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ORIGINAL ARTICLE

Neuro-Ophthalmological Findings in Children and Adolescents with Chronic Ataxia

Michael S. Salman[1,2] and Bernard N. Chodirker[2,3]

[1]*Section of Pediatric Neurology, Department of Pediatrics and Child Health, College of Medicine, Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada,* [2]*Winnipeg Children's Hospital, Winnipeg, Manitoba, Canada,* [3]*Section of Genetics and Metabolism, Department of Pediatrics and Child Health, and Department of Biochemistry, College of Medicine, Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada*

ABSTRACT

Chronic ataxia is a challenging problem in paediatric neurology. It is caused by a multitude of disorders that at least initially have similar or non-specific phenotype. Some of these disorders have associated neuro-ophthalmological signs (N-OS). The aims of this study are to describe the N-OS and their frequencies in general and by disease aetiology in paediatric patients with chronic ataxia. The authors identified 184 patients under age 17 years with chronic ataxia (>2 months duration or recurrent) during 1991–2008 from multiple sources. Diagnoses and N-OS were ascertained following charts review. Mean age (SD) was 15 (7.7) years. Median duration of follow-up was 6.4 years. There were 214 N-OS in 115 patients (median = 2, range = 1–5 N-OS/patient). Strabismus was present in 29.3% of patients, nystagmus 27.7%, impaired smooth pursuit 23.4%, hypometric saccades 10.3%, decreased visual acuity 9.2%, abnormal optic discs 8.7%, abnormal pupillary examination 2.7%, hypermetric saccades 2.2%, impaired ductions 1.6%, and abnormal visual fields in 1.1% of patients. N-OS were reported most commonly among patients with the following disorders (commonest N-OS): hypoxic-ischaemic encephalopathy following birth (strabismus), episodic ataxia (nystagmus), neuronal ceroid lipofuscinosis (abnormal optic discs), neuronal migration disorder (strabismus), ischaemic stroke (nystagmus), Joubert syndrome–related disorders (strabismus), leukodystrophy (nystagmus), Friedreich ataxia (hypometric saccades, impaired smooth pursuit, nystagmus), mitochondrial disease (strabismus, nystagmus), ataxia telangiectasia (impaired smooth pursuit), and Angelman syndrome (strabismus). N-OS occur commonly in children with chronic ataxia. Although non-specific, they vary with disease aetiology, potentially aiding in the assessment of these patients.

Keywords: Chronic ataxia, neuro-ophthalmology, paediatrics

INTRODUCTION

Ataxia is a relatively common presentation in paediatrics. The annual crude incidence of chronic ataxia is 3.2 per 100,000 children and adolescents less than 17 years old.[1] Ataxia is caused by a multitude of disorders.[2] The clinical features, their evolution, and a detailed family history may point to the diagnosis.[2] Brain magnetic resonance imaging (MRI) remains an important investigation for establishing the diagnosis and excluding sinister aetiologies of ataxia such as brain tumour or haemorrhage.[3] For many benign aetiologies, e.g., some infectious or post-infectious cerebellitis, the ataxia resolves within several days to a few weeks. In patients with persisting or recurrent ataxia, the diagnosis may be challenging especially if neuroimaging is normal or shows non-specific abnormalities.

The visual and ocular motor systems may be affected by many disorders that are associated with ataxia.[2,4] Therefore, neuro-ophthalmological symptoms and signs (N-OS) should be looked for in these

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Correspondence: Michael S. Salman, MBBS, PhD, Section of Pediatric Neurology, Children's Hospital, AE 308, 820 Sherbrook Street, Winnipeg, MB R3A 1R9, Canada. E-mail: msalman@hsc.mb.ca

patients because they may aid in their assessment. In prior studies of a large cohort of children with chronic ataxia, we reported on the epidemiology and ethnic distribution of the various aetiologies encountered.[1,5] In this study, our aims were to describe the N-OS and their frequencies in general and by disease aetiology more specifically in paediatric patients with chronic ataxia in Manitoba, Canada. We hypothesised that neuro-ophthalmological features occur commonly in diseases that cause paediatric chronic ataxia and they vary with disease aetiology.

