Abstract—Adult Onset Alexander’s Disease (AOAD) is caused by mutation of the glial fibrillary acidic protein (GFAP) gene, leading to astrocyte dysfunction. The disease is often associated with the classic MRI findings of medullary and cervical cord atrophy with corresponding T2 hyperintense signal changes with or without enhancement. We describe a 67-year-old woman who presented with progressive neurologic impairment, starting with gait and urinary dysfunction. Her MRI prompted genetic testing for AOAD and discovery of a novel GFAP S393R mutation. To our knowledge, this is the first published case of this specific S393R GFAP mutation associated with AOAD.

Keywords—Adult Onset Alexander’s Disease, Glial fibrillary acidic protein (GFAP) mutations, MRI.

I. INTRODUCTION

Alexander’s disease, initially described by W.S. Alexander in 1949 as an infantile disease, is now recognized to occur into adulthood. It is a disorder of astrocytes characterized by mutations in glial fibrillary astrocytic protein (GFAP), a protein involved in the formation of intermediate filaments in astrocytes. These gain of function mutations cause excess accumulation of GFAP, which then aggregate forming Rosenthal fibers seen pathologically. There is a growing literature of mutations within the GFAP gene that lead to the clinical phenotype of Adult Onset Alexander’s Disease (AOAD). We present a novel missense mutation in a sporadic case of suspected AOAD.

II. CASE REPORT

A 67-year-old Caucasian woman presented with progressive gait and urinary dysfunction. Symptoms started insidiously three years prior as headache, vertigo with head turn, and imbalance. This progressed to multiple falls and leg weakness. Eventually the patient became wheelchair-bound. She developed mild short-term memory impairment, dysphagia, numbness and tingling on her thighs, urinary retention requiring catheterization, and bowel incontinence. Medical history included rheumatoid arthritis (RA), bilateral sensorineural hearing loss, hypothyroidism, cystocele, rectocele, and depression. Notably, she had never been on a TNF-α inhibitor for longer than a few months for her RA.

Exam revealed mild memory impairment and bulbar dysfunction, including hoarse voice with palatal weakness and slowed tongue movements. She had nystagmus in all directions of gaze. Her arms demonstrated mild weakness, but she had complete paraplegia from the hips down. Bulk and tone were normal. Arm deep tendon reflexes were 3+ bilaterally, while leg reflexes were 1-2+. Toes were upgoing bilaterally and there was left ankle clonus. Sensation on the right leg was decreased with gait and urinary dysfunction. Symptoms started insidiously

MRI findings were striking. Brain MRI with and without gadolinium showed prominent medullary and cervical cord atrophy (figure 1A). There were also a small number of periventricular white matter T2 hyperintensities. Cervical spine MRI revealed a 2 mm T2 hyperintense lesion at the cranio-cervical junction and a C2 lesion, both enhancing. The spine MRI appearance worsened slightly over 10 months with


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persistence of prior enhancing lesions and addition of a T2 signal abnormality at C3-4, also enhancing (figure 1B,C).

Visual evoked potentials and serum neuromyelitis optica antibody testing were normal.

Based on the MRI appearance, AOAD was suspected and genetic analysis obtained. The patient was found to have a novel S393R missense mutation in the GFAP gene, representing a non-consecutive amino acid substitution of arginine for serine. Another missense change at this same codon (S393I) associated with pathologically proven familial AOAD has been previously published. Therefore, our patient’s mutation was considered a strong candidate as pathogenic, supporting the diagnosis of AOAD; however the possibility that it was a benign variant could not be excluded. It was hypothesized that the patient’s missense mutation was de novo as she did not have a family history of the disease and two asymptomatic siblings did not carry the same mutation.

