

# Primary Autoimmune Cerebellar Ataxia (PACA)



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Unlike autoimmune diseases that have a clear target organ or clear target cell specificity (e.g. pancreatic islet cells in type 1 diabetes, thyroid in Hashimoto's thyroiditis, melanocytes in vitiligo), in autoimmune diseases affecting the CNS the concept of target specificity is perhaps less well appreciated because the brain is often viewed (mainly by non-neurologists) as one "organ". The brain however, is made up by such a diverse collection of cells and systems that it is probably more appropriate to think of it as a collection of well integrated but nonetheless multiple "organs".

The cerebellum, in particular, is one of the largest, oldest and most structurally conserved structures in the vertebrate nervous system with a remarkable homogeneity across species.<sup>1</sup> Despite its name (cerebellum – Latin for little brain), its structure and complexity suggest that its role within the central nervous system matches in importance, that of the cerebral cortex. It has a limited number of morphologically well-defined classes of cells with Purkinje cells perhaps being the most important of all. They certainly constitute the most important efferent element of the cerebellum, reflected by the fact that each can accommodate up to 160,000 synapses. This is the largest number of synapses seen in any neuron of the mammalian brain. Purkinje cells are often the target of immune mediated insults such as those seen in the context of paraneoplastic cerebellar degeneration. This disease is characterised diagnostically by a number of specific antibodies against different Purkinje cell antigens, pathologically by loss of Purkinje cells, and clinically by a rapidly progressive ataxia.<sup>2</sup> The cerebellum can also be an immune target in the context of other diseases such as post infectious cerebellitis<sup>3</sup> and gluten sensitivity (gluten ataxia).<sup>4</sup>

In addition to these specific entities where autoimmunity is triggered by another disease (cancer, infection, gluten ingestion) there is evidence to suggest that the cerebellum can be an organ specific autoimmune disease,<sup>5</sup> hence the proposed term of Primary Autoimmune Cerebellar Ataxia (PACA). This term implies no obvious trigger factor for the development of immune mediated damage to the cerebellum. The evidence in support of PACA comes from a number of observations:

Firstly, the Human Lymphocyte Antigen (HLA) type DQ2 is significantly overrepresented in patients with idiopathic sporadic ataxia (74% vs 35% in the healthy population). The prevalence of this HLA type in patients with genetically characterised ataxias is no different to the one found in the healthy population.<sup>5</sup> The HLA DQ2 has been shown to have a strong

association with autoimmune diseases, such as coeliac disease, gluten ataxia, type 1 diabetes mellitus, Stiff-Person syndrome (SPS), autoimmune thyroid disease and autoimmune polyendocrine syndromes.<sup>6,10</sup> One interpretation of this observation is that at least some cases of idiopathic sporadic ataxias have an autoimmune basis.

Secondly, it has been shown that there is a significantly higher prevalence of one or more autoimmune diseases in patients with idiopathic sporadic ataxia when compared to the general population and to patients with genetic ataxias (47%, 3% and 5% respectively).<sup>5</sup> Other autoimmune diseases encountered in the context of idiopathic sporadic ataxia include thyroid (usually Hashimoto's disease but also thyrotoxicosis), type 1 diabetes, primary biliary cirrhosis, vitiligo, pernicious anaemia, Sjogren's syndrome, alopecia, but also autoimmune diseases involving the nervous system and muscle such as Isaac's syndrome, polymyositis and SPS (unpublished observation).

Thirdly, it has been shown that cerebellar antibodies can be present in at least 60% of patients with idiopathic sporadic ataxia in contrast to 5% in patients with genetic ataxias.<sup>5</sup> Four different staining patterns were observed in this study, three of which resembled those seen in patients with gluten ataxia (cytoplasmic with processes, cytoplasmic alone, nuclear) and the fourth showing staining of the granular layer of the cerebellum. Further characterisation of such antibodies may prove to be helpful in the diagnosis of PACA. This is very important because PACA may well account for a substantial number of patients with idiopathic sporadic ataxia. Idiopathic sporadic ataxia accounts for 24% of all ataxias attending a specialised ataxia clinic run by the author at the Royal Hallamshire Hospital, Sheffield UK (see Table 1).

