

# HETEROGENEOUS PHENOTYPES AND TYPICAL MRI FINDINGS IN 3 CASES OF ADULT POLYGLUCOSAN BODY DISEASE (APBD)

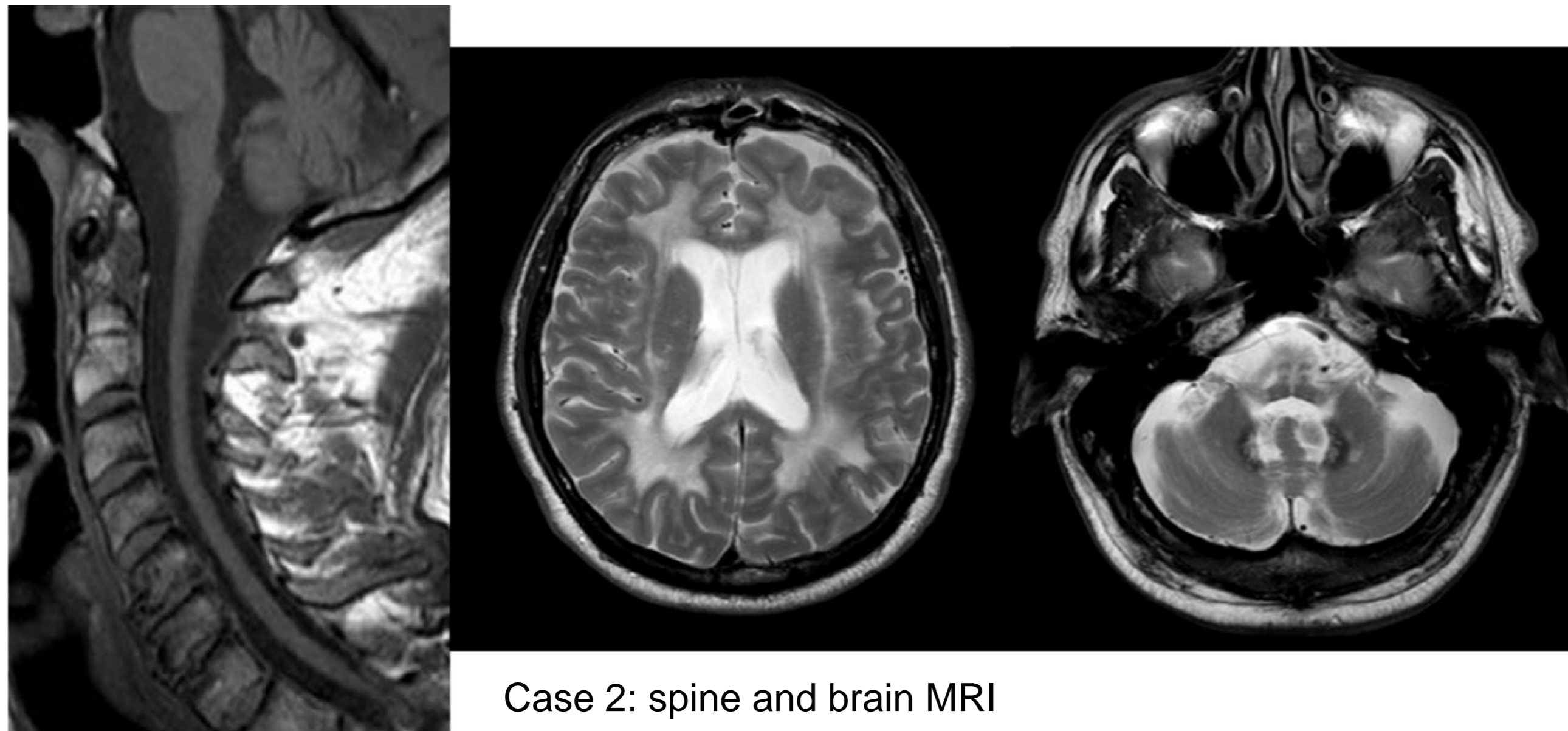
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**Introduction:** Adult Polyglucosan Body Disease (APBD) is a very rare leukodystrophy (less than 100 cases described), with autosomal recessive inheritance. Various mutations in GBE1 gene are implied, causing deficiency of Glycogen Branching Enzyme, which leads to accumulation of polyglucosan bodies (PBs) in the central and peripheral nervous system, muscle, skin and other tissues. Progressive spastic paraparesis, neurogenic bladder and peripheral neuropathy presenting in 5<sup>th</sup>-6<sup>th</sup> decade are considered hallmarks of APBD; cognitive impairment may be associated. Key magnetic resonance imaging (MRI) findings are: diffuse leucoencephalopathy with infratentorial involvement and spine atrophy. APBD is allelic to Glycogen Storage Disease Type IV (GSD-IV), a severe infantile disease with liver impairment and cardiomyopathy. The clinical spectrum of GBE deficiency may include intermediate forms, either with myopathic limb girdle-like phenotype or with fluctuating neurological deficit resembling multiple sclerosis; recently PBs myopathies associated with RBCK1 and GYG1 mutations were described. Heterogeneous phenotypes may cause debate and induce a misdiagnosis, so APBD is thought to be underdiagnosed. We describe our experience with APBD. We observed 3 patients with variable phenotypes, in which typical clinical findings, though not completely, were present. An extensive workup directed to explore the possible etiologies was performed. On the basis of MRI findings, which we considered strongly suggestive, APBD was suspected. In 2 cases genetic and biochemical analysis confirmed the diagnosis, while in 1 the diagnosis is still uncertain.