METHODS

Several databases and hospital information resources were searched to find paediatric patients with chronic ataxia, who received care at Winnipeg Children's Hospital over the period 1991–2008. The patients were assessed by one or more of the following specialists: paediatric neurologists, ophthalmologists, neuro-ophthalmologists, geneticists, and metabolic specialists. Methodological details have already been described.[1] Ethical approval for the study was granted by the Research Ethics Board of the University of Manitoba. Relevant information was collected from the patients' hospital medical charts, including age, gender, aetiology, and N-OS, as follows: decreased visual acuity (best corrected is less than 20/40 from any cause including amblyopia and cortical visual impairment); abnormal visual fields on clinical examination or perimetry; abnormal pupillary examination including abnormal pupillary size, reaction to light or accommodation, or relative afferent pupillary light defect; abnormal optic discs on funduscopy, e.g., pallor; impaired ductions (i.e., eye movements checked in each eye alone) caused by III, IV, or VI cranial nerve palsy; saccadic dysmetria; saccadic (jerky) smooth ocular pursuit; pathological nystagmus; and ocular misalignment, e.g., strabismus.

The inclusion criteria were patients who presented to Winnipeg Children's Hospital, the sole paediatric tertiary hospital in the province of Manitoba, with chronic ataxia during 1991–2008 and were under 17 years old at the time of their presentations. We defined chronic ataxia as persistent or recurrent ataxia that is more than 2 months in duration. We excluded patients whose ataxia was not a predominant feature of their disorder or if their ataxia was caused solely or primarily by diseases of the vestibular system and peripheral nerves, or by primary brain tumours. Patients who were clumsy or had developmental coordination disorder were also excluded.

Statistical analyses were conducted using a Statistical Package for Social Sciences, version 22.0 (IBM, Armonk, NY, USA). Normality of the data was investigated using mean, median, standard deviation (SD), skewness, and kurtosis. The data were described using the mean and SD if they were normally distributed or median and ranges if they had skewed distribution. The frequency of each of the N-OS in general and for different aetiologies was expressed as a percentage.

RESULTS

One hundred and eighty-four patients (92 males) met the inclusion criteria. Most patients ($n = 177$) resided in the province of Manitoba, Canada, during the study period. Seven patients from neighbouring provinces were also included, since they resided in towns or villages whose medical needs were served by Winnipeg Children's Hospital. The mean age (SD) of the patients was 15.0 (7.7) years at the end of the study period in 2008. The median age (range) at symptom onset was 1.25 (0–16.9) years, whereas the median age (range) at first clinical assessment was 2.5 (0–16.9) years. The median duration (range) of follow-up was 6.4 (0–28.1) years. There were 10 sibling pairs with the following disorders: acetazolamide-responsive episodic ataxia (2 pairs), Friedreich ataxia (2 pairs), neuronal migration disorder, non-progressive ataxia with developmental delay of unknown aetiology, Salla disease, neuronal ceroid lipofuscinosis, ataxia telangiectasia, and autosomal recessive cerebellar hypoplasia in the Hutterites (dysequilibrium syndrome). Further demographic details have already been published on this cohort.[1] The aetiology of chronic ataxia was known in 128 patients. One hundred and fifteen of 184 patients had 214 N-OS (median = 2, range: 1–5 N-OS per patient). The aetiology was known in 82 of these 115 patients. The 82 patients with the known disease aetiology had 148 N-OS (median = 1.5, range: 1–5 N-OS per patient).

The three most common N-OS were strabismus, which was present in 54 patients, nystagmus in 51, and impaired smooth pursuit in 43 patients. Further details on the frequency of the N-OS are shown in Table 1. Among the more frequent disease aetiologies encountered in our cohort with at least five patients affected, N-OS were reported in at least 80% of patients with hypoxic-ischaemic encephalopathy following birth, acetazolamide-responsive episodic ataxia, neuronal ceroid lipofuscinosis types 1–3, Joubert syndrome–related disorders, and disorders of neuronal migration. Table 2 displays other disorders commonly associated with N-OS, the most common N-OS, and their frequencies.

