Non-progressive congenital ataxia with cerebellar hypoplasia in three families

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Abstract

Aim: Non-progressive ataxias with cerebellar hypoplasia are a rarely seen heterogeneous group of hereditary cerebellar ataxias. *Method:* Three sib pairs from three different families with this entity have been reviewed, and differential diagnosis has been discussed. *Results:* In two of the families, the parents were consanguineous. Walking was delayed in all the children. Truncal and extremity ataxia were then noticed. Ataxia was severe in one child, moderate in two children, and mild in the remaining three. Neurological examination revealed horizontal, horizonto-rotatory and/or vertical nystagmus, variable degrees of mental retardation, and pyramidal signs besides truncal and extremity ataxia. In all the cases, cerebellar hemisphere and vermis hypoplasia were detected in MRI. During the follow-up period, a gradual clinical improvement was achieved in all the children.

Conclusion: Inheritance should be considered as autosomal recessive in some of the non-progressive ataxic syndromes. Congenital non-progressive ataxias are still being investigated due to the rarity of large pedigrees for genetic studies. If further information on the aetiopathogenesis and clinical progression of childhood ataxias associated with cerebellar hypoplasia is to be acquired, a combined evaluation of metabolic screening, long-term follow-up and radiological analyses is essential.

Key Words: *Cerebellar hypoplasia, congenital non-progressive ataxic syndromes*

Hereditary ataxic syndromes are not common during childhood. Friedreich's ataxia and ataxia-telangiectasia are the two best-known examples of such rare syndromes characterized both by their progressive nature and ability to involve more than one neurological system [1]. An even rarer and clinically non-progressive form of hereditary ataxia is the one accompanied by cerebellar hypoplasia and exhibiting the same clinical signs as the cerebellar system. Some forms of hereditary ataxia syndromes together with cerebellar hypoplasia are extremely rare, and their pathophysiology is still poorly understood. To the authors' knowledge, there are only a few studies on the long-term follow-up results of patients with this entity; besides, molecular studies on this entity are also rare [2–5].

Methods and patients

In this study, the clinical and laboratory findings of three sib pairs with non-progressive ataxia together with cerebellar hypoplasia have been evaluated. They were followed up in our department for 4–8 y. The factors indicating the aetiology, clinical features, prognosis and the possible genetic transmission have been discussed.

Patients 1 and 2 (first family)

Two brothers aged 5 and 7 of unrelated parents presented with a history of slurred speech and difficulty of gait. Both cases were born at term after an uneventful pregnancy and delivery. They had a history of markedly delayed milestones, and they had been unable to keep their balance while walking at 2.5 y. Neurological examination revealed cerebellar dysarthria, mild/moderate truncal ataxia and dysmetria more significant in the lower extremities. Both cases had horizontal nystagmus, with moderate frequency and amplitude, accompanied by vertical nystagmus in one. Deep tendon reflexes were brisk, and there was bilateral Babinski's sign in both cases. The IQ score of the elder brother was 70, and that of the younger was 68. During the 8-y follow-up period, progression was not observed in either of the brothers. On the contrary, there was a gradual relative improvement. The elder case, who was 15 y of age when last examined, still had nystagmus and some difficulty in tandem walking, with hyperreflexia in the lower extremities. Although the younger case significantly improved, mild/moderate truncal ataxia was still noticeable, and he was unable to read or write at the age of 13.

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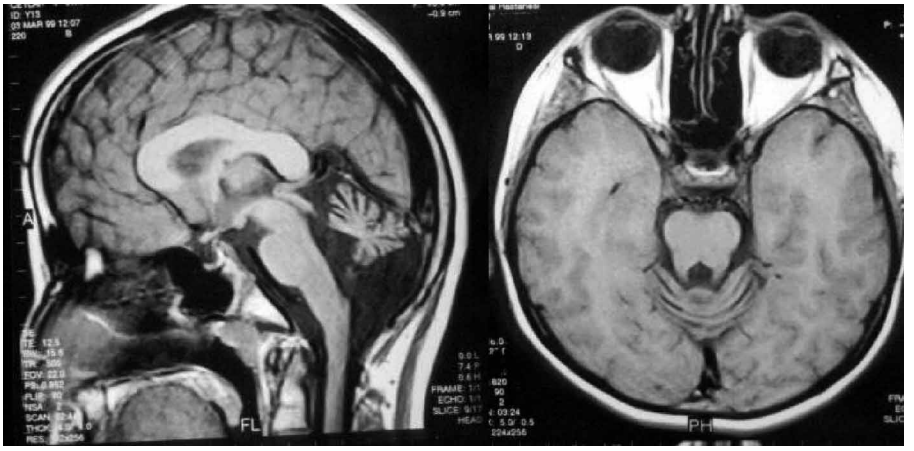

Figure 1. First family, 1st child: cerebellar vermian hypoplasia (T1 axial and sagittal).