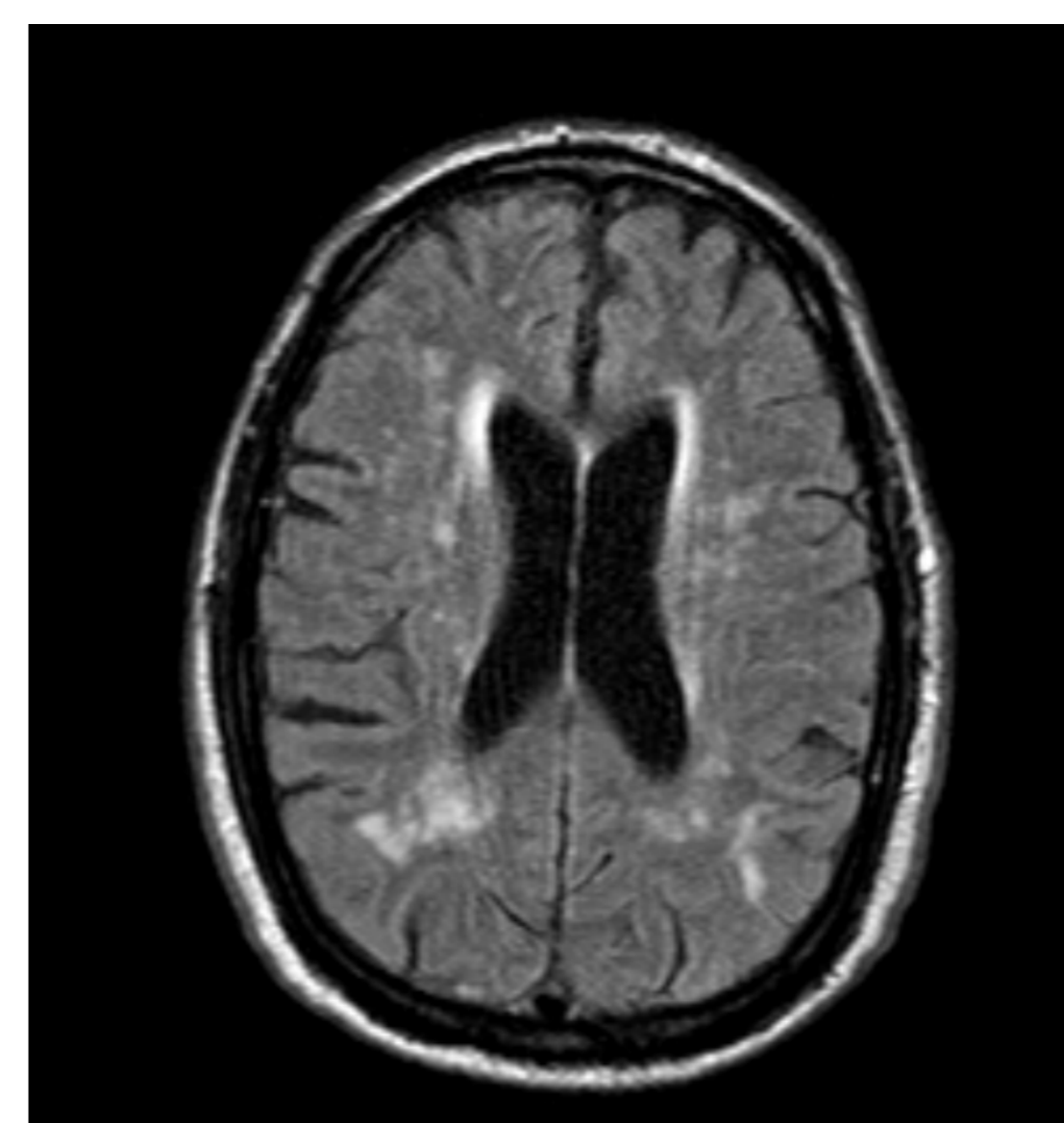
Case 2: spine and brain MRI

**Discussion and Conclusions:** APBD is exceedingly rare, recurring mainly in Ashkenazi-Jewish people. Though infrequent, it should be suspected in every ethnicity if progressive paraparesis, neurogenic bladder and peripheral neuropathy arise in adult life. Clinical course is generally homogeneous in the same family, but notable exceptions may be observed, such as in the siblings here reported: case 2 was affected by peripheral neuropathy and PBs were detectable in his muscle biopsy, whereas his sister (case 3) was not. Atypical presentations may cause debate on diagnosis, particularly facing a sudden onset or a fluctuating course. A recent review underlines the frequency of misdiagnosis of APBD (including cerebrovascular disease, ALS, MS, various peripheral neuropathies). On the contrary our case 1 demonstrates that the presence of PBs at nerve or muscle biopsy cannot be considered pathognomonic of APBD, as known. MRI typical findings should be considered an important clue: the presence of diffuse leucoencephalopathy, with confluent hyperintensities both supra- and infratentorial associated with spine atrophy, is a main hallmark of APBD. In case 1 these findings were not so definite though suggestive. In conclusion APBD should be thoroughly investigated when facing the intriguing problem of adult-onset leucoencephalopathies.

**Case 1:** male, aged 76, suffering from hypertension and mild NIDDM, since 6-7 years complained of progressive brainstem involvement with rhinolalia, dysarthria and dysphagia; moderate weakness of lower limbs with ataxic-paraparetic gait; neurogenic bladder was absent. A severe sensorimotor generalized neuropathy, both axonal and demyelinating, was associated. Initially motor neuron disease was suspected, due to bulbar symptoms with denervation both in spinal and bulbar muscles at EMG, though notable sensory deficit was present. X-SBMA was excluded by proper genetic testing. Subsequently the lack of clinical progression induced to hypothesize cerebrovascular disease, as MRI showed a diffuse