The following disorders were associated with the highest number of N-OS: neuronal ceroid lipofuscinosis types 1–3, a hypomyelinating leukodystrophy of unknown aetiology, genetically confirmed acetazolamide-responsive episodic ataxia, suspected pontocerebellar hypoplasia type 3 (5 N-OS in each disorder), and multiple sclerosis (4 N-OS). In the Appendix,

Tables A and B show details of the neuro-ophthalmological findings reported in our cohort by disease aetiology. Table C in the Appendix highlights the main features of some of the syndromes encountered in our cohort.

Patients with neuronal ceroid lipofuscinosis types 1–3 accounted for the most frequent cause of decreased visual acuity (23.5%), abnormal pupillary reaction to light (60%), and abnormal optic discs (31.3%). Acetazolamide-responsive episodic ataxia and a hypomyelinating leukodystrophy of unknown aetiology accounted for most patients with hypermetric saccades (75%). Patients with ataxia telangiectasia, ischaemic stroke involving posterior fossa structures, and acetazolamide-responsive episodic ataxia accounted for 23.3% of impaired smooth ocular pursuit, whereas patients with the latter two disorders accounted for 21.6% of nystagmus. Patients with Friedreich ataxia had a variety of ocular motor abnormalities (hypometric saccades, impaired smooth ocular pursuit, nystagmus), whereas strabismus and optic disc abnormalities were infrequent. Surprisingly, saccade initiation delay (ocular motor apraxia) was not reported.

TABLE 1 The frequency of neuro-ophthalmological features in 115 paediatric patients with chronic ataxia.

Neuro-ophthalmological features	Frequency (%)
Afferent visual system abnormalities	
Decreased visual acuity	17 (9.2)
Abnormal optic discs	16 (8.7)
Abnormal pupillary examination	5 (2.7)
Abnormal visual fields	2 (1.1)
Efferent visual system abnormalities	
Strabismus	54 (29.3)
All types of pathological nystagmus	51 (27.7)
Gaze-evoked nystagmus*	27 (14.7)
Impaired smooth pursuit	43 (23.4)
Hypometric saccades	19 (10.3)
Hypermetric saccades	4 (2.2)
Impaired ductions	3 (1.6)

*Subset of all patients with nystagmus.

DISCUSSION

Some neuro-ophthalmological signs occur relatively commonly in otherwise healthy children. For example, the prevalence of strabismus is 0.29% in school-aged children, whereas the prevalence of amblyopia is 1.9% in preschool- and school-aged children.[6,7] In our investigation, a variety of N-OS were reported quite frequently in children with chronic ataxia. Despite being non-specific in general, N-OS varied with disease aetiology, which may potentially aid in the initial assessment of these patients.

Ocular motor abnormalities and strabismus as opposed to afferent visual system abnormalities predominated in our cohort, likely because of the high prevalence of disorders affecting structures within the posterior fossa. The brainstem and cerebellum are essential for processing various types of eye movements and also participate in ocular axes alignment.[8,9] Saccadic smooth pursuit and gaze-evoked nystagmus occur with flocculus/parafloccullus lesions, whereas saccade dysmetria (hypometria or

TABLE 2 Paediatric disorders with chronic ataxia in which neuro-ophthalmological signs (N-OS) occur frequently are displayed with the commonest N-OS and their frequencies.

