Parrot proventricular dilatation disease: a possible model of Guillain-Barré syndrome?

G. Rossi, L. Crosta, S. Pesaro

ABSTRACT

Proventricular Dilatation Disease (PDD) affects parrots with clinico-pathological aspects similar to those of the Guillain-Barré syndrome (GBS), a human neurophathy. We observed that in sera of PPD-affected parrots antibodies to gangliosides were detectable, similarly to that observed for GBS, and that quantification of such antibodies could be diagnostic for PDD. Then, we proved that administration of purified gangliosides to parrots, elicited autoimmune response and a pathological outcome similar to that of natural PDD. We propose this model not only for better studying PDD, but also as the basis for developing a reliable animal model of GBS.

Patients with Guillain-Barré syndrome (GBS) suffer from an acute onset of autoimmune neuropathy, that can lead to death or significant disability. Relatively little is known about aetiology of GBS. Early diagnosis, which is important as prompt intervention can arrest or reverse the disease, can be difficult. The presence of anti-ganglioside antibodies can confirm the diagnosis. GBS is commonly classified into four major subtypes: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome (MFS). MFS is closely associated with antibodies to GQ1b and AMAN with antibodies to GM1, but antibodies to other gangliosides have also been reported.

In recent decades wasting syndrome was described in macaws and other parrot species, spreading at an alarming rate. Now known as Proventricular Dilatation Disease (PDD), it is a segmental neuropathy characterised by a non-suppurative lymphocytic, plasmacytic ganglioneuritis of central and peripheral nerve tissue. Besides the classical syndrome of weight loss associated with regurgitation and the passage of undigested food in the faeces, clinical signs also include ataxia, abnormal head movements, progressive paresis, proprioceptive deficits, anorexia, lethargy and, occasionally, sudden death.

Many clinico-pathological aspects of parrot PDD resemble those of human GBS. The scientific literature is controversial about the nature and aetiology of both pathologies. For more than 30 years, PDD, similarly to GBS, has been a mysterious disease and, being a killer of captive parrots, has sent chills of terror down the spines of bird lovers. Several viral aetiological agents have been proposed [4]. and immune-mediated reactions to an unknown viral agent has been hypothesized to be at the origin of the disease; however, experimental evidence is lacking. Some studies reported the presence of viral-like particles in fresh faeces from affected birds, and also in the brain. The disease was experimentally transmitted by exposing susceptible birds to a tissue homogenate presumably containing these particles; however to date, this viral-like agent has not been identified, recently, a type of bornavirus, a family of viruses that cause encephalitis in horses and livestock, has been implicated in PDD.

Presently, although a presumptive diagnosis of PDD may be based on clinical signs and gross pathology, definitive diagnosis requires histology. Antemortem evaluation of crop biopsies is diagnostic in approximately 75% of birds with PDD. Detection of serum antibodies to certain viruses has been unsuccessful as a diagnostic method and in establishing a viral aetiology.

We hypothesized for PPD an autoimmune mechanism involving gangliosides. Thus, we purified gangliosides from the peripheral nervous system of parrots. Anti-ganglioside antibodies were detected by ELISA and Dot blot in 121 out of 505 parrot sera, 86 (17%) corresponding to symptomatic and histology-positive birds, and 35 (7%) belonging to asymptomatic parrots. These latter were subjected to histopathological analysis, revealing periganglia infiltrates in crop biopsies, thus indicating an early stage of disease, no binding to GT1b was observed in any of the sera. All

negative sera came from normal parrots. These results suggest that anti-ganglioside antibodies are involved in PDD and that their detection can be a sensitive diagnostic tool for PDD.

To further investigate the role of anti-ganglioside autoimmunity in the disease, we administered purified gangliosides twice, one month apart, to 6 cockatiels, by intraperitoneal or oral route adjuvanted with 1 mg of parrot extract gangliosides (patented). Two weeks later, 100% of intraperitoneally inoculated and 33% of orally challenged parrots developed typical signs. Four inoculated and symptomatic cockatiels showed typical ganglioneuritis in crop biopsies (Fig.).

These data prove that anti-ganglioside autoantibodies are implicated in the pathogenesis of PDD. However, the viral hypothesis of the disease remains plausible because an autoimmune basis is known for various acute, postinfectious polyneuropathies, associated with a wide range of bacterial and viral infections in animals and humans.