Patients 3 and 4 (second family)

A female child aged 11 and a male aged 6 of consanguineous parents with three sons and two daughters presented with impaired walking and speech difficulty. The relatives did not have a similar history. There was a history of difficult delivery in both cases. The elder one walked with assistance until 7–8 y. She was reported to have walked unaided for the previous 2 y. The younger one could walk with assistance at age 5, after which age his walking gradually improved. Neurological examination revealed brisk deep tendon reflexes significant in the lower extremities, cerebellar findings and moderate/severe truncal ataxia in both cases. According to the Denver Developmental Scale, the elder patient's development corresponded with that of a 6-y-old child and the younger patient's with that of a 4-y-old child. They were followed up for 4 y, and minimal improvement in walking was achieved in both, with the result that their walking was still mildly/moderately ataxic.

Patients 5 and 6 (third family)

A 12-y-old boy and a 6-y-old girl of consanguineous parents presented with slowness in speech and impaired walking. Pregnancy and delivery of both the patients were normal. The elder one walked at 2. However, he was never able to keep his balance properly while doing so. He was physically slack compared to his peers, spoke slowly and often fell down while walking. The younger child walked at 1.5. Though she could not balance well in her first years, her walking gradually improved. On neurological examination, the patients were discovered to have dysarthria, bilateral dysmetria more significant in the left, disdiadochokinesia, hypotonia in the extremities, mild/moderate truncal ataxia and increased reflex activity in the lower extremities. The elder patient's IQ score was 90, and his sister's was 68. The follow-up period was 4.5 y in these patients.

There was no history of neurological diseases in any of the relatives. In neither the cases nor their parents were the below disorders discovered: optic atrophy, skeletal anomaly, any skin lesions or telangiectasias, or other organ involvement. The haemogram, cholesterol, lipid electrophoresis, IgA, M, G, alpha-fetoprotein, TORCH antibodies, abdominal ultrasonography, ECG, telecardiography and conventional skeletal X-rays were all normal in all the children. No metabolic diseases were detected in the below tests: screening tests for inborn errors (amino aciduria, quantitative amino-acid profile, organic aciduria, tandem mass acyl carnitine profile), histochemical staining of muscle biopsy specimens, serum lactate and pyruvate levels, serum transferrin level for glycosylation disorders, and galactosidase enzymes activities for lysosomal storage diseases.

Below is an overall analysis of the findings of the three families. Cranial CT and MRIs of all the families revealed that the cases had cerebellar hypoplasia prominent in the vermis (Figures 1–9); spinal MRIs of the cases in the third family were all normal, and so were the MRIs of the two healthy brothers in the first family, who had no ataxic symptoms.

Discussion

In clinical practice, Friedreich's ataxia, ataxia-telangiectasia and abetalipoproteinaemia are widespread among ataxic syndromes characterized by autosomal recessive (AR) inheritance [1]. Some conditions with cerebellar involvement can be summarized as follows: disturbed metabolism of amino and organic acid (Hartnup's disease, maple syrup disease, etc.), urea cycle defects, lactic acidosis, congenital disorders of glycosylation syndrome, and disorders of lysosomal