Finally, studies have shown that idiopathic sporadic cerebellar ataxia is consistently associated with a high prevalence of glutamic acid decarboxylase antibodies (anti-GAD).<sup>11</sup> These antibodies are a marker of multiple autoimmunity. They were first identified in type 1 diabetes,<sup>12</sup> and subsequently found in patients with SPS.<sup>13</sup> Evidence for anti-GAD antibodies being a marker of multiple autoimmunity comes from the observation that one or more additional autoimmune disorders are present in 60% of anti-GAD positive patients with SPS versus 6% in anti-GAD negative patients.<sup>14</sup> Similarly, patients with anti-GAD antibodies and IDDM have a higher prevalence of autoimmune thyroiditis than anti-GAD negative ones.<sup>15</sup> Thus the findings of a high prevalence of anti-GAD antibodies in patients with idiopathic sporadic

**Table 1: Cause of ataxia in 640 patients with progressive ataxia attending the ataxia clinic, Royal Hallamshire Hospital, Sheffield, UK.**

<b>Total number of patients assessed</b>			<b>640</b>
<b>familial ataxia</b>			<b>124/640 (19%)</b>
autosomal dominant inheritance	90/124	(73%)	
autosomal recessive inheritance	34/124	(20%)	
genetic characterisation	49/124	(40%)	
(15 SCA6, 13 EA2, 8 FA, 4 SCA2, 2 SCA8, 1 SCA3, 1 SCA1, 1 SCA7, 1 SCA28, 1FAP, 1FBD, 1GSS)			
<b>sporadic ataxia</b>			<b>516/640 (81%)</b>
idiopathic sporadic	154/516	(30%)	
gluten ataxia	113/516	(22%)	
clinically probable MSA-C	87/516	(17%)	
genetic diagnosis	76/516	(15%)	
(28 FA, 12 mitochondrial cytopathy, 8 SCA6, 7 EA2, 7 cerebellar dysgenesis/congenital, 3 Cockayne syndrome, 2 SCA 2, 2 CTX, 1 SCA7, 1 Tay-Sachs, 1 Krabbe's, 1 AOA 2, 1 XP, 1 AHGH, 1 FX)			
alcohol related	65/516	(13%)	
paraneoplastic ataxia	18/516	(3%)	
anti-GAD associated ataxia	8/516	(2%)	
opsoclonus-myoclonus	8/516	(2%)	
<b>idiopathic sporadic out of total</b>			<b>154/640 (24%)</b>
<b>total presumed genetic (124+76)</b>			<b>200/640 (31%)</b>
SCA=spinocerebellar ataxia, FA=Friedreich's ataxia, EA=episodic ataxia, FAP=familial amyloid polyneuropathy, FBD=familial british dementia, MSA-C=cerebellar variant of Multiple System Atrophy, CTX=Cerebrotendinous xanthomatosis, AOA=ataxia oculomotor apraxia, XP=xeroderma pigmentosum, AHGH=ataxia with hypogonadotrophic hypogonadism, GSS=Gerstmann-Straussler-Scheinker syndrome, FX=Fragile X syndrome.			

ataxia who often have an additional autoimmune disease may signify that the ataxia in these cases is due to autoimmunity.

The autoimmune mechanism by which the cerebellum is damaged in the context of autoimmunity remains unclear. In paraneoplastic cerebellar degeneration, a number of well characterised antibodies (e.g. anti-Yo in association with ovarian cancer) appear to be reactive with both tumour and Purkinje cell antigens ultimately resulting in the loss of Purkinje cells and the development of ataxia. Nobody has so far been able to convincingly induce ataxia in an animal model, using serum from patients with paraneoplastic cerebellar degeneration. Thus a pathogenic role of such antibodies in the paraneoplastic cerebellar degeneration remains doubtful. In the case of gluten ataxia, antigliadin antibodies have been shown to cross react with Purkinje cell epitopes. Sera from patients with gluten ataxia have been shown to possess additional antibodies (e.g. transglutaminase antibodies) that react with cerebellar tissue.<sup>16</sup> Support for an antibody mediated pathogenesis in this type of immune mediated ataxia comes from work demonstrating induction of ataxia in a mouse model using serum from patients with gluten ataxia.<sup>17</sup> Another study has demonstrated that ataxia associated with anti-GAD antibodies may be the direct consequence of antibody-mediated neuronal dysfunction, but the precise characterisation of the antibody involved is lacking.<sup>18</sup> This antibody(s) may be unrelated to GAD antibodies. All the evidence however, suggests that the cerebellum and Purkinje cells in particular, are good immunological targets.

The next step in unravelling and consolidating PACA as a disease entity is a trial of immunosuppression as a means of treatment. Assessment of the value of immunosuppression in these patients will be challenging. Monitoring of treatment response may prove very difficult because of the variable and mostly slowly progressive nature of the disorder and the crude nature of ataxia rating scales. There is emerging evidence however, that MR spectroscopy of the cerebellum may well be an important and accurate tool in monitoring disease.<sup>19</sup> Whilst the final common pathological outcome in PACA, as in other cerebellar ataxias, is the irreversible loss of Purkinje cells, evidence derived from treatment of other immune mediated ataxias suggests that early intervention may not only stabilise the ataxia but could also salvage malfunctioning cells as evident by the demonstration of improvement of the ataxia.<sup>20</sup>

