

ELECTRONIC LETTER

Progressive cerebellocerebral atrophy: a new syndrome with microcephaly, mental retardation, and spastic quadriplegia

B Ben-Zeev, C Hoffman, D Lev, N Watemberg, G Malinger, N Brand, T Lerman-Sagie

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The combination of microcephaly, spasticity, and profound mental retardation is usually found in children with severe perinatal asphyxia or congenital infection. These children are commonly diagnosed as having cerebral palsy. However, in some children there is no evidence of a perinatal insult and there may be familial recurrence.¹ The London Dysmorphology Database² offers 104 genetic syndromes that include these features. However, most of them also show dysmorphism and other organ involvement. Twenty-three of these syndromes are the result of an identified inborn error of metabolism. In some genetic syndromes the microcephaly may be progressive and brain neuroimaging may show cortical or cerebellar atrophy.³ Cerebellar atrophy can be associated with spasticity and profound mental retardation in pontocerebellar hypoplasia type 2 (PCH 2).

We describe seven patients from six non-consanguineous Sephardi Jewish families with a previously undescribed syndrome of profound mental retardation, progressive microcephaly, and severe spasticity. Radiologically, repeat magnetic resonance imaging showed progressive cerebellar atrophy followed by cerebral atrophy involving both white and grey matter. An extensive metabolic evaluation was normal.

PATIENTS

Table 1 shows seven patients (five female), identified in two paediatric neurology clinics in Israel, with a similar clinical picture of profound mental retardation, progressive microcephaly, and severe spasticity. All had the same radiological features consistent with progressive cerebellar atrophy and cerebral atrophy involving both white and grey matter.

Five patients were isolated cases and two were sisters. All families were non-consanguineous Sephardi Jews of either Moroccan or Iraqi origin. All the parents and unaffected sibs were healthy and neurologically intact. Age range was 18 months to 19 years.

All patients were the product of a normal pregnancy and delivery. Head circumference was normal at birth. Progressive

Key points

- We describe seven children from six families with similar clinical and radiological features: profound mental retardation, progressive spastic quadriplegia with joint contractures, progressive microcephaly, generalised seizures, and irritability; repeat magnetic resonance imaging (MRI) showed progressive cerebellar atrophy followed by cerebral atrophy involving both white and grey matter.
- The clinical and radiological presentation of this group of patients most closely resembles PCH 2. However, this disorder can be ruled out because the cerebellar changes were progressive and not recognised at birth, there was no pontine involvement, and the patients developed severe spasticity.
- We suggest that this is a new autosomal recessive syndrome in Sephardi Jews.

microcephaly became evident during the first year of life, ranging from 2 to 5 SD below the norm. They were non-dysmorphic and did not have any major or minor malformations.

All patients showed severe developmental delay and did not achieve any significant developmental milestones except smiling. Spasticity became evident in the first year of life (age range 3–12 months). The spasticity was progressive and the patients developed painful contractures. All children had

Abbreviations: CSF, cerebrospinal fluid; CT computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; PCH, pontocerebellar hypoplasia; PEHO, progressive encephalopathy with oedema, hysarrhythmia, and optic atrophy

Table 1 Patient characteristics

Patient	Age (y)	Origin	Sex	Age HC SD	Most advanced milestone	No of unaffected sibs	Visual pursuit	Behavioural features	Seizures	Chorea
1	4	Iraq/Morocco	F	26M 45.2 2	Smile	2	No	Irritability	No	No
2	6	Iraq	F	4.5Y 44.5 4	Smile	2	Yes	Irritability, laughing episodes	No	Yes
3	2.5	Morocco/Iraq	M	15M 44 -2	None	2	Partial	Irritability, laughing episodes	Partial, myoclonic, GTC, tonic	Yes
4	9	Morocco	F	4Y 46 -3	Smile	2	Yes	Irritability	Tonic, myoclonic, GTC	Yes
5*	4.5	Morocco	F	2Y 44 -3	Smile	2	Yes	Irritability	GTC, myoclonic, tonic	No
6*	19	Morocco	F	17Y 51 -2.5	None	2	No	No	GTC, myoclonic	No
7	7.5	Iraq	M	5Y 46 -4	None	3	Nystagmus	Irritability	GTC, myoclonic, tonic	No

*Sisters. GTC, generalised tonic-clonic.

