by lying supine [44]. In cases in which the cause of DHS remains unclear, it is considered a manifestation of a non-inflammatory myopathy restricted to the neck extensors (isolated neck extensor myopathy, INEM, Table 1) [15, 19, 23, 24, 25, 31, 40, 41, 45]. The etiology of INEM is unknown, but it is assumed to be due to either focal myositis or kyphotic postural changes and loss of tissue elasticity with advancing age, placing increasing workload on the paraspinal muscles [23]. Muscle biopsy from the neck extensors in INEM shows necrotic and regenerating fibres, fibrosis and fatty replacement, and sometimes a few ragged-red fibres [42]. In some cases, the histological findings may be consistent with inflammatory myopathy [42]. DHS is very disabling with the inability to lift the

chin off the chest (maximal head drop), impaired forward vision and cervical pain [40]. DHS has to be delineated from camptocormia (bent spine syndrome), characterised by pronounced flexion and limited extension of the trunk in the erect position, which decrease in the supine position [44].

Most frequently, DHS is associated with Parkinsonism (Table 1). The prevalence of DHS in Parkinsonism is reported to be 1.5% [2]. The cause of DHS in Parkinsonism is unknown. Some authors propose DHS in Parkinsonism is caused by imbalanced muscle rigidity between the anterior and posterior neck muscles [2, 46]. Weakness of the neck extensors was not reported in these cases. It has also been suggested that mechanical stretching produces injury to the neck muscles [23]. Kyphotic postural changes and loss of elastic tissue due to ageing may place increasing workload on the cervical spinal muscles, thus leaving some individuals susceptible to muscular decompensation [2]. Patients with Parkinsonism may be more vulnerable because of their typical posture [2]. However, when head drop precedes Parkinsonism by years, Parkinsonism cannot explain neck muscle weakness [2].

To explain the abnormalities in our patient, all differential diagnoses were considered (Table 1). Parkinsonism as the sole cause was excluded because it could not explain myopathy and the abnormal lactate stress test. Despite the normal MIBG-SPECT multi-system atrophy was excluded, because of absent deficits of speech, swallowing or upgaze. Borreliosis was considered because of the history, IgG antibodies against *Borrelia*, and dilative cardiomyopathy, but was excluded because of myopathy, the abnormal lactate stress test and the family history. INEM was excluded because weakness was not restricted to the neck extensors. Vascular multi-infarct Parkinsonism was excluded because blood pressure was well controlled and further thromboembolic risk factors were negative. Lastly, the described abnormalities were attributed to mitochondriopathy with multi-organ involvement, comprising myopathy, short stature, osteoporosis, dilative cardiomyopathy, and Parkinsonism. The suspicion was substantiated by the abnormal lactate stress test, the reduced staining for cytochrome oxidase, leucencephalopathy and the family history. Furthermore, mitochondrial abnormalities have been previously described in patients with DHS (Table 1) [2, 5, 40]. Mitochondriopathy has also been described in association with Parkinsonism [14]. Unfortunately, no ultrastructural investigations of the mitochondria, no biochemical investigations of the muscle homogenate, and no screening for mtDNA mutations have been carried out. Other myogenic causes were excluded by clinical presentation and muscle biopsy.

There is no established therapy of DHS. Cervical collars, neck braces, and other methods of supporting the head are of limited benefit [40]. Prednisone in a patient with INEM did not have any substantial effect [40]. Other reports confirmed that corticosteroids are ineffective in

the majority of the cases [15]. Treatment failure has been attributed to irreversible stretch injury of the neck extensor muscles [23, 40]. In a patient with INEM associated with tick-borne disease, azathioprine resulted in a marked clinical improvement [40]. In a patient with DHS due to focal myositis, methylprednisolone and prednisone led to complete recovery, 10 months after initiation of therapy [7]. A favourable response to corticosteroids has been also described in a patient with DHS due to polymyositis [15]. Cases with DHS associated with Parkinsonism repeatedly improved with levodopa, but not with dopamine agonists [17]. In the case of concomitant dystonia of the

head flexors, botulinum toxin may have a beneficial effect. Overall, there is no clearly defined role for immunosuppressive or other pharmacotherapy in DHS [44]. Patients without spontaneous improvement of head ptosis should be considered for cervical fusion, which allows the patient to maintain a functionally useful head position.

It is concluded that DHS may be due to multi-system mitochondriopathy manifesting as myopathy, Parkinsonism, tetraspasticity, short stature, osteoporosis, leucencephalopathy, and dilated cardiomyopathy. Anti-Parkinson medication, corticosteroids and botulinum toxin are of limited effect.

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