Published in final edited form as:

J Child Neurol. 2012 September ; 27(9): 1121–1132. doi:10.1177/0883073812448680.

Diagnostic Approach to Childhood-onset Cerebellar Atrophy: A 10-Year Retrospective Study of 300 Patients

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Abstract

Hereditary ataxias associated with cerebellar atrophy are a heterogeneous group of disorders. Selection of appropriate clinical and genetic tests for patients with cerebellar atrophy poses a diagnostic challenge. Neuroimaging is a crucial initial investigation in the diagnostic evaluation of ataxia in childhood, and the presence of cerebellar atrophy helps guide further investigations. We performed a detailed review of 300 patients with confirmed cerebellar atrophy on magnetic resonance imaging over a 10-year period. A diagnosis was established in 47% of patients: Mitochondrial disorders were most common, followed by the neuronal ceroid lipofuscinoses, ataxia telangiectasia, and late GM2-gangliosidosis. We review the common causes of cerebellar atrophy in childhood and propose a diagnostic approach based on correlating specific neuroimaging patterns with clinical and genetic diagnoses.

Keywords

ataxia; cerebellar atrophy; diagnosis; genetics

Introduction

The hereditary ataxias associated with cerebellar atrophy are a heterogeneous group of disorders. In the pediatric age group, the most common genetic cerebellar ataxias are those with autosomal recessive inheritance, although disorders characterized by autosomal dominant, X-linked, and mitochondrial inheritance also play an important role.¹ The exact prevalence of childhood-onset cerebellar atrophy is not accurately known. The number of recognizable phenotypes associated with cerebellar atrophy is increasing, and the discovery

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Author Roles

AAM wrote the first draft of the manuscript and reviewed the clinical data, SB reviewed all neuroimaging studies and GY reviewed the clinical data and provided overall supervision for this study. All authors contributed to critique and review of the final draft of the manuscript.

Conflict of Interest

The authors have no conflicts of interest to disclose. The study was approved by the Research Ethics Board of the Hospital for Sick Children.

of the genetic basis of these conditions is advancing at a rapid pace. Yet selection of appropriate clinical and genetic tests for patients with cerebellar atrophy poses a diagnostic challenge and is complicated by both clinical and genetic heterogeneity. Accurate clinical and genetic diagnosis of ataxia associated with cerebellar atrophy remains difficult.¹

Neuroimaging is a crucial initial investigation in the diagnostic evaluation of ataxia in childhood. Brain magnetic resonance imaging and magnetic resonance spectroscopy yield valuable information regarding abnormalities of the cerebellum (atrophy or hypoplasia of the cerebellar hemispheres and/or vermis, and signal changes of cerebellar white matter), in addition to evaluation of extracerebellar structures (brainstem, white matter, and basal ganglia).² The presence of cerebellar atrophy on magnetic resonance imaging, in addition to careful initial clinical evaluation, can help prioritize further specialized investigations, including appropriate genetic testing in children with suspected genetic cerebellar ataxia.

Although previous studies have evaluated imaging findings in the childhood ataxias, we report on the prevalence of disorders associated with the imaging feature of childhood-onset cerebellar atrophy at the Hospital for Sick Children over a 10-year period, and correlate specific neuroimaging patterns with clinical and genetic diagnoses. Lastly, we propose a diagnostic algorithm for the clinical and genetic evaluation of patients with cerebellar atrophy, based on our experience.

Materials and Methods

We conducted a retrospective study of all patients referred to the Hospital for Sick Children, Toronto, Canada from 1999 to 2010, who had cerebellar atrophy on magnetic resonance imaging. Subjects were identified as part of an institutional research ethics board-approved protocol, using a radiology report text search program (ISYS™, Denver Technology Center, Denver, Colorado). Patients with cerebellar atrophy due to confirmed treated posterior fossa tumors, posterior fossa surgery, cerebellar hemorrhage, and ischemia (including perinatal ischemic insult) were excluded. Asymmetric cerebellar atrophy was assumed to be secondary to a prior insult and those patients were also excluded. A total of 402 patients were identified (Figure 1). Of these, 66 patients had posterior fossa malformations and were not included in the study. The posterior fossa malformations included Dandy-Walker and Arnold-Chiari malformations, Joubert syndrome, rhombencephalosynapsis, mega cisterna magna, Blake's pouch, arachnoid cyst, and crossed cerebrocerebellar diaschisis. Nongenetic etiologies of cerebellar atrophy were identified in an additional 36 patients, including immune-mediated (multiple sclerosis and systemic lupus erythematosus), viral infection (cerebellitis and congenital infection), drug-induced (chronic multiple anticonvulsant therapy, mercury exposure), and paraneoplastic syndromes. These patients were also excluded from the study.