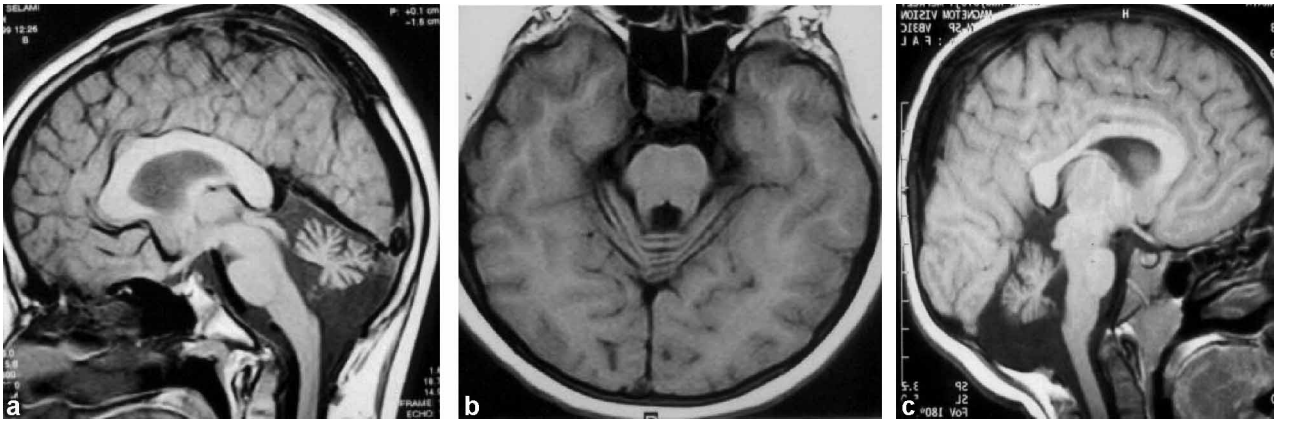

Figure 2. (a) First family, 2nd child: cerebellar hypoplasia (T1 sagittal); (b) 2nd family, 1st child: cerebellar hypoplasia prominent in the vermis (T1 axial); (c) 2nd family, 2nd child: cerebellar hypoplasia (T1 sagittal).

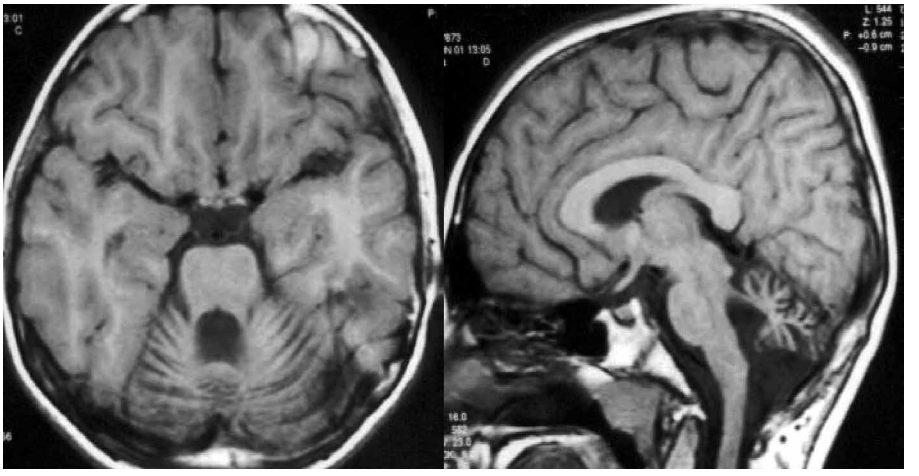

Figure 3. Third family, 1st child: cerebellar hypoplasia prominent in the vermis (T1 axial and sagittal).

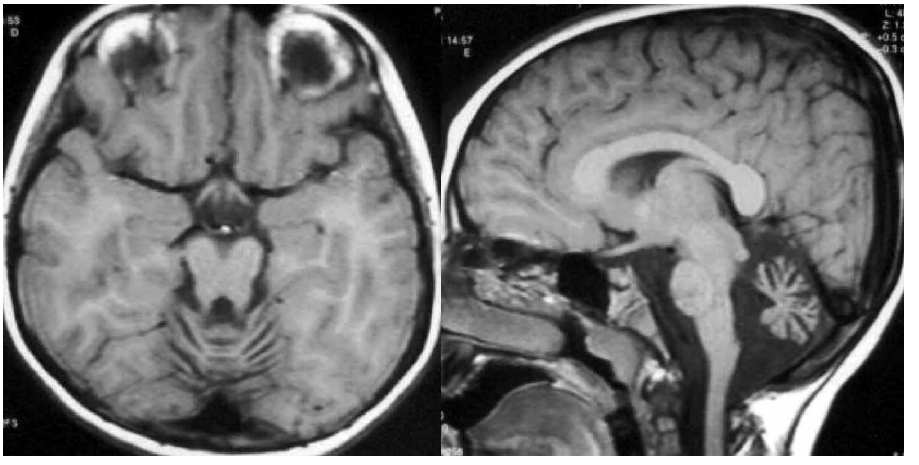

Figure 4. Third family, 2nd child: cerebellar hypoplasia prominent in the vermis (T1 axial and sagittal).

