

## SHORT REPORT

## Adult polyglucosan body disease associated with an extrapyramidal syndrome

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### Abstract

**A 50 year old patient is described who presented with parkinsonism, frontal dementia, peripheral neuropathy, neurogenic bladder, and upper motor neuron signs. No improvement in objective measurements of extrapyramidal dysfunction were seen with an incremental apomorphine test or more prolonged oral dopamine challenge. Neurophysiology disclosed changes compatible with a diffuse axonal neuropathy and pathological examination of a length of sural nerve taken at biopsy showed multiple polyglucosan bodies characteristic of adult polyglucosan body disease (APGBD). This case underlines the diverse clinical presentation of this rare neurological disease and the importance of recognising the unusual association of clinical features in making the diagnosis. APGBD should be included in the differential diagnosis of parkinsonism unresponsive to dopaminergic therapy.**

(*J Neurol Neurosurg Psychiatry* 1998;65:788-790)

Keywords: adult polyglucosan body disease, parkinsonism

Adult polyglucosan body disease (APGBD) was first described in 1980<sup>1</sup> and remains a rare neurological disease with some 25 cases so far reported (table). It derives its name from the accumulation of rounded intra-axonal inclusion bodies in the central and peripheral nervous system. Its most consistent features are onset in the fifth to seventh decades (88%), peripheral neuropathy (80%), dementia (64%), neurogenic bladder (72%), and upper motor neuron signs (80%),<sup>2</sup> although most patients have one or more of these features missing and some rarer clinical phenomena have been noted. Here we report on a woman with classic features of APGBD and the unusual association of an extrapyramidal syndrome underlining the diverse clinical presentation of this disease.

### Case history

A fifty year old woman who until six months previously had worked as a teacher initially presented with a 2 year history of speech disturbance consisting of slow, low volume speech. One year later she had developed poor balance, frequent falls, tremor predominantly affecting her right hand, urinary urgency, and

### Reported cases of adult polyglucosan body disease

Author	Age at onset	Sex	Upper motor neuron signs	Neuropathy	Dementia	Urinary dysfunction	Other
Suzuki <i>et al</i> <sup>18</sup>	59	M	+	+	+	-	
Peres <i>et al</i> <sup>19</sup>	47	M	+	+	+	+	
Robitaille <i>et al</i> <sup>1</sup>	43	M	+	+	+	+	
	47	F	+	+	+	-	
	51	F	+	+	-	+	
	45	F	+	+	-	+	
Okamoto <i>et al</i> <sup>20</sup>	64	F	+	+	+	+	
Vos <i>et al</i> <sup>2</sup>	46	F	+	+	+	+	
Gray <i>et al</i> <sup>10</sup>	68	M	+	+	-	+	
	63	M	+	+	+	+	
	74	F	-	+	+	+	
Cafferty <i>et al</i> <sup>2</sup>	53	F	+	+	-	+	
	44	F	+	+	-	+	
Lossos <i>et al</i> <sup>11</sup>	51	M	+	+	+	+	Amyotrophy
	55	F	+	+	+	+	
Sugiyoma <i>et al</i> <sup>21</sup>	71	F	+	-	+	-	Optic atrophy
	47	F	-	-	-	-	
Bruno <i>et al</i> <sup>17</sup>	38	F	+	+	-	+	Cerebellar atrophy
	50	M	-	+	-	-	
	40	M	+	+	+	+	Cerebellar signs
	84	M	+	+	+	+	Amyotrophy
McDonald <i>et al</i> <sup>13</sup>	50	F	+	-	+	-	Amyotrophy
	66	F	+	+	+	+	Amyotrophy
Matsumuro <i>et al</i> <sup>22</sup>	70	F	-	+	-	-	
Boulan-Predseil <i>et al</i> <sup>16</sup>	65	F	-	-	+	+	
	M:F 1:2.8		20/25 (80%)	21/25 (84%)	16/25 (64%)	18/25 (72%)	