Currently, an adequate animal model for GBS is not available. The similarities of GBS with PDD suggest the possible use of naturally affected parrots as model for human disease. In the past, in attempts at setting up models for neurological diseases such as multiple sclerosis (MS) or GBS, neural tissue from quail embryo was transplanted into chicken embryos. After birth, chickens mounted a prolonged immune response and rejected the graft, resulting in tissue damage similar to that occurring in MS. However, this model shows important differences with human disease. In particular, in the human disease the symptoms can be transient, but do not exhibit periods of remission on the spinal cord chimeras model. Additionally, human disease affects central and peripheral nervous tissue, whereas lesions in bird chimeras are initially confined to the grafted tissue.

An early report of a motor neuropathy induced by rabbit immunization with GM1, was controversial because of lack of reproducibility. A similar model by immunization with GM1 was recently reported. The most important criticism to these models of GBS is the high variability of the onset time and severity of the induced disease. In this panorama, PDD could represent a valid alternative as a natural model to study human GBS.

On the basis of our results we propose further investigation on anti-ganglioside antibodies in PDD-affected birds, to better determine the involvement of this autoimmune mechanism in the pathogenesis and to develop a reliable model for GBS. Meanwhile, we propose the non-invasive serological test, based on detection of specific anti-ganglioside antibodies, as a tool for early PDD diagnosis.

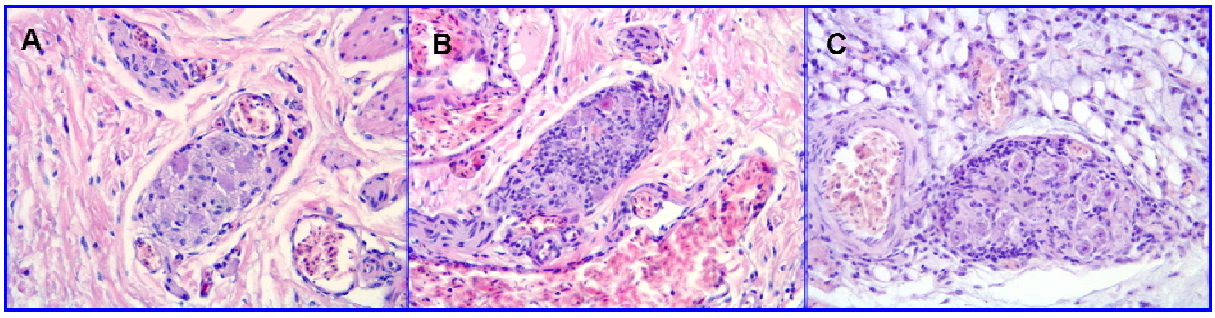

Fig.: Microscopical aspect of crop biopsies belonging to parrot normal (A), PDD naturally affected (B), and experimentally inoculated with ganglioside purified extract (C). Note the similar pattern of non-suppurative lymphocytic-plasmacytic ganglioneuritis in B and C.

Reference

CARPO M., PEDOTTI R., ALLARIA S. et al.. Clinical presentation and outcome of Guillain–Barré syndrome and related syndromes in relation to anti-ganglioside antibodies. J. Neurol. Sci**.** 168 (1999), pp. 78–84.

KISTLER A.L., GANEZ A., CLUBB S., et al. Recovery of divergent avian bornaviruses from cases of proventricular dilatation disease : identification of a candidate etiologic agent. Virol J. 2008 Jul 31; 5: 88.

MOYANOA.L., COMIN R., LARDONE R.D. et al. Validation of a rabbit model of a neuropathy induced by immunization with ganglioside. J Neurol Sci. 2008 Sep 15; 272(1-2):110-4. Epub 2008 Jun 24.

ROSSI G., CROSTA L., PESARO S.. Parrot proventricular dilation disease. Vet Rec. 2008 Sep 6;163(10):310.

VILLANUEVA I., GRAY P., TIZARD I. Detection of antigen specific for proventricular dilatation disease in psittacine bird. Vet Rec. 2008 Oct 4; 163 (14): 426.

WILLISON H.J. AND YUKI N., Peripheral neuropathies and anti-glycolipid antibodies, Brain 125 (2002), pp. 2591–2625.