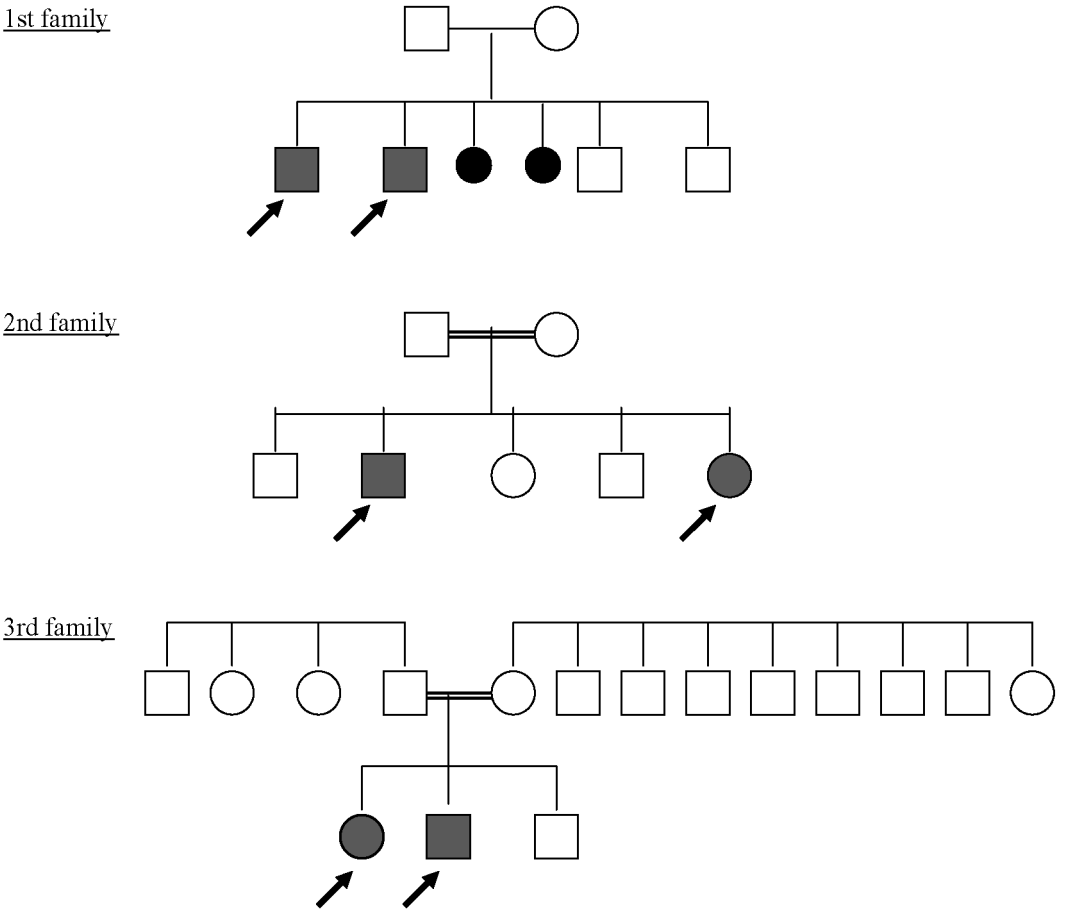

Figure 5. The pedigrees of the families.

enzymes, copper metabolism, lipoprotein metabolism, peroxisom and cholesterol synthesis [6–10]. These conditions are clinically, genetically and biochemically well characterized. However, in our cases, there were no specific clinical signs or positive data in the screening tests with regard to these diseases, and they showed no clinical progression in the long-term follow-up period. Characterized by a high proportion of familial cases, non-progressive ataxia is a small entity [11,12] and has been known since the beginning of the 20th century [13]. Jervis et al., who were the first to attempt to classify them, described some families in whom the disease was not progressive and was characterized by AR inheritance, severe truncal ataxia and mental retardation [14].

Esscher et al. reported that 27% of their cases had infratentorial pathology, morphologically supporting a congenital non-progressive cerebellar ataxia, and identified this group as having a heterogenous clinico-radiological entity [4,12]. Generally, non-progressive ataxias are known to have a recessive transmission, and autosomal dominant (AD) cases are rarely reported [2,3,15] (Table I). Delague et al. have mapped a non-progressive AR cerebellar ataxia in a family at 9q34-9qter [5]. The pictures of the families correspond more with AR inheritance, for these were marriages of first cousins, and while some of their sons and daughters were equally and adversely affected, others were not.