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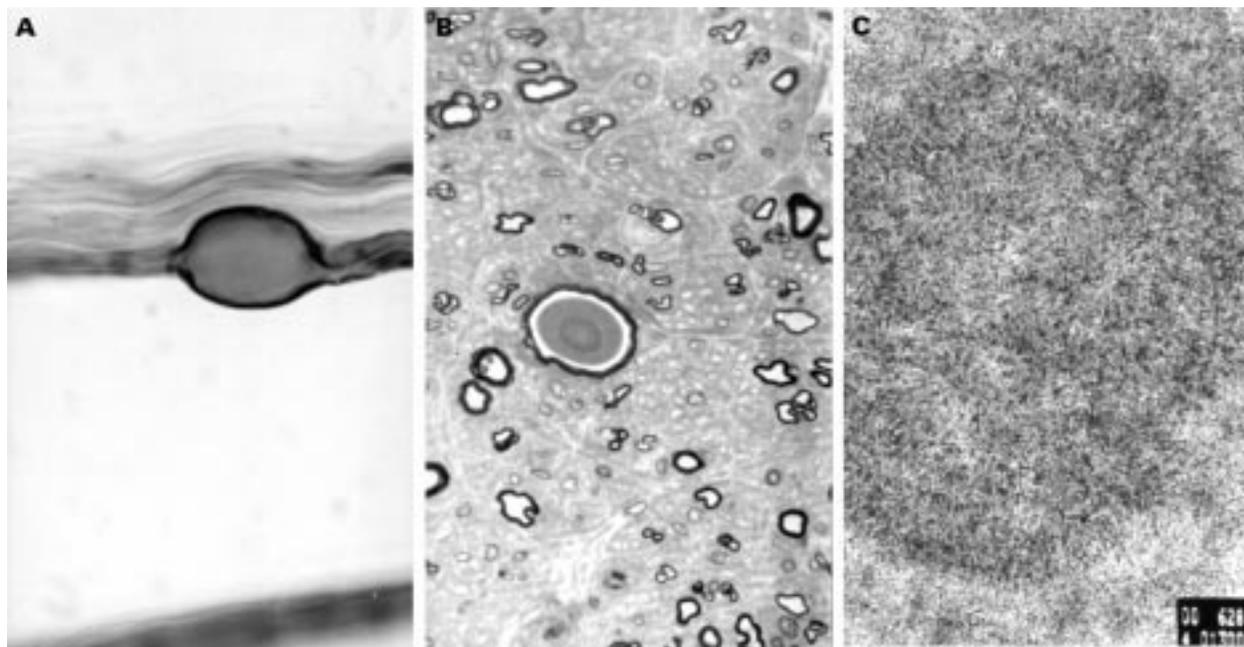
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Received 5 February 1998  
and in revised form  
7 May 1998  
Accepted 15 May 1998



(A) Teased fibre preparation demonstrating an ellipsoid dilatation of an axon due to a polyglucosan body. (B) Resin preparation demonstrating diffuse loss of myelinated fibres. One axon contains a large polyglucosan body (approximately 30  $\mu\text{m}$ ) with a round profile in transverse section. It has a laminated appearance with a slightly denser core. The surrounding myelin sheath is thinned. (originally  $\times 600$ ). (C) The polyglucosan body has an electron dense core with a less dense periphery and a characteristically fibrillary pattern (originally  $\times 21100$ ).

impaired concentration and episodic memory. The neurological deterioration was gathering pace so that she was soon unable to walk without bilateral support around the house and required a wheelchair for longer distances. There was no history of neurological disease in her family, her parents were not consanguinous, and there was no history compatible with epilepsy or myoclonus from the patient.

On examination she had slow, hypomimic speech with a paucity of facial expression and variable dysphonia, extraocular eye movements were intact and there was no jaw jerk. In her limbs she had a coarse resting tremor, most marked in the right arm with no associated cerebellar signs but cogwheeling rigidity and bradykinesia. There was wasting in the small muscles of the hands and below the level of the knees bilaterally with mild weakness of all ankle movements and high arched feet. Deep tendon reflexes were absent at the ankle, brisk at the knees, and associated with bilateral extensor plantar responses. Sensation to vibration was absent to the mid-shins and impaired to light touch and pin prick to the knees. Her gait was slow, festinating, and bradykinetic. Formal neuropsychological evaluation disclosed impaired mental arithmetic, immediate and delayed recall, weak verbal fluency, and impaired executive function suggesting frontal lobe dysfunction. Tests of concentration, naming, and visuospatial analysis were normal.

Cranial CT was normal and a whole spine MRI demonstrated moderate degenerative changes only. No improvement in objective measurements of extrapyramidal dysfunction were seen with an incremental apomorphine test or more prolonged oral dopamine challenge. Neurophysiology showed changes compatible with a diffuse axonal neuropathy but extensive blood and serological tests failed to

disclose a cause for this so a sural nerve biopsy was taken.

