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Parsonage-Turner syndrome associated with anti-bovine viral diarrhoea virus antibodies

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Summary

The Parsonage-Turner syndrome, a rare form of neuralgic amyotrophy of unknown aetiology, was diagnosed in a patient involved in an outbreak of bovine viral diarrhoea virus (BVDV). The patient, suffering from inflammation of the right shoulder with a permanent atrophy, developed anti-BVDV antibody titres which remained very high during the four following years of monitoring.

Keywords

Antibodies, Bovine viral diarrhoea virus, Parsonage-Turner syndrome, Veterinary public health.

Bovine viral diarrhoea virus (BVDV) is an established species of the genus *Pestivirus* of the family *Flaviviridae* (19), responsible for a cosmopolitan disease affecting cattle and other ruminants. The disease presents a wide range of clinical manifestations, including abortions, congenital malformations, enteric, respiratory and neurological disorders. A haemorrhagic syndrome with severe thrombocytopenia and high mortality also occurs. The infection is characterised by a transitional but severe and multi-factorial immune depression which explains the high frequency of BVDV-associated infections. Vertical infection occurs frequently and can induce immune tolerance and permanent viraemia.

Pestivirus infections were thought to occur exclusively in animals until the presence of specific anti-BVDV antibodies in up to 87% of animal handlers and veterinarians were reported (7). Since then, lower prevalence (15-16%) has been reported in adults (8, 21). Among children under two years of age, *Pestivirus* antigens were present in 24% of specimens from diarrhoea episodes that could not be explained by more common enteric pathogens (22).

The role of pestiviruses in human pathologies remains unknown. Until now, no direct relationship between *Pestivirus* infections in animals and clinical disease has been proved. Nevertheless, observations suggest that *Pestivirus* has the potential of causing emerging infections in humans.

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During a seroepidemiological survey undertaken in northern Italy, 15% seropositivity against BVDV strain Treviso milza (spleen) second isolation (TVM2) (indirect immunofluorescence [IIF] and serum neutralisation [SN] tests) were detected in animal caretakers in contact with infected animals. The Parsonage-Turner syndrome (15), a rare form of neuralgic amyotrophy of unknown aetiology and due to brachial plexus inflammation, was diagnosed in a patient involved in a severe outbreak of BVDV of significant virulence of the strain involved. Clinically, the patient suffered from an intense and painful inflammation of the right shoulder for approximately one week. He had high fever, no reaction to medical treatments, and the inflammation resulted in a permanent atrophy of the involved muscles (Fig. 1). The patient developed anti-BVDV antibody titres which remained very high (1:1 215) during the four years of monitoring that followed (Table I), showing an absence of cross- or non-specific reactions, with higher affinity for non cytopathic strains and with a clear immune reaction against BVDV antigen (Fig. 2). Western blot testing (WBT) showed specific

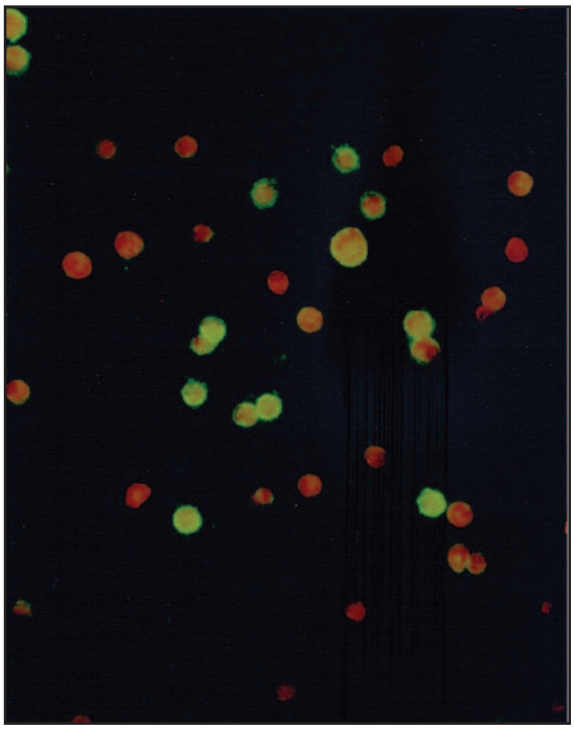

Figure 2
Positive reaction of human serum to the indirect immunofluorescence test for antibodies against bovine viral diarrhoea virus
Green-stained cells: infected
Red-stained cells: not infected
Magnification x400