Disorders with at least five patients	Number of patients with N-OS/Total number of patients with the disorder (%)	Commonest N-OS	Number of patients with the commonest N-OS
Hypoxic-ischaemic encephalopathy following birth	5/5 (100)	Strabismus	4
Episodic ataxia*	6/7 (85.7)	Nystagmus	5
Neuronal ceroid lipofuscinosis‡	5/6 (83.3)	Abnormal optic discs	5
Joubert syndrome–related disorders	4/5 (80)	Strabismus	4
Neuronal migration disorder	4/5 (80)	Strabismus	4
Ischaemic stroke†	7/9 (77.8)	Nystagmus	6
Friedreich ataxia	5/7 (71.4)	Hypometric saccades/ impaired SP/nystagmus	2 for each sign
Mitochondrial disease	6/9 (66.7)	Strabismus/nystagmus	2 for each sign
Severe epilepsy syndrome	3/5 (60)	Impaired visual acuity	2
Ataxia telangiectasia	6/13 (46.2)	Impaired SP	4
Angelman syndrome	5/16 (31.3)	Strabismus	3

SP = smooth pursuit.
*Acetazolamide-responsive episodic ataxia, proven on DNA testing in three patients, whereas the other four patients have positive family history of episodic ataxia that was not confirmed on DNA testing.
‡Consists of five patients with types 1 and 2 and one patient with type 3.
†Consists of one prenatal and eight postnatal thrombo-embolic and vasculitic aetiologies.

hypermetria), impaired smooth pursuit initiation, and horizontal ocular misalignment result from lesions of the dorsal vermis and posterior portion of the fastigial nucleus.[8]

Several factors play an important role in explaining the different types of the N-OS reported. Disease aetiology and the site of brain pathology are important determinants of N-OS. With disorders that primarily involve the cerebellum, e.g., episodic ataxia, ocular motor symptoms, and signs are expected to predominate. On the other hand, in neurodegenerative diseases that additionally involve the cerebral cortex and optic nerves, e.g., neuronal ceroid lipofuscinosis, N-OS that are suggestive of visual pathway dysfunction will also be present.[10] The majority of our patients with neuronal ceroid lipofuscinosis had pale optic discs and poor vision.

Supratentorial structures such as the cerebral cortex, thalamus, and basal ganglia are also known to participate in ocular motor control[11] and in the coordination of limbs movements.[3] Therefore, it is important to look for other clinical features, such as epilepsy and pyramidal tract signs, to help localise the site(s) of disease pathology further and beyond posterior fossa structures.

Although strabismus is a non-specific and frequent sign encountered in paediatric patients in general, it occurs quite frequently (about 50%) in patients with cerebral palsy.[12] We also found that diseases associated with non-progressive cerebral or cerebellar abnormalities, e.g., hypoxic-ischaemic encephalopathy following birth, disorders of neuronal migration, and Joubert syndrome–related disorders were associated with high prevalence of strabismus. On the other hand, nystagmus is seen more frequently in children with ataxic or ataxia/spastic cerebral palsy.[12] In our study, nystagmus was commonly reported in patients with diseases that involve structures within the posterior fossa such as posterior circulation ischaemic stroke or acetazolamide-responsive episodic ataxia. The cerebellum and several nuclei in the brainstem such as the nucleus prepositus hypoglossi and medial vestibular nucleus are essential for gaze holding, and dysfunction in these structures cause nystagmus.[8,11]

Friedreich ataxia is associated with a variety of N-OS such as impaired smooth pursuit, dysmetric saccades, and nystagmus, whereas optic atrophy is rare,[13] consistent with our study findings. Dysfunction in extracerebellar structures projecting to the cerebellum in Friedreich ataxia may be responsible in part for some of the eye movement abnormalities[13]; however, the range of eye movement abnormalities suggest that neurological dysfunction also involves brainstem, vestibular, and cortical pathways.[14]

Impaired smooth pursuit was more frequently seen in patients with ataxia telangiectasia. This is consistent with involvement of the cerebellum in this disorder and emphasises the important role of the cerebellum in processing smooth pursuit.[8]

Age at disease onset, age at which the medical assessment was performed, the examiners' medical specialty and experience, adequate documentation in the hospital chart, and stage of the disease and its natural history are other important determinants that likely influenced the frequency of the N-OS reported in this investigation. As such, the frequencies reported in this investigation represent the minimum figures for the cohort. The same factors may also explain the reason for the absence of some N-OS in diseases that are known to be associated with certain N-OS, e.g., saccade initiation delay (ocular motor apraxia), dysmetric saccades, and saccadic smooth pursuit in Joubert syndrome–related disorders.