Three hundred patients (149 males and 151 females; age range, newborn to 18 years) met our criteria. Detailed clinical data, including gender, age of onset of symptoms, age at diagnosis, mode of presentation, consanguinity, family history, and ambulatory status, were collected. Results of laboratory investigations, including metabolic studies (pyruvate, lactate, mitochondrial, peroxisomal and lysosomal enzyme activity, lipid profiles, alpha-fetoprotein, amino acids, organic acids, and transferrin isoelectric focusing), immunological studies, cytogenetic and molecular genetic tests, electromyography, nerve conduction velocity tests echocardiography, and muscle and skin biopsies, were reviewed when available.

Brain imaging (1.5 T magnetic resonance imaging [MRI]) was carried out at least once on each patient. All examinations included sagittal T1- weighted and axial/coronal T2-weighted

images. Fluid-attenuated inversion-recovery imaging, diffusion-weighted imaging, and magnetic resonance spectroscopy studies were reviewed when available. Follow-up magnetic resonance imaging was obtained in 72% of patients, with the interval ranging from 6 months to 14 years. The mean age at initial magnetic resonance imaging was 6.2 years (range, newborn to 17.6 years), median age at initial magnetic resonance imaging was 4.2 years. All magnetic resonance images and neuroradiology reports were reviewed by one of the study authors (S.B.). The presence of atrophy involving the cerebellar vermis, anterior and posterior lobes, or hemispheres; T2-weighted signal abnormality of the cerebellar cortex; abnormalities of the cerebellar white matter or dentate nucleus; hypoplasia, malformation or atrophy of the brainstem; and abnormalities of the supratentorial white matter, cortex, and basal ganglia were recorded.

Results

A diagnosis was established (laboratory results either preceded or were instigated by the imaging study) in 142 of 300 (47%) patients with cerebellar atrophy, which represents a similar diagnostic rate compared with previously reported studies (Table 1).³⁻⁶

Mitochondrial disorders were the common cause of cerebellar atrophy in our cohort and were confirmed in 37 of 300 (12.3%) patients. Nine of the 37 patients (4 males, 5 females) were diagnosed with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke syndrome. Two of the patients with this syndrome presented before 1 year of age with developmental delay, deafness, cardiomyopathy, and hypotonia, whereas the other 7 presented after age 5 years with headache and stroke. In all cases, cerebellar atrophy was present after the age of 3 years, but prior to the initial episode of stroke. In the 2 patients with infantile presentation the syndrome, cerebellar atrophy was diagnosed at 3.1 and 3.4 years of age, respectively. Three of the 37 patients were diagnosed with mitochondrial depletion syndrome with confirmed mutations of the *POLG1* gene; all presented between ages 12 to 24 months with developmental delay and seizures. Kearns-Sayre syndrome was diagnosed in 3 of 37 patients. Age at presentation ranged from 11 months to 9 years and presenting symptoms included developmental delay, seizures, and ophthalmoplegia. One of the 37 patients was diagnosed with neuropathy, ataxia, and retinitis pigmentosa and 2 of 37 had Leber's hereditary optic neuropathy. The remaining 19 of 37 patients had respiratory chain defects confirmed by enzyme analysis in skin or muscle biopsies; one patient had a confirmed mutation of the *SURF1* gene. The initial clinical symptoms included developmental delay, seizures, visual dysfunction, ataxia, hearing loss, myopathy, and or cardiomyopathy. Plasma lactate was elevated in most patients. Additional MRI findings in this group included deep gray matter signal abnormality (high T2-weighted, low T1-weighted), white matter abnormalities suggestive of leukodystrophy, and elevated lactate on magnetic resonance spectroscopy.

Neuronal ceroid lipofuscinoses were diagnosed in 25 patients (12 males, 13 females). The family history was positive (a previously affected sibling) in 37.5% of patients with neuronal ceroid lipofuscinoses. Five patients had the infantile form (average age at onset, 15 months), 16 of 25 had late infantile neuronal ceroid lipofuscinoses (average age at onset, 3 years), and 4 of 25 had juvenile neuronal ceroid lipofuscinoses (average age of onset, 6 years). Mutations in the *CLN1*, *2*, *3*, *5*, *6*, *7* or *CLN8* genes were confirmed in 18 of 25 patients. Six had classical findings on conjunctival or skin biopsy but no mutations were identified on screening of the known neuronal ceroid lipofuscinoses genes. Genetic confirmation for one patient with typical clinical and neuroradiological findings is currently pending. Cerebellar atrophy was prominent and additional MRI findings included mild diffuse supratentorial secondary demyelination, especially of the optic radiation as it traversed the peritrigonal area, and of the posterior limb of the internal capsule. Dark

thalami on T2-weighted imaging was a universal sign in all patients. Punctuate necrosis of the corticospinal tract was observed in few patients and increased signal on Fluid-attenuated inversion-recovery imaging of the cerebellar cortex developed very late in the disease course.