leucoencephalopathy (T2-weighted subcortical hyperintensities, both supra- and infratentorial), ascribed to chronic cerebrovascular disease. MMSE was normal. A complete laboratory workup directed to explore the etiology of peripheral neuropathy was unremarkable, including CSF analysis. Nerve biopsy was finally performed, which demonstrated accumulation of PBs. Neither GBE1 mutation could be demonstrated at Sanger sequencing, nor enzymatic deficiency on skin fibroblasts. The diagnosis is still uncertain.

**Case 2:** male, aged 55, complained since 1 year of distal paresthesias and muscular cramps in his lower limbs; later he developed moderate weakness and urinary urgency. On examination he had signs of diffuse involvement of pyramidal tracts and decrease of pallesthetic sensation in lower limbs; consequently he progressed to a paraparetic-ataxic gait. MMSE was normal. Routine blood exams, as well as CSF analysis, were normal. Peripheral involvement was confirmed by EMG abnormalities, mainly demyelinating. MRI showed diffuse hyperintense supra- and infratentorial white matter abnormalities, mainly periventricular, and spine atrophy. Muscle and nerve biopsy demonstrated accumulation of PBs. The diagnosis was confirmed by absent GBE activity. Genetic analysis showed compound heterozygosity for a novel missense c.1064G>A (p.Arg355His) besides the known mutation c.1064A>G (p.Tyr535Cys).

**Case 3:** female, aged 56, sister of the previous case, since 4 years developed gait difficulties and later urinary incontinence. Medical history included mild hypercholesterolemia and depression with apathy and isolation. On examination diffuse pyramidal signs and paraparetic gait were demonstrated, whereas muscle strength and sensation were preserved. Nerve conduction study and muscle biopsy were unremarkable. MRI abnormalities were similar to her brother's ones. MMSE was normal. Enzymatic assay and genetic analysis demonstrated, too, the same familiar pathological pattern previously described in case 2.



Case 1: brain MRI



Case 3: spine MRI

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