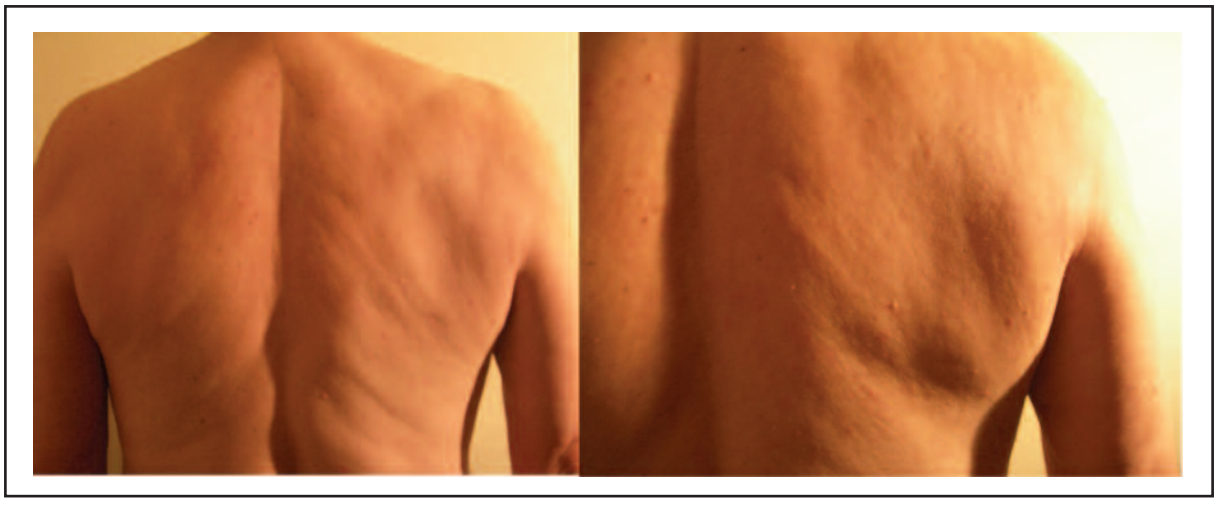

Figure 1
Right shoulder muscles showing permanent atrophy in a male patient aged 66 years (2006)
The Parsonage-Turner syndrome was diagnosed at the Second Division of Neurology, Civil Hospital of Brescia, on the basis of clinical investigations and electro-neuromyography performed for six months following commencement of symptoms

Table I
Serological profile of a patient against cytopathic and non-cytopathic bovine viral diarrhoea virus strains

Sampling date	Test	Antibody titres*				
		CP TVM2	CP NADL	CP C24V	NCP A19	NCP Jensal
Year 1 (5.6.86)	IIF SN	>1:135 1:4	–	–	–	–
Year 2 (12.1.87)	IIF	–	1:45	1:45	1:1 215	>1:405
Year 3 (28.1.88)	IIF ELISA	–	– 1 605	1:45	1:1 215	–
Year 4 (13.6.89)	IIF	–	1:15	Negative	1:405	1:45

* cross reactions with yellow fever, hepatitis C, rubella and classical swine fever have been excluded
CP cytopathic
TVM2 Treviso milza (spleen) second isolation
NADL National Animal Disease Laboratory
NCP non-cytopathic
IIF indirect immunofluorescence
SN serum neutralisation
ELISA enzyme-linked immunosorbent assay

immune response against BVDV National Animal Disease Laboratory (NADL) strain 120 kDa protein. The coincidence with disease in animals, serological findings obtained in the patient examined and further successful attempts at *Pestivirus* isolation in man, confirmed by polymerase chain reaction (PCR) and sequencing of *Pestivirus* strain *Europa* isolated from human buffy coat samples during viraemia that lasted 31 days (9), supported the hypothesis that brachial plexus neuritis could be related to BVDV infection. To date, the aetiology of the Parsonage-Turner syndrome remains obscure. Various hypotheses have been proposed, including autoimmune mechanisms (12); no links with *Pestivirus* infections have been reported previously. Other studies suggested a link between *Pestivirus* and neurological disorders in humans. In the USA, specific anti-BVDV antibodies were reported from mothers with microcephalic infants (17) and from identical twins discordant for schizophrenia (23) (Table II). Recently, infection during pregnancy and a possible association with some forms of cerebral white matter damage (WMD) in preterm neonates have been investigated, suggesting *Pestivirus* involvement (4, 5, 14, 18). Transplacental viral infection of the foetus during the first or second quarter of pregnancy could induce inflammation resulting in damage to vulnerable oligodendrocyte precursor cells and long-term WMD. Cytokines are presumably involved in a pro-inflammatory cascade eventually leading to prostaglandin-induced preterm uterine contractions (10). WMD is the most important predictor of childhood neuromotor disability among those born preterm. About 50% of infants subsequently develop cerebral palsy (3). Microcephaly, hypomyelination, dysmyelination and glial proliferation are associated with *Pestivirus* infection in animals (1, 2, 16). Infection with the BVDV *Pestivirus* leads to extensive necroses and cysts in

Table II
Serological studies on *Pestivirus* in humans in the United States of America in relation to neurological disorders

Patients	No. of samples	Positive (%)	Test	Ref.
Women (mothers with microcephalic infants	129	1.5[a]	SN	17
Controls	129	0		
Infants (identical twins discordant for schizophrenia)	25	40[a, b]	WBT	23
Controls (healthy twins)	16	6.2		

(a) cytopathic National Animal Disease Laboratory strain
(b) cross-reactions with dengue, Venezuelan equine encephalitis, rubella and West Nile were excluded

SN serum neutralisation
WBT Western blot testing

the periventricular white matter and enlarged ventricles in lamb foetuses (11). This type of damage closely resembles that of WMD in preterm human neonates (13, 20). In addition, BVD infection is accompanied by a decrease in thyroid hormone activity in lambs (1). Low thyroid hormone values are also an important indicator of maldevelopment among preterm infants (6). Given *Pestivirus* tropism for nervous cells in animal pathology, these findings deserve further evaluation in order to examine the full extent of the problem in the human population.

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