Ataxia telangiectasia was diagnosed in 11 patients (average age of onset, 2 years; range, 1 year to 3 years). Elevated alpha-fetoprotein levels and low immunoglobulin levels were universally observed, and the diagnosis confirmed by *ATM* gene mutation analysis and/or ATM protein assay. Ataxia with oculomotor apraxia type 1 was diagnosed in one patient, and ataxia with oculomotor apraxia type 2 in 2 patients. Age of onset in ataxia with oculomotor apraxia type 1 was 2 years and in ataxia with oculomotor apraxia type 2 was after the age of 10 years. All patients presented with ataxia, and developed oculomotor apraxia later in the disease course. MRI studies revealed isolated cerebellar atrophy in this group, with no extracerebellar findings.

Late-onset GM2-gangliosidosis was identified in 10 patients (4 males, 6 females) and confirmed by decreased levels of beta-hexosaminidase A enzyme activity. Average age at clinical presentation was 9.5 years (range, 3 years to 12 years). All presented with behavioral changes or psychotic symptoms, then developed ataxia, seizures, spasticity, and cognitive regression by 17 years. MRI at initial assessment revealed diffuse cerebellar atrophy in all patients, and magnetic resonance spectroscopy was characterized by low N-acetylaspartate levels in the cerebellum. All patients had abnormal focal supratentorial white matter signal of the corona radiata, while the internal capsule and optic radiation in the peritrigonal region were relatively spared. Fluid-attenuated inversion-recovery imaging signal of the cerebellar cortex was mildly increased in patients with advanced disease and severe cerebellar atrophy.

Infantile neuroaxonal dystrophy was diagnosed in 8 patients, all of whom have confirmed mutations of the *PLA2G6* gene. Seven had the infantile form, with onset by 12 months, and clinical course characterized by psychomotor delays, hypotonia, rapid progression to a non-ambulatory state by 5 years, and mean age of death of 10 years. One patient had atypical infantile neuroaxonal dystrophy, and presented at 3 years with abnormal behavior and delays in fine, gross motor, and language development. MRI findings seen in all patients included cerebellar vermal atrophy, hypertrophy of the clava, chiasmatic atrophy, and abnormal signal surrounding the peritrigonal optic radiations. All developed signal hyperintensity on T2-weighted imaging of the cerebellar cortex. Globus pallidus iron deposition was seen in 4 patients. Only 1 child developed significant supratentorial atrophy.

Congenital disorders of glycosylation type 1 were identified in 7 patients (4 males, 3 females). The diagnosis was confirmed by transferrin isoelectric focusing and/or mutation analysis. Four patients were diagnosed with congenital disorders of glycosylation type 1a, one patient had congenital disorders of glycosylation type 1d, and one patient had congenital disorders of glycosylation type 1i. Average age of onset was 3 months (range, newborn to 8 months). All presented with developmental delay, seizures, hypotonia, and/or dysmorphic features, and had minimal development by 1 year of age. MRI studies revealed diffuse severe cerebellar atrophy, primarily affecting the vermis. After the newborn period, severe rapid development of cerebellar atrophy with cerebellar cortex signal hyperintensities on fluid-attenuated inversion-recovery imaging and early loss of pontine volume typically occurred in patients with congenital disorders of glycosylation type 1a. The corpus callosum was thin and supratentorial structures were normal for delayed myelination in one patient. Two patients with congenital disorders of glycosylation type 1a had an inferior crescent at the posterior fossa. The one patient with congenital disorders of glycosylation type 1d had predominant cerebellar hypoplasia with mild cerebellar atrophy.

Three patients were diagnosed with spinocerebellar ataxia (2 males, 1 female). Two siblings were diagnosed with maternally-inherited spinocerebellar ataxia 5, and one child was diagnosed with maternally-inherited spinocerebellar ataxia 7. Two patients were found to have de novo missense mutations of the *CACNA1A* gene. Both presented before 1 year of age with profound developmental delay and seizures, and one patient developed recurrent stroke and hemiparesis in addition to cerebellar atrophy, which was noted early in the course of the disease. Spinal cord atrophy and focal white matter abnormalities were also observed.

Pelizaeus-Merzbacher disease was identified in 4 patients, all were males. Age of symptom onset (global developmental delay) was between 3 to 9 months and no patient developed seizures or psychomotor regression. All had a confirmed *PLP1* gene mutation. In our cohort, cerebellar atrophy did not develop until age 10 years. In contrast, hypomyelination, the cardinal imaging feature of Pelizaeus-Merzbacher disease, was present in all patients at initial evaluation.