A 1cm length of sural nerve was submitted for histopathological examination. Ten nerve fascicles were present in cross section, all of which showed moderate diffuse loss of both small and large myelinated axons. The presence of occasional axonal clusters were indicative of axonal sprouting. Several axons (almost one per fascicle on average, two within some fascicles) contained large, rounded intra-axonal inclusions which were metachromatic with toluidine blue staining. The inclusions, which were a maximum of 30  $\mu\text{m}$  in diameter, had a darker staining centre with a lighter halo and stained strongly positive with periodic acid Schiff (PAS). The appearances were typical of polyglucosan bodies. Teased fibre preparations demonstrated a few fibres in late stage wallerian degeneration and an occasional polyglucosan body (figure). The appearances were those of axonal neuropathy with polyglucosan body deposition and in the context of the clinical picture were consistent with a diagnosis of APGBD.

### Discussion

The presence of polyglucosan bodies on their own is a non-specific finding as they are also found in normal subjects with increasing age (although they occur less commonly in sural nerves compared with intramuscular nerves<sup>3,4</sup>), and occasionally in diabetic neuropathies and primary axonal neuropathies.<sup>4-6</sup> However, they are also characteristically seen in some clinical situations including Lafora body disease and type IV glycogenosis,<sup>7,8</sup> but they occur in much greater frequency in APGBD, particularly in nerve processes rather than perikarya (by contrast with Lafora bodies) and astrocytes. The diagnosis may be made by the association of

the appropriate clinical phenotype with excessive numbers of polyglucosan bodies seen on peripheral nerve biopsy predominantly in myelinated fibres,<sup>1,2,9-11</sup> which is considered to be highly specific. Some authors have advocated axillary skin biopsy as a less invasive diagnostic method, which discloses an abundance of polyglucosan bodies in myoepithelial cells of apocrine glands.<sup>12</sup>

In one third of cases of APGBD there is a positive family history<sup>2</sup> indicating a significant genetic component inherited in an autosomal recessive pattern. Polyglucosan bodies are seen throughout the central and peripheral nervous system as well as myocardium and non-neural tissues at postmortem, suggesting a generalised storage disorder. The presence of polyglucosan bodies before the age of 5 on peripheral nerve biopsy is always pathological and the diagnosis should also be considered in adults when there is more than one polyglucosan body per nerve fascicle or the presence of extraneuronal polyglucosan bodies or unusually large bodies (>30 µm).<sup>8</sup> Histochemically they stain positively with PAS (diastase resistant), silver proteinate, and iodine, but are negative with Sudan black, luxol fast blue, and congo red. On electron microscopy they consist of branching filaments with amorphous and granular material. They are composed predominantly of abnormally branched glycogen (amylopectin) and are identical in composition to corpora amylacea and Lafora and Bielschowsky bodies.

Clinical phenomena usually consist of a mixture of lower and upper motor neuron signs, dementia, and urinary dysfunction. Features may be asymmetric, and reports of presentation with an amyotrophic lateral sclerosis picture<sup>13</sup> as well as multiple entrapment neuropathy,<sup>14</sup> supranuclear gaze palsy and some features of parkinsonism<sup>15</sup> and pure frontal lobe dementia<sup>16</sup> have been made. The course of the disease is variable with survival of between 1 and 14 years in reported cases.<sup>2</sup>

The pathogenesis is not yet known but glycogen branching enzyme deficiencies in leucocytes and peripheral nerve but not in muscle have been noted in two Ashkenazi Jewish families.<sup>13,17</sup> In addition, children of these patients have intermediate branching enzyme activity. A similar abnormality has not been found in sporadic cases or those from non-Jewish descent, which suggests that APGBD is a heterogeneous condition but that a small subgroup may be explained on the basis of an inherited tissue specific defect of a branching isoenzyme.

In this patient the presence of an axonal neuropathy, mild frontal dementia, upper motor neuron signs, and a history of urinary

dysfunction associated with excessive numbers of polyglucosan bodies on sural biopsy is characteristic of APGBD. It remains possible that the presentation of an extrapyramidal syndrome merely represents a chance association of a rare disorder with a more common one. However, the lack of response to dopamine, as well as the fact that polyglucosan bodies are known to accumulate pathologically within the CNS in APGBD, seems to indicate that it is more likely to be directly the result of the more widespread pathological process and is almost certainly another example of the heterogeneous nature of this unusual disease.

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