Cerebellar hypoplasia on MRI and the non-progressive characteristic of the condition of our cases were the main inclusion criteria adopted in our study. To the authors' knowledge, there are only a few studies on long-term follow-up of such cases in the literature [2–4]. Our cases did not deteriorate, and seemed to compensate for their motor uncoordinations through the years, which was similar to the results achieved by Steinlin [4]. Our cases had varying degrees of ataxia and mental retardation. The degrees varied to such an extent that this makes it possible to consider the cases clinically heterogeneous despite the similarities between the MRI findings of the sib pairs, as in the third family. It has been reported that such manifestations as dystonia, spasticity and epilepsy are possible in non-progressive ataxias with cerebellar hypoplasia [16]. However, except for brisk reflexes and Babinski's sign, our group was more homogenous compared to those in the literature. There was no clear relationship

Table I. Some clinical and imaging findings of different groups.

	Age (y) and sex	Ataxia	Walking	DTR	IQ	Nystagmus	MRI
Furman et al. (AD)	32 F (mother)	Mild	Unkw	N	N	Vert + Hor	Vermian atrophy
	8 F (daughter)	Mild	Unkw	N	IQ = 81	Vert + Hor	”
	4 F (daughter)	Mild	Unkw	N	N	Vert + Hor	”
	9 M (son)	–	Unkw	N	N	Vert + Hor	N
Rivier et al. (AD)	11 F (daughter)	Mild	20 mo	N	IQ = 70	–	Cll hypoplasia
	3 F (daughter)	Mild	18 mo	N	IQ = 75	–	Vermian hypoplasia
	38 F (daughter)	Mild	2 y	N	N	–	”
Imamura et al. (AD)	33 F (mother)	Moderate	18 mo	Brisk	N	Hor	Cll atrophy
	4 F (daughter)	Mild	18 mo	Brisk	IQ = 61	–	Vermian and cll hemisphere atrophy
Our cases	7 M (1st family)	Mild	2.5 y	Brisk (lwr)	IQ = 70	Vert + Hor	Vermian > Cll hypoplasia
	5 M (1st family)	Moderate	4 y	Brisk	IQ = 68	Hor	”
	11 F (2nd family)	Severe	9 y	Brisk (lwr)	Moderate MR	–	”
	6 M (2nd family)	Moderate	5.5 y	Brisk	Mild MR	–	”
	12 M (3rd family)	Mild	20 mo	Brisk (lwr)	IQ = 90	–	”
	6 F (3rd family)	Moderate	18 mo	Brisk (lwr)	IQ = 68	–	”

N: normal; vert: vertical; hor: horizontal; ver: vermis; unkw: unknown; cll: cerebellum; lwr: in the lower extremities; MR: mental retardation.

between morphology and function, as MR was rather uniform, whereas clinical signs were variable without evidence, however, for involvement of additional systems.

It has been histologically shown that non-progressive ataxias with cerebellar hypoplasia affect the superior vermis in particular and cause the cerebellum to lose granular cells [13,14]. Our cases can not be classified as certain genetic and metabolic diseases due to a number of differential diagnoses as follows [6–12]: absence of clinical progression or deterioration with multiorgan dysfunction, involvement of only the cerebellum and no other systems, absence of dysmorphic symptoms or anomalies of the brain stem or white matter in MRI, normal myelination, absence of intracranial malformations of posterior fossa or midline structures. It is in support of this view that the below test results of all our cases were negative: amino acidopathy, organic aciduria, abnormal tandem mass acyl carnitine profile, elevated lactate and pyruvate, pathological histochemical staining for mitochondrial diseases, and systemic involvement. Hypoplasia was not limited to the anterior vermis in our cases. Furman [2], Revier [3] and Imamura reported cases with CTs and MRIs revealing cerebellar hypoplasia prevailing in the vermis/anterior vermis [15] (Table I). According to the imaging-based classification [17], our images were compatible with “vermian hypoplasia in association with hypoplasia of the cerebellar hemispheres”. Associated supra-infratentorial anomalies, such as agenesis corpus callosum, lissencephaly and hypoplasia of pons, were not detected in our cases. It is obvious that clinical and neuroradiological data obtained from our cases and those obtained from the literature will not authorize us to determine the subgroups of ataxias that are not progressive in nature. Besides, it is not possible to establish a direct relation between MRI findings and the severity of ataxia and cognitive impairment.

Although the region responsible for non-progressive ataxias with cerebellar hypoplasia was mapped, further investigations are needed to discover the genes causing this entity. If further information on the aetiopathogenesis of childhood ataxias associated with cerebellar hypoplasia is to be acquired, a combined evaluation of metabolic and radiological analyses as well as long-term follow-up are indispensable elements for definitive diagnosis to be carried out.

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