Three patients had Cockayne syndrome (1 male, 2 female). Average age of onset was 5 months (range, 1 to 9 months). All presented with developmental delay and severe failure to thrive, with later development of photosensitivity. All had early-onset cerebellar atrophy and dysmyelination, and one had calcification of the basal ganglia on MRI. Marinesco-Sjögren syndrome (*SIL1* mutations) was confirmed in 3 male patients, who presented within the first 6 months of life with severe hypotonia, developmental delay, congenital cataract, and failure to thrive. In addition to cerebellar atrophy on MRI, 2 patients were noted to have mild signal hyperintensity of the cerebellar cortex on T2-weighted/fluid-attenuated inversion-recovery imaging at the ages of 2 and 1.2 years. The third patient whose MRI was performed before the age of 1 year did not have increased fluid-attenuated inversion-recovery imaging signal of the cerebellar cortex. Hypomyelination with atrophy of the basal ganglia and cerebellum was present in 2 female patients who presented at the age of 1.5 and 2.5 years. They presented with developmental delay and spasticity, and later developed extrapyramidal signs and abnormal movement. MRI showed hypomyelination, cerebellar atrophy, and severe atrophy of the basal ganglia.

Chromosomal abnormalities were present in 8 patients (5 males, 3 females). Average age at presentation was 2 months (range, newborn to 24 months). They presented with developmental delay, limb, cardiac or renal malformations, and/or dysmorphic features. Some patients received multiple anticonvulsant therapy for severe epilepsy or recurrent status epilepticus, which may be a contributing factor to cerebellar atrophy. Additional MRI findings in this group were thin corpus callosum or dysgenesis/agenesis of the corpus callosum.

Chromosomal abnormalities included 9p deletion, 13q deletion, 4q12 deletion, 2q23 deletion, tetrasomy 12p, 17p11 duplication, and 5q32 duplication. One patient with 10p15.3 duplication presented with developmental delay and ataxia at 2 years of age. There was no history of seizures. MRI revealed significant vermian atrophy with sparing of the hemispheres and normal fluid-attenuated inversion-recovery imaging signal of the cerebellar cortex.

Other cerebellar atrophy patients with confirmed genetic diagnoses included (one patient each): Russell-Silver syndrome, Alexander syndrome, arthrogryposis multiplex, orofacial digital syndrome, Charcot-Marie-Tooth 1X (*GJB1* mutation), and Christianson syndrome. Other metabolic diagnoses (one patient each) included adrenoleukodystrophy, metachromatic leukodystrophy, cobalamin B deficiency, cobalamin C deficiency, hypobetalipoproteinemia, molybdenum cofactor deficiency, and folinic acid-dependent seizure disorder. Two patients had short-chain acyl-coenzyme A dehydrogenase deficiency.

Cerebellar Atrophy With Unknown Diagnoses

A diagnosis was not able to be established in 158 of 300 (53%) patients (95 males, 63 females) despite extensive metabolic, genetic, and pathological investigations. Age at presentation was highly variable. Eighty-nine of 158 (56%) patients presented within the first year of life, of whom 22 presented in the newborn period. Forty of 158 (26%) presented between age 1 year to 2 years of age, and 29 of 158 (18%) presented between age 2 years to 18 years, 7 of whom presented after 10 years of age. Global developmental delay was present in 77 % of patients, and those who presented before 1 year of age had more severe developmental delay, compared with children who presented later. Seizures were present in 41 of 158 (26%) patients, and for 23 patients, seizures were the initial symptom at presentation. Forty-one of 158 (26%) patients presented with ataxia and/or dysarthria at initial assessment. Psychomotor regression was noted in 20% of patients. Family history was negative in 125 patients (81%), and positive in 29 (19%) patients. There were 8 sibships with 2 or more affected siblings, and the prevalence of consanguinity in our cohort was 7%. The most common MRI finding in this group was diffuse cerebellar atrophy in 71%, and the cerebellar hemispheres were affected more than the vermis in 8% of patients. Vermian atrophy with sparing of the hemispheres was present in 29% of patients with unknown diagnoses. Increased T2-weighted signal of the cerebellar cortex was noted in 21% of this cohort.

Neuroradiological Patterns

We analyzed the neuroradiological patterns observed in all 300 patients, and classified them as one of the following (Figures 2 and 3): (1) isolated cerebellar atrophy with no extracerebellar involvement, (2) cerebellar atrophy with T2-weighted or fluid-attenuated inversion-recovery imaging signal hyperintensities of the cerebellar cortex, (3) cerebellar atrophy with supratentorial white matter abnormalities (secondary demyelination or specific tracts), (4) cerebellar atrophy with supratentorial hypomyelination, and (5) cerebellar atrophy with abnormalities of the basal ganglia and/or thalami (bright T2W signal and dark T2-weighted signal).