Case identification in PACA is also problematic. As the HLA DQ2 is found in up to 35% of healthy individuals, this test alone cannot serve as the only marker of patients with autoimmune ataxia. Indeed out of the 154 patients with idiopathic sporadic ataxia (Table 1) 54 would have had the HLA DQ2 by chance. The presence of additional autoimmune diseases in either the patient or their first degree relatives may be another helpful pointer. Ultimately characterisation of the cerebellar antibodies in patients with idiopathic sporadic ataxia may prove to be a very useful marker for those cases that may be

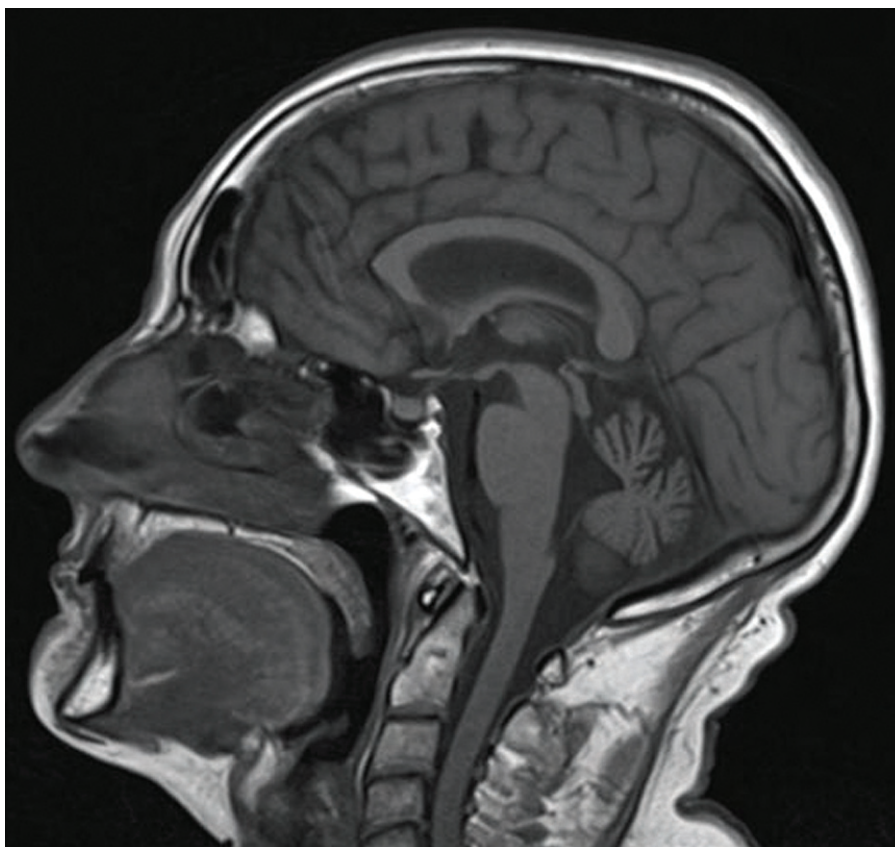


Figure 1: MR imaging demonstrating cerebellar atrophy in a patient with slowly progressive ataxia due to PACA. This patient presented in 1999 at the age of 51. She has the HLA DQ2 and at presentation apart from the ataxia she was positive for thyroid peroxidase antibodies but had normal TSH. She developed hypothyroidism 2 years later. She developed insulin dependent diabetes mellitus 5 years after the onset of the ataxia. Finally she was recently found to have low vitamin B12 with positive parietal antibodies in keeping with pernicious anaemia.

amenable to immunomodulatory therapy.

The clinical characteristics of such patients may also assist in case identification and in some cases distinguish them from other causes of ataxia. Patients with PACA tend to develop ataxia in their early 50s. The ataxia in general tends to be slowly progressive but in a few cases there may be a rather acute onset (a picture not dissimilar to that often seen at presentation in paraneoplastic cerebellar degeneration). Subsequently, however such patients follow a much more benign course. In fact some of these patients may have originally been diagnosed as having post infectious cerebellitis, the difference being that they continue to progress rather than improve, in contrast to patients with post-infectious cerebellitis.<sup>21</sup> Additional autoimmune diseases may be already present or may manifest subsequent to the development of the ataxia (Figure 1). Patients with PACA almost always have cerebellar atrophy on MRI but the severity of atrophy depends on disease duration.<sup>5</sup> These patients are also easily distinguished from patients with cerebellar variant of Multiple System Atrophy (MSA) by the absence of autonomic involvement and the slower progression.

The next logical step in consolidating this disease entity is an adequately-powered study comparing immunosuppressive treatment with placebo. The results of such a study will not only clarify and consolidate the concept of PACA but will hopefully offer hope for a substantial number of patients with progressive sporadic "idiopathic" ataxia. ♦

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