Our study limitations include missing patients with chronic ataxia during the study period due to errors in coding these patients. However, our detailed and multiple search strategies likely minimised this potential problem.[1] Our investigation is based on a hospital sample and assessments by multiple specialists, which may bias our findings. As in all retrospective studies, some information was missing, inaccurate, poorly or inadequately documented (e.g., type of nystagmus), or incomplete. Therefore, the figures represent the minimum frequency of N-OS expected in children and adolescents with chronic ataxia. When a patient was not seen by an ophthalmologist, a dilated funduscopy examination was not performed. Therefore, macular or peripheral retinal abnormalities may have been missed in some patients. Finally, the ability to make definitive diagnoses between 1991 and 2008 changed significantly with more advanced genetic and MRI techniques.

In conclusion, our investigation underscores the importance of a thorough examination of the visual and ocular motor systems, as reflected in the high frequency of N-OS and their variations with disease aetiology in paediatric chronic ataxia. Such information may aid in the assessment of these challenging patients.

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APPENDIX

TABLE A The frequency of afferent visual system abnormalities in disorders associated with pediatric chronic ataxia.

Disorder	Number of patients	Decreased visual acuity	Abnormal visual fields	Abnormal pupillary exam	Abnormal optic discs
Angelman syndrome	16	1			
Ataxia telangiectasia	13	2			
Postnatal stroke†	11		1		1
Friedreich ataxia	7				1
Acetazolamide-responsive episodic ataxia	7				1
Neuronal ceroid lipofuscinosis	6	4	1	3	5
Hypoxic ischemic encephalopathy following birth	5	1			1
Neuronal migration disorder	5	1			
Severe epilepsy syndrome	5	2			
Brain trauma	2				
Dandy-Walker syndrome	2	1			
Marinesco-Sjogren syndrome	2	1			
Multiple sclerosis	2			1	2
Prematurity	2				1
Neuronopathic Gaucher disease	1			1	
Hypomyelinating leukodystrophy of unknown etiology	1	1			1
Pontocerebellar hypoplasia type 3	1				1
Wernicke's encephalopathy	1				1
Acute disseminated encephalomyelitis	1				

†Eight patients had postnatal ischemic stroke and three had postnatal hemorrhagic stroke. No neuro-ophthalmological signs were reported in the single patient with the prenatal ischemic stroke.

TABLE B The frequency of efferent visual system abnormalities in disorders associated with pediatric chronic ataxia.

Disorder	No. of patients	Impaired ductions	Hypometric saccades	Hypermetric saccades	Impaired SP	Str	All Nys (GEN)
Angelman syndrome	16					3	1 (1)
Ataxia telangiectasia	13		1		4	1	2 (2)
Postnatal stroke†	11	1			3	4	6 (2)
Mitochondrial disorder	9		1		1	2	2
Friedreich ataxia	7		2		2	1	2 (1)
Acetazolamide-responsive episodic ataxia	7			2	3	1	5 (4)
Neuronal ceroid lipofuscinosis	6					1	
Hypoxic ischemic encephalopathy following birth	5		1		2	4	1
Joubert syndrome related disorders	5		1			4	1
Neuronal migration disorder	5					4	
Severe epilepsy syndrome	5						1
Rett syndrome	4					1	
Salla disease	4				1	1	1
Brain trauma	2	1				1	
Cerebellar hypoplasia in the Hutterites (dysequilibrium syndrome)	2				1	1	
Dandy-Walker syndrome	2	1				1	1
Marinesco-Sjogren syndrome	2					2	1
Multiple sclerosis	2				1	1	1 (1)
Prematurity	2					1	1 (1)
Ataxia telangiectasia- like disease	1		1		1		1 (1)
Acute disseminated encephalomyelitis	1				1		1 (1)
Glucose transporter type 1 deficiency	1		1			1	
Homocystinuria	1					1	
Hypomyelinating leukodystrophy of unknown etiology	1			1	1		1 (1)
Adrenoleukodystrophy	1						1
Neuronopathic Gaucher disease	1		1				
Soto syndrome	1				1	1	1 (1)
Pontocerebellar hypoplasia type 3	1		1		1	1	1 (1)
Wernicke's encephalopathy	1						1 (1)
Post infectious ataxia	1				1		1