Isolated Cerebellar Atrophy

Sixty-three of 300 patients (21%) had isolated cerebellar atrophy with no extracerebellar involvement. Forty-four of 63 (70%) were patients with unknown diagnoses, 11 of 63 (17%) had ataxia telangiectasia, 3 of 63 (5%) had ataxia with oculomotor apraxia 1 or 2, 3 of 63 (5%) had late onset GM2-gangliosidosis, and 2 of 63 (3%) had *CACNA1A* mutations.

Cerebellar Atrophy with T2-Weighted or Fluid-Attenuated Inversion-Recovery Imaging Signal Increase of the Cerebellar Cortex

This neuroradiological pattern was observed in 71 of 300 (24%) of patients. Thirty-three of 71 (46%) had unknown diagnoses, 11 of 71 (15%) had mitochondrial disorders, and 8 of 71 (11%) had infantile neuroaxonal dystrophy. Mildly increased fluid-attenuated inversion-recovery imaging signal was noted in 7 patients with advanced stage late-onset GM2-gangliosidosis (10%), 7 patients with congenital disorders of glycosylation type CDG1a (10%), 3 patients with spinocerebellar ataxia (5%), and 2 patients with Marinesco-Sjögren syndrome (3%).

Cerebellar Atrophy with Supratentorial White Matter Abnormalities (Secondary Demyelination or Specific Tracts)

One-hundred of 300 patients (33%) had this neuroradiological pattern, of which 30 of 100 (30%) patients had unknown diagnoses. This pattern was observed in all patients with

mitochondrial disorders (37 of 100 [37%]), neuronal ceroid lipofuscinosis (25 of 100 [25%]), and infantile neuroaxonal dystrophy (8 of 100 [8] %). Patients with late-stage neuronal ceroid lipofuscinosis had mildly increased fluid-attenuated inversion-recovery imaging signal of the cerebellar cortex as an additional finding.

Cerebellar Atrophy With Supratentorial Hypomyelination

Twenty-one of 300 patients (7%) had this neuroradiological pattern. Fourteen of 21 (67%) patients had unknown diagnoses, 4 of 21 (18%) patients had Pelizaeus-Merzbacher disease, 2 of 21 (10%) patients had Hypomyelination with atrophy of the basal ganglia and cerebellum (HABC), and one patient had a 5q32 duplication.

Cerebellar Atrophy With Abnormalities of the Basal Ganglia and/or Thalami

Fifty-two of 300 patients (17%) had this neuroradiological pattern. Decreased T2-weighted signal of the thalami was observed in all 25 patients with neuronal ceroid lipofuscinosis (48%) and heterogeneous decreased thalamic signal was seen in the 10 patients with late-onset GM2-gangliosidosis (19%). Fourteen of 52 (27%) of patients had unknown diagnoses. One patient with Cockayne syndrome had calcifications of the basal ganglia and 4 patients with infantile neuroaxonal dystrophy had decreased T2-weighted signal of the globus pallidus.

Discussion

Development of an organized approach to the diagnosis of hereditary ataxia in children is the cornerstone of providing appropriate clinical care for the affected child and genetic counselling for the family. Cerebellar atrophy is a common finding in the hereditary ataxias and was formerly thought to be a relatively nonspecific finding.² Recent advances in understanding the genetic basis of cerebellar atrophy have laid the foundation for studying relevant mechanisms of pathogenesis, and for some conditions, have guided efforts in developing effective therapies, rendering an accurate diagnosis crucial.⁷ There are currently 155 conditions associated with cerebellar atrophy (OMIM, December 2011), and this number continues to expand. The presence of cerebellar atrophy on neuroimaging can facilitate selection of appropriate further investigations when combined with clinical features such as age of symptom onset, symptom progression, involvement of non-neurological systems, and family history.⁸

We present a 10-year retrospective study of cerebellar atrophy at a large tertiary care pediatric center in Canada and report on the prevalence of specific diagnoses associated with the radiologic feature of cerebellar atrophy over this time period. The largest group in our cohort (53%) had a yet undiagnosed cause of cerebellar atrophy. In the group with a known diagnosis, mitochondrial disease was the most common cause of cerebellar atrophy. This finding is similar to the previously published studies (summarized in Table 1). The neuronal ceroid lipofuscinoses were the second most common cause of cerebellar atrophy, followed by ataxia telangiectasia, congenital disorders of glycosylation, infantile neuroaxonal dystrophy, and late onset GM2-gangliosidosis.