Table 2 Neuroimaging findings

Patient	Mode of study	Age	Cerebellar atrophy	Cerebral atrophy	White matter			
					Corpus callosum	Myelination	Decreased volume	Signal abn
1	MRI	8 m	-	-	Thin	Delayed	+	-
	MRI	23 m	++	-	N	N	++	-
2	MRI	5 m	-	-	N	N	-	-
	MRI	28 m	++	Frontal parasylvian	Thin	N	-	-
3	MRI	5 m	-	-	N	N	-	-
	MRI	12 m	+	Frontal parasylvian	Thin	Delayed	+	-
4	MRI	23 m	++	Diffuse	Thin	Delayed	++	-
	CT	8 m	-	-	N	-	-	-
5	MRI	24 m	++	Frontal parasylvian	Thin	N	+	-
	MRI	7 y	+++	Diffuse	Thin	N	++	-
6	CT	9 m	-	-	N	-	-	-
	MRI	18 m	+	Diffuse	Thin	-	+	+
7	MRI	3.5 y	++	Diffuse	Thin	-	+	++
	MRI	19 y	+++	Diffuse (severe)	Thin	-	++	++
7	CT	7 m	-	-	N	-	N	-
	MRI	11 m	+	N	Thin	Delayed	+	-
	MRI	24 m	++	Mild	Thin	Delayed	++	-
	MRI	45 m	+++	Diffuse	Thin	Progressed	++	-

N, normal.

sustained and widespread clonus. Intermittent and mild choreiform movements were seen in three patients. Epileptic seizures, including myoclonic, simple motor, and occasional generalised tonic-clonic seizures appeared during the second year of life in five patients. Seizures were reasonably controlled by anticonvulsant drugs. Major management difficulties included sleep disorder and severe irritability, most prominent in the first 3 years of life, unrelated to gastro-oesophageal reflux. Fundoscopic examination was normal and did not disclose optic atrophy or retinopathy. However, three patients had cortical blindness and one had rotatory nystagmus. Dyskinesia did not occur in any patient.

LABORATORY EVALUATION

Electroencephalography showed progressive slowing of the background in all patients. Multifocal independent spikes and polyspikes were eventually noted after the onset of epilepsy. Brain stem auditory and visual evoked responses (six patients) were normal. Nerve conduction studies were obtained in five patients and did not show any evidence of peripheral neuropathy.

Metabolic evaluation

Blood lactate, pyruvate, ammonia, creatinine, uric acid, very long chain fatty acids, amino acids, homocysteine, carnitine, isoelectric focusing of transferrin, and urinary organic acids were normal in all patients. Other normal results in some of the patients included urinary purines in three, urinary sulphites in four, lysosomal enzymes in five, cerebrospinal fluid (CSF) protein, glucose, cells, amino acids, and lactate in four. CSF neurotransmitters and pterins were normal in four patients. 5-methyltetrahydrofolate in CSF was low in one of four patients tested (courtesy of Professor N Blau, Zurich). Muscle biopsies (histology, electron microscopy, and assay of respiratory chain enzymes in isolated mitochondria and spectrophotometry) were obtained in four patients, full thickness skin biopsy (including nerve endings) in two, nerve biopsy in one, and rectal biopsy in one. All were normal.

Neuroimaging studies

Table 2 shows the results of the neuroimaging studies. MRI studies were performed using a 1.5 T system. T1 and T2 weighted images were obtained in transverse, sagittal, and coronal sections. The first MRI or CT obtained between 5 and 8 months of age in six of the seven patients did not show any

cerebral or cerebellar atrophy (figs 1A, 2A, and 3A). However, myelination was delayed at 8 months in one patient, who also had a paucity of cerebral white matter (fig 4). Repeated MR studies showed progressive atrophy of both cerebellum and cerebrum. This atrophy was first noticed in the vermis (fig 1B, 2B). Atrophy of the cerebellar and cerebral hemispheres appeared at a later age (fig 3A, B). The cerebral involvement progressed in the anterior to posterior direction. There was a