The patient’s symptoms progressed over the next 5 years to include significant dysarthria and dysphagia, spastic weakness, and ataxia. While these are the most frequent symptoms, there is clear phenotypic variability in the disease in regards to the degree of dysfunction and presence of other signs and symptoms, such as dysautonomia and sleep disturbances. Palatal myoclonus, though not always present and not seen in our patient, should raise suspicion for the diagnosis. Onset of symptoms is typically insidious and slowly progressive. There can be fluctuations in symptoms and based on this, along with the clinical symptoms described above, patients may be incorrectly diagnosed with multiple sclerosis. Other common misdiagnoses include cervical myelopathy and amyotrophic lateral sclerosis. Diagnosis is often elusive and MRI can play a critical role in suggesting the diagnosis and prompting genetic testing. The classic MRI findings are medullary and cervical cord atrophy with corresponding T2 hyperintense signal changes with or without enhancement. There are at least 20 GFAP mutations reported in the literature in association with AOAD. There is no clear pattern established that correlates genotype with phenotype in AOAD. Both sporadic cases with de novo mutations and familial autosomal dominant cases have been described. Family history of Alexander’s disease is often negative, which is likely an effect of both de novo mutations and misdiagnosis in affected family members in the era before genetic testing. To our knowledge, we present the first published case of suspected AOAD with this specific S393R mutation. Although pathologic

Figure 1: Baseline and ten month follow up MRI. 1A, Baseline sagittal T1 brain MRI demonstrating marked atrophy of the medulla and upper cervical spinal cord. 1B, Ten month follow up cervical sagittal T2 IR image demonstrating a T2 lesion 3.2 cm in length occupying the length of the medulla, a 2 cm lesion at C2, and a 1.5 cm lesion at C3-4. 1C, All three lesions enhanced after gadolinium administration.

III. DISCUSSION

Adult onset Alexander’s disease presents most commonly with bulbar symptoms, such as dysarthria and dysphagia, spastic weakness, and ataxia. While these are the most frequent symptoms, there is clear phenotypic variability in the disease in regards to the degree of dysfunction and presence of other signs and symptoms, such as dysautonomia and sleep disturbances. Palatal myoclonus, though not always present and not seen in our patient, should raise suspicion for the diagnosis. Onset of symptoms is typically insidious and slowly progressive. There can be fluctuations in symptoms and based on this, along with the clinical symptoms described above, patients may be incorrectly diagnosed with multiple sclerosis. Other common misdiagnoses include cervical myelopathy and amyotrophic lateral sclerosis. Diagnosis is often elusive and MRI can play a critical role in suggesting the diagnosis and prompting genetic testing. The classic MRI findings are medullary and cervical cord atrophy with corresponding T2 hyperintense signal changes with or without enhancement. There are at least 20 GFAP mutations reported in the literature in association with AOAD. There is no clear pattern established that correlates genotype with phenotype in AOAD. Both sporadic cases with de novo mutations and familial autosomal dominant cases have been described. Family history of Alexander’s disease is often negative, which is likely an effect of both de novo mutations and misdiagnosis in affected family members in the era before genetic testing. To our knowledge, we present the first published case of suspected AOAD with this specific S393R mutation. Although pathologic
confirmation was not obtained, the classic symptoms and associated MRI findings in the setting of a GFAP mutation makes the diagnosis of AOAD very likely. The classic MRI findings can help clinicians attain earlier diagnoses for their patients, and when reported, expands the list of known pathogenic GFAP mutations for AOAD along with the range of clinical phenotypes.\cite{2,5,6}

References


Questions (please choose one single answer):

1. What is the classic pathological finding associated with Alexander’s disease?
   a. Neurofibrillary tangles
   b. Rosenthal fibers
   c. Cowdry B inclusions
   d. Lewy bodies

2. What gene is mutated in Alexander’s disease?
   a. SOD1
   b. C9Orf72
   c. GFAP
   d. PARK

3. The classic MRI findings in Adult Onset Alexander’s Disease include atrophy of which of the following structures?
   a. Medulla
   b. Occipital lobes
   c. Cervical spinal cord
   d. Thalamus
   e. A and C

Correct answer: 1: B; 2: C; 3: E