The concept of selective vulnerability and pattern recognition on neuroimaging studies was introduced by van der Knaap and Valk in 1991.⁹ The importance of using recognizable patterns of abnormalities on neuroimaging in the diagnostic approach to childhood-onset cerebellar atrophy has been highlighted by several studies. Steinlin and colleagues⁵ reviewed 47 patients with confirmed inborn errors of metabolism, of whom 14 had cerebellar involvement. They established criteria for pattern recognition of cerebellar abnormalities in metabolic disorders. Ramaekers and colleagues⁶ reviewed 78 patients (age

range, 1 year to 16 years) with cerebellar abnormalities, and were able to establish a diagnosis in 23 patients with predominant cerebellar atrophy. D'Arrigo and colleagues⁴ reviewed the clinical and neuroradiological features of 51 patients with structural abnormalities of the cerebellum (age range, 3 months to 14 years 9 months). They classified patients according to the type of cerebellar abnormality (hypoplasia or atrophy) and location (vermis or hemispheres), and were able to establish a diagnosis in 12 of 18 patients with cerebellar atrophy (Table 1).

Poretti and colleagues² published a comprehensive differential diagnosis of conditions associated with childhood-onset cerebellar atrophy. They emphasized the importance of MRI pattern recognition in guiding further investigations, and categorized cerebellar atrophy patterns as being isolated or associated with additional signs (ie, hypomyelination, progressive white matter abnormalities, basal ganglia involvement, or cerebellar white matter changes). The basic categories of MRI patterns described by these authors have been used in subsequent studies of cerebellar atrophy, including the present study.

Boddaert and colleagues³ proposed an MRI cerebellar algorithm to guide genetic or biochemical investigations for patients with cerebellar ataxia. They studied 158 patients who presented with cerebellar ataxia in childhood. Cerebellar atrophy was found present on 95 of 158 patients and a diagnosis was established in 46 of 95 patients with cerebellar atrophy, using the proposed algorithm. Terracciano and colleagues¹⁰ reviewed 34 patients who presented with ataxia and had cerebellar atrophy on MRI, and a diagnosis was established for 10 patients with the addition of muscle biopsy to their diagnostic protocol (Table 1).

Integration of neuroimaging patterns with clinical information is essential to appropriate investigation of childhood-onset cerebellar atrophy. Detailed clinical and radiological review of our cohort of 300 patients enabled identification of the most common conditions associated with cerebellar atrophy diagnosed at The Hospital for Sick Children over a 10-year period, and delineation of the cardinal clinical and radiological features of these conditions (summarized in Table 2). Age at symptom onset, the presence of neurological and non-neurological clinical features, and family history combined with analysis of neuroimaging patterns allowed for selection of metabolic and genetic investigations that yielded a diagnosis in 47% of our entire cohort in this retrospective study. We propose a diagnostic approach to the investigation of cerebellar atrophy in childhood based on the integration of specific neuroimaging patterns with clinical features (Figure 4).

This is the largest study of childhood-onset cerebellar atrophy published to date. Strengths of this study include the study site—a major pediatric tertiary care center with a province-wide referral base—all patients had equitable access to genetic testing due to the province-wide single-payer insurance system, and all MRIs were initially interpreted by a pediatric neuroradiologist and re-reviewed by a single pediatric neuroradiologist (S.B.). All clinical data was reviewed by 2 study authors (A.A.M. and G.Y.), which reduced bias due to inter-rater discrepancies. Weaknesses of the study included its retrospective design and potential referral bias. A major source of potential bias is the rapid discovery of genes associated with disorders causing cerebellar atrophy over the 10-year study period and the difference in availability of clinical genetic testing at different time points during the study.

Conclusion

The diagnostic approach to childhood-onset cerebellar atrophy requires integration of neuroimaging results with clinical information. The use of neuroimaging pattern-recognition is extremely useful in considering differential diagnoses and in the selection of further investigations. The discovery of new genes and availability of new clinical genetic tests will

necessitate constant revision and evaluation of the diagnostic approach to cerebellar atrophy in childhood.

Acknowledgments

This study was supported by a grant from the Rare Disease Foundation. This paper is based on a presentation given at the Neurobiology of Disease in Children Symposium: Childhood Ataxia, in conjunction with the 40th Annual Meeting of the Child Neurology Society, Savannah, Georgia, October 26, 2011. Supported by grants from the National Institutes of Health (2R13NS040925-14 Revised), the National Institutes of Health Office of Rare Diseases Research, the Child Neurology Society, and the National Ataxia Foundation. We thank Melanie Fridl Ross, MSJ, ELS, for editing assistance.

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Figure 1.

Clinical characteristics of patients with cerebellar atrophy in our cohort.

Abbreviations: MRI, magnetic resonance imaging.

Figure 2.

Neuroradiological patterns associated with cerebellar atrophy.

Mild vermian atrophy is present on T1W sagittal image (a) in an 8 year old with MELAS.

Note increased visualization of the interfoliate sulci of both anterior and posterior lobes.