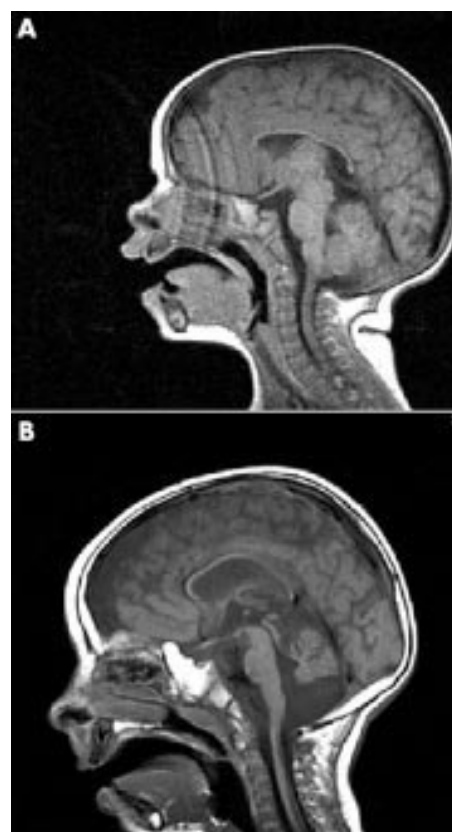


Figure 1 Patient 1. (A) Sagittal T1 weighted image at the age of 8 months showing normal vermis and cisterns around the cerebellum. (B) Sagittal T1 weighted image at 25 months. The vermis is atrophied and the cisterna magna is enlarged.



Figure 2 Patient 3. (A) Sagittal T1 weighted image at the age of 5 months showing a normal vermis. (B) Sagittal T1 weighted image at the age of 23 months. The vermis is atrophied and the cisterna magna is enlarged.

gradual decrease in white matter volume with thinning of the corpus callosum. An abnormal periventricular white matter signal was found in four of the seven patients. Myelination was delayed in two boys. The brain stem and basal ganglia remained intact. Magnetic resonance spectroscopy (MRS) was obtained in two patients at the ages of 23 and 36 months. There was decreased N-acetyl aspartate (NAA), NAA/creatine, and NAA/choline in the cerebellar hemispheres. The basal ganglia spectrum was normal.

DISCUSSION

We report on seven patients with infantile onset of progressive cerebellar and cerebral atrophy. Early onset progressive cerebellar atrophy can be seen in metabolic or neurogenetic disorders. Metabolic conditions include defects in amino acids and organic acids, the urea cycle, purines, cholesterol, glutathione, lipoproteins, glycoproteins, proteolipid protein, copper, molybdenum, mitochondria, lysosomes, and peroxisomes.⁴ The neurogenetic syndromes include infantile neuroaxonal dystrophy, disturbances in DNA synthesis and repair mechanisms, neuronal ceroid lipofuscinosis, infantile onset spinocerebellar atrophy,⁵ Marinesco-Sjogren disease,⁶ Norman syndrome of congenital cerebellar granular cell hypoplasia and mental retardation,⁷ and various phenotypically described familial syndromes.⁴ All these syndromes could be ruled out in our patients because of a normal extensive metabolic and neurophysiological evaluation and different clinical features and course.

Cerebellar hypoplasia combined with pontine atrophy is found in a separate and well defined group of autosomal recessive disorders. Ramaekers *et al*⁸ divided them into five entities: carbohydrate deficient glycoprotein syndrome type 1

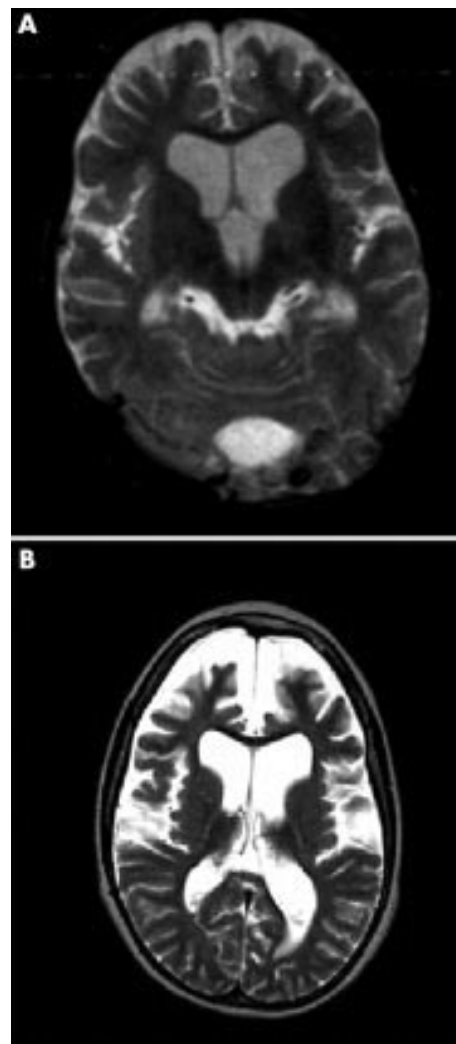


Figure 3 Patient 4. The cerebellar atrophy is followed by prominent cerebral atrophy in a frontoparietal to parieto-occipital direction. (A) Axial T2 weighted image of patient 4 at 2 years shows mild enlargement of the lateral ventricles and widening of CSF spaces around the cerebral hemispheres. (B) Axial T2 weighted image of patient 4 at 7 years shows no change of the ventricular size but further widening of the CSF spaces of the anterior parts of the brain. The sylvian fissure is wide open and the frontal lobes are atrophic.

and 2, and progressive encephalopathy with oedema, hypsarrhythmia, and optic atrophy (PEHO), PCH 1 with spinal muscular atrophy, and PCH 2 with extrapyramidal dyskinesias.