Note: number, SP: smooth pursuit, str: strabismus, nys: nystagmus, GEN: gaze evoked nystagmus (a type of pathological nystagmus), † Eight patients had postnatal ischemic stroke and three had postnatal hemorrhagic stroke. No neuro-ophthalmological signs were reported in the single patient with the prenatal ischemic stroke.

TABLE C Main clinical features of the syndromes encountered in our cohort of pediatric patients with chronic ataxia.

Syndrome	Main clinical features	Diagnostic test
Angelman syndrome	Intellectual disability, developmental delay, no or minimal use of words, epilepsy, ataxia, tremulous limbs, hypotonia, happy attitude, and microcephaly	Genetic testing for impaired expression of the maternal allele for the *UBE3A* gene
Cerebellar hypoplasia in the Hutterites (dysequilibrium syndrome)	Intellectual disability, developmental delay, hypotonia, severe disturbance of posture and balance, strabismus, and cerebellar hypoplasia and simplified gyral pattern on brain MRI	Genetic testing for mutations in the *VLDLR* gene
Glucose transporter type 1 deficiency	Intractable seizures, developmental delay, hypotonia, and a movement disorder consisting of ataxia, spasticity, and dystonia	CSF/blood glucose ratio of 0.33–0.37 and CSF glucose <2.2 mmol/l, genetic testing
Joubert syndrome and related disorders	Developmental delay, intellectual disability, dysmorphic features, hypotonia, ataxia, nystagmus and other ocular motor abnormalities, breathing abnormalities, and retinal, hepatic or renal involvement in some	Molar tooth sign on Brain MRI. Molecular genetic testing should also be considered

(*continued*)

Syndrome	Main clinical features	Diagnostic test
Marinesco-Sjogren syndrome	Congenital cataracts, intellectual disability, hypotonia, cerebellar ataxia, progressive myopathy, short stature, skeletal deformities, and hypergonadotrophic hypogonadism,	Genetic testing for *SIL1* gene
Neuronal ceroid lipofuscinosis	Epilepsy, developmental regression, myoclonus, dyskinesia, ataxia, spasticity, and impaired vision	Enzymatic assays or DNA testing
Neuronopathic Gaucher disease	Horizontal supranuclear gaze palsy, bilateral 6^{th} nerve palsy followed by full extraocular paralysis, trismus, progressive spasticity, dysphagia, and seizures	Assay of acid beta-glucocerebrosidase in leukocytes, fibroblasts, or urine
Pontocerebellar hypoplasia type 3	Severe developmental delay, progressive microcephaly, hypotonia, optic atrophy, hyperreflexia, and pontocerebellar hypoplasia on brain MRI	Brain MRI and clinical features, (gene is mapped to chromosome 7q11–q21)
Rett syndrome	Loss of purposeful hand use, vocabulary loss, intellectual disability, head growth deceleration, gait abnormalities, scoliosis, autistic behavior, hand wringing, ataxic movements, spasticity, and hyperpnea	Testing for *MECP2* gene
Salla disease	Developmental delay, ataxia, subtle coarse facial features, and brain MRI findings of hypomyelination and hypoplastic corpus callosum	Urine sialic acid, genetic testing for mutations in *SLC17A5* gene
Soto syndrome	Overgrowth and learning disability	Clinical features and *NSD1* gene testing. If negative then *NFIX* gene testing