Severe vermian atrophy is seen (b) in an 11 year old with AOA2. There is widening of the interfoliate sulci, loss of vermian height and a large infravermian cistern.

Mild hemispheric atrophy is present on FLAIR in a 14 year old with juvenile onset GM2 (c). The cortex is normal in signal (arrow). FLAIR axial (d) in a 6 year old with NCL demonstrates markedly increased signal intensity (arrow).

Figure 3.

Supratentorial clues to a diagnosis in cerebellar atrophy cases may be present.

Heterogeneous signal (arrow) is present in GM2 (a). Secondary demyelination of the posterior limb of the internal capsules (arrow) is seen on T2W axial (b) in NCL. There is also supratentorial atrophy. Severe hypomyelination is present on axial T2W image (c) in an 8 year old with H-ABC. Severe atrophy of the caudate (arrow) and putamina is present. Occipital stroke-like lesion (arrow) with cortical swelling is present on T2W image in another 8 year old with MELAS (d).

Figure 4.

Approach to investigation of childhood-onset cerebellar atrophy. Abbreviations: AFP, alpha-fetoprotein; AOA1/2, ataxia with oculomotor apraxia type 1 or type 2; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; ATLD, ataxia telangiectasia-like disorder; CA, cerebellar atrophy; CBC, complete blood count; CDG, congenital disorders of glycosylation; CK, creatine kinase; CSF, cerebrospinal fluid; DD/MR, developmental delay/mental retardation; DRPLA, dentatorubral pallidoluysian atrophy; ECG, electrocardiography; EMG, electromyography; EVP, evoked potentials; HABC, hypomyelination with atrophy of the basal ganglia and cerebellum; INAD, infantile neuronal axonal dystrophy; LAHH, leukoencephalopathy with ataxia, hypodontia, and hypomyelination; LFT, liver function tests; MRI, magnetic resonance imaging; NCL, neuronal ceroid lipofuscinoses; NCV, nerve conduction velocity studies; NPC, Niemann-Pick disease type C; PEHO, progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy; PMD, Pelizaeus-Merzbacher disease; SCAN1, spinocerebellar ataxia, autosomal recessive with axonal neuropathy.

Table 1**Summary of Patients Reported With Cerebellar Atrophy**

Study	Total	Unknown	Known
Present study	300	158 (52%)	142 (48%)
			37 Mitochondrial (26%)
			25 Neuronal ceroid lipofuscinoses (17.7%)
			14 Ataxia telangiectasia & AOA1 or 2 (9.2%)
			10 Late-onset GM2 (7%)
			8 Infantile neuroaxonal dystrophy (5.6%)
			8 Chromosomal (5.6%)
			5 SCA and <i>CACNA1A</i> mutations (3.5%)
			7 CDG1 (5%)
			3 Cockayne syndrome (2.17%)
			3 Marinesco-Sjögren syndrome (2.1%)
			4 Pelizaeus-Merzbacher disease (2.8%)
			2 HABC (1.4%)
			1 Adrenoleukodystrophy (0.7 %)
			1 Metachromatic leukodystrophy (0.7 %)
			14 Other genetic causes (see text)
Boddaert and colleagues (2010)	95	49 (52%)	46 (48%)
			23 Respiratory chain disorder
			21 CDG Ia
			1 INAD
			1 Sulphite oxidase deficiency
Ramaekers and colleagues (1997)	37	14 (37%)	23 (62%)
			5 Neuronal ceroid lipofuscinosis
			3 Pontocerebellar hypoplasia type 2
			3 Mitochondrial
			2 CDG1
			2 Pelizaeus-Merzbacher disease
			2 Ataxia teleangiectatica
			1 Pontocerebellar hypoplasia type I
			1 PEHO syndrome
			1 Fatty aldehyde dehydrogenase deficiency
			1 Boucher-Neuhauser syndrome ⁺
			1 Mannosidosis
			1 Marinesco-Sjogren syndrome
Terracciano and colleagues (2011)	34*	24 (70%)	10 (29%)
			1 Coenzyme Q10
			1 Marinesco-Sjogren syndrome
			8 low CoQ10 levels in muscle biopsy and decrease activity of complex II and III (no mutations detected)
D'Arrigo and colleagues (2005)	18	6 (33%)	12 (67%)

Study	Total	Unknown	Known
Steinlin and colleagues (1998)	14	NA **	3 CDG 1a
			2 Cockayne syndrome
			2 INAD
			2 Methylmalonic aciduria with homocystinuria
			1 Ataxia-telangiectasia
			1 PEHO-like syndrome
			1 Mitochondrial encephalopathy (complex IV)
			5 Neuronal ceroid lipofuscinosis (all types)
			4 Mitochondrial diseases
			2 Niemann-Pick disease type C
			1 CDG1a
			1 Late-onset GM2 gangliosidosis
			1 Pelizaeus-Merzbacher disease