Congenital disorders of glycosylation (previously called carbohydrate deficient glycoprotein syndromes) were ruled out in our patients by normal isoelectric focusing of transferrin. Our patients showed progressive cerebellar atrophy and profound mental retardation as seen in PEHO syndrome; however, none showed the typical features of this syndrome including generalised hypotonia and oedema of the face and limbs and optic atrophy.^{8,9} Although most of them had early onset seizures, none had infantile spasms, and the EEG was not consistent with hypsarrhythmia.

In PCH 1 and PCH 2 the cerebellar hypoplasia is present from birth but can be progressive.¹⁰ In type 1 the hallmark is the presence of spinal anterior horn degeneration similar to Werdnig-Hoffmann disease. Presentation in the neonatal period is characterised by respiratory insufficiency, frequent congenital contractures, and a combination of central and peripheral motor signs. Patients die early, usually before 1 year

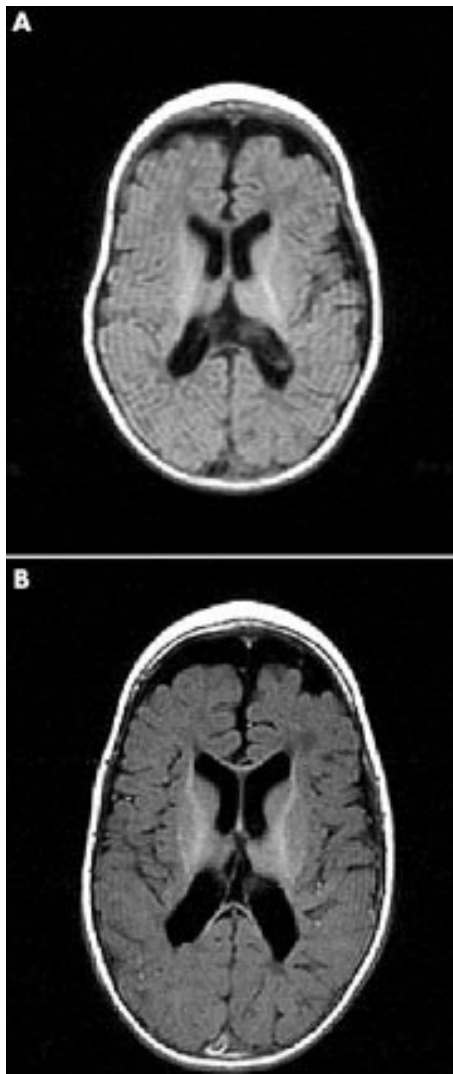


Figure 4 Delayed myelination in patient 3. (A) Axial T1 weighted image at 5 months shows maturation of white matter compatible with a normal 4 month old brain. (B) Axial T1 weighted image at 12 months shows no progression in myelination, which remains at the same maturation level.

of age.¹¹ This syndrome was ruled out in our patients owing to the lack of anterior horn disease. The hallmark of PCH 2 is the presence of chorea/dystonia, which is often severe, whereas spinal anterior horn pathology is absent. Patients have microcephaly and severely impaired mental and motor development. They often die during childhood.¹¹

There have been single case reports of patients with PCH that do not fit into the two major subtypes. In older publications there are descriptions of multisystem involvement and PCH, which would probably be diagnosed today as one of the subtypes of the congenital disorders of glycosylation.^{12–13} Zelnik *et al*¹⁴ described three patients from two sibships with congenital microcephaly, initial hypotonia rather than spasticity, optic atrophy, and abnormal eye movements. Two variants have been described of familial PCH with milder neurological involvement consistent with achievement of independent walking and protracted course.^{15–16} In one report there was additional white matter involvement¹⁵ and in the other there were dysmorphic features.¹⁶ Prenatal involvement (polyhydramnios), myoclonus, spasticity, and apnoeic episodes (hyperekplexia-like picture), and fatal outcome in infancy were described in several reports^{17–19}

The clinical presentation of our group of patients is most similar to that of PCH 2: neurological involvement from birth,

virtually absent developmental milestones, spasticity, progressive microcephaly, and myoclonic jerks. However, choreoathetosis/dystonia was absent in our patients and seizures were more prevalent.