⁺Chorioretinal dystrophy, spinocerebellar ataxia, and hypogonadotropic hypogonadism

^{*}Ruled out known common conditions like ataxia-telangiectasia syndrome, autosomal dominant ataxia type 2, and congenital disorders of glycosylation syndrome

^{**}Study included only patients with confirmed inborn errors of metabolism

Abbreviations: AOA 1 or 2, ataxia with oculomotor apraxia type 1 or type 2; CDG, congenital disorders of glycosylation; HABC, hypomyelination with atrophy of the basal ganglia and cerebellum; INAD, infantile neuronal axonal dystrophy; PEHO, progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy.

Table 2
Summary of Clinical and Radiological Features of Common Conditions Associated With Cerebellar Atrophy

Clinical													Radiological						
Onset	Disease	Significant DD/MR	Regression	Spasticity and/or extrapyramidal	Seizures	Polyneuropathy	Apraxia	Ocular findings			Cerebellar atrophy			↑ or ↓ T2-weighted signal			Hypomyelination diffuse	Other or focal WM abnormalities	
								Cataract	Optic atrophy	Retinal	Additional signs	Early	Late	Cerebellar cortex T2 signal	Brain stem	Calcifications			Putamina/caudate
Infancy (0–1 y)	Pontocerebellar hypoplasia type 1 and 2	•		•															
	Infantile neuroaxonal dystrophy	•	•	•	•												↓		• POR
	Pelizaeus-Merzbacher disease	•		•													↓		• Early
	CDG1a	•		•	•	•											↓		•
	Infantile-onset spinocerebellar ataxia			•	•	•													• CBLL
Late infancy (1–2 y)	Cockayne syndrome		•																
	NCL (infantile)	•	•	•	•													↓	• PV
	SCAN1				•	•													
	Mevalonate kinase deficiency	•																	
	3-methylglutaconic aciduria	•		•	•												↑	↑	•
	Salla disease																		
	PEHO			•															
	HABC	•		•	•												↓	↓	
	Ataxia telangiectasia			•															
	Marinesco-Sjögren syndrome	•																	
Early and late childhood (2–18 y)	NCL (late infantile)	•	•	•	•													↓	•
	Ataxia with oculomotor apraxia 1			•		•													
	Ataxia with oculomotor apraxia 2					•													
	Ataxia telangiectasia-like disorder																		
	Spastic ataxia of Charlevoix-Saguenay			•		•													• SC
	Cerebrotendinous xanthomatosis	•				•													
	Myoclonic epilepsy of Unverricht and Lundborg																		•

Clinical											Radiological											
Onset	Disease	Significant DD/MR	Regression	Spasticity and/or extrapyramidal	Seizures	Polyneuropathy	Apraxia	Ocular findings			Cerebellar atrophy			↑ or ↓ T2-weighted signal			Other or focal WM abnormalities					
								Cataract	Optic atrophy	Retinal	Additional signs	Early	Late	Cerebellar cortex T2 signal	Brain stem	Calcifications		Putamina/caudate	GP	Thalamus		
Variable	Coenzyme Q10 deficiency	•	•		•	•				•	Highly variable phenotype		•									
	Episodic ataxia I			•	•						Myokymia		•									
	CACNA1A-related disorders				•						Vertigo; interictal nystagmus		•									
	LAHH	•									Hypodontia		•									
	Juvenile DRPLA		•	•	•								•			•				• PV		
	NCL (late infantile/ juvenile)	•	•	•	•									•					↑			
	Late-onset GM2 gangliosidosis		•	•	•						Behavioral disturbance											
	Mitochondrial	•	•	•	•	•				•	Multisystem involvement		•		•		•		↑	↑		•
	Spinocerebellar ataxia(s)			•	•	•					Phenotypic variability				• SC							•
	Niemann-Pick disease type C		•	•	•	•					Vertical gaze palsy; visceromegaly											• PV
	Adrenoleukodystrophy		•	•	•	•					Adrenal dysfunction			•								• CBLL

DD, developmental delay; MR, mental retardation; GP, globus pallidus; WM, white matter; CDG, congenital disorders of glycosylation; NCL, neuronal ceroid lipofuscinosis; SCAN1, spinocerebellar ataxia, autosomal recessive with axonal neuropathy; PEHO, progressive encephalopathy with edema, hypersarhythmia, and optic atrophy; HABC, hypomyelination with atrophy of the basal ganglia and cerebellum; LAHH, leukoencephalopathy with ataxia, hypodontia, and hypomyelination; DRPLA, dentatonubral pallidolusyan atrophy; SC, spinal cord; POR, peritrigonal optic radiations; CBLL, cerebellar; PV, periventricular.