The neuroimaging criteria for PCH 2 have been outlined by Uhl *et al*²⁰: (1) hypoplastic cerebellum situated close to the tentorium; the hypoplastic cerebellum has a reduced number of folia; (2) the cerebellar hemispheres are reduced to bean-like or wing-like structures; (3) markedly hypoplastic ventral pons; (4) slight atrophy of the supratentorial gyral pattern; (5) dilated cerebromedullary cistern and fourth ventricle; (6) delayed myelination of the white matter; (7) there is no significant disorganisation of brain architecture and no marked defects of the corpus callosum.

The MRI findings in our patients differ from those seen in PCH 2. They have the following characteristics. (1) The initial scans in the first months of life were normal; (2) The cerebellum had a normal number of folia and became progressively atrophied (vermis before hemispheres); (3) there was sparing of brain stem structures including the ventral pons; (4) the cerebral and cerebellar hemisphere atrophy proceeded at the same time; (5) The cortical atrophy proceeded in an anterior to posterior direction; (6) at the end stage the cerebral atrophy included both grey and white matter and was as pronounced as the cerebellar degeneration; (7) in some of the patients myelination was delayed.

As in PCH 2, ataxia (despite early and severe cerebellar involvement) did not occur in our patients and spasticity rather than hypotonia was a prominent feature. The lack of ataxia is the result of onset of symptoms before intentional motor patterns develop.¹¹ Because cerebellar hypoplasias are often part of complex syndromes, cerebellar symptomatology may be obscured. Spasticity can probably be attributed to early involvement of the pyramidal tracts even before atrophy of the cerebral grey and white matter is detected. The degenerative process in both conditions starts in utero, as the clinical presentation is already evident in the first weeks of life. However, onset is earlier in PCH 2, probably taking place between 20 and 28 weeks of gestation, affecting the stages of organisation of the cerebellar cortex and of the related grey nuclei.²¹ The lack of pontine involvement in our patients may be the result of onset of the process after connection of cerebellar to hindbrain structures has been established. The dyskinesia seen in PCH 2 cannot be explained anatomically as the basal ganglia remain intact radiologically and pathologically.²² Symptoms of neocortical involvement (profound mental retardation and epilepsy) are evident in PCH and in our patients at birth and are probably related to abnormal cerebellar-cerebral connectivity and an ongoing neurodegenerative process. The low NAA, NAA/creatine, and NAA/choline found on MRS in our patients probably reflects primary axonal loss. Nevertheless, not until the discovery of the genes responsible for PCH 2 and this newly described syndrome will we be able to establish whether these two entities are allelic.

This new syndrome represents a progressive neurodegenerative process with onset in infancy affecting both the cerebrum and cerebellum. Its pathogenesis can be related to unstable structural proteins, increased apoptotic processes, or as an as yet unidentified toxic/metabolic effect.

In conclusion, we report on a new autosomal recessive syndrome characterised by profound mental retardation, progressive spastic quadriplegia with joint contractures, generalised seizures, irritability, and progressive microcephaly following normal head circumference at birth. These patients have no dysmorphic features or congenital anomalies and have no evidence of a known neurometabolic or degenerative disease. Although this syndrome bears some resemblance to PCH, it shows enough clinical and imaging features to warrant its classification as a separate disease.

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Authors' affiliations

B Ben-Zeev, N Brand, Paediatric Neurology Unit, Sheba Medical Centre, Ramat-Gan, Israel
C Hoffman, Neuroradiology Unit, Sheba Medical Centre, Ramat-Gan, Israel
D Lev, N Watemala, T Lerman-Sagie, Metabolic-Neurogenetic Clinic, Paediatric Neurology Unit, Wolfson Medical Centre, Holon, Sackler School of Medicine, Tel-Aviv University, Israel
G Malinge, Fetal Neurology Clinic, Wolfson Medical Centre, Holon, Sackler School of Medicine, Tel-Aviv University, Israel

Correspondence to: Dr T Lerman-Sagie, Paediatric Neurology Unit, Wolfson Medical Centre, Holon 58100, Sackler School of Medicine, Tel-Aviv University, Israel; asagie@post.tau.ac.il

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