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Abstract

We present the phenotype of an infant with the largest ATN1 CAG expansion reported to date (98 repeats). He presented at 4 months with developmental delay, poor eye contact, acquired microcephaly, failure to thrive. He progressively developed dystonia-parkinsonism with paroxysmal oromandibular and limbs dyskinesia and fatal outcome at 17 months. Cerebral MRI disclosed globus pallidus T2-WI hyperintensities and brain atrophy. Molecular analysis was performed post-mortem following the diagnosis of dentatorubral–pallidoluysian atrophy (DRPLA) in his symptomatic father. Polyglutamine expansion defects should be considered when neurodegenerative genetic disease is suspected even in infancy and parkinsonism can be a presentation of infantile-onset DRPLA.

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Introduction

Dentatorubral–pallidoluysian atrophy (DRPLA) (OMIM 125370) is one of the nine autosomal dominant polyglutamine (polyQ) defects, a group of clinically and genetically heterogeneous neurodegenerative diseases.[1,2] DRPLA is caused by the expansion of a trinucleotide cytosine-adenineguanine (CAG) repeat in exon 5 of atrophin-1 (ATN1) gene.[3] The CAG repeat expansion demonstrates genetic anticipation, especially when inherited through the paternal lineage and becomes pathogenic when expanded beyond 48 trinucleotide repeats. The clinical phenotype is heterogeneous, and the length of the repeat is correlated to poor prognosis: early onset, severity, functional impairment and eventually fatal outcome.[1] Two main phenotypes have been described.[1,2] The first phenotype (CAG repeats ≥65) presents a juvenile onset (<20 years) with progressive myoclonic epilepsy (PME) and encephalopathy. The second phenotype (CAG repeats <65), also called the non-PME phenotype is characterized by adult-onset (≥20 years), ataxia, choreoathetosis, cognitive impairment, and psychiatric symptoms clinically mimicking Huntington's disease.[1,2]

In this report, we characterize the infantile-onset (<1 year of age) phenotype of the individual with the largest ATN1 CAG expansion reported up to now (98 repeats).

Patients and Methods

The individual was assessed in the pediatric neurology clinics at Montpellier University Medical Center. Legal guardians provided written informed consent for samples and data to be used in research and publication, including the videos.

CAG repeat number in the ATN1 gene was analyzed by a polymerase chain reaction with fluorescence-labeled primers as described elsewhere.[4] The number of repeats was determined by capillary electrophoresis using an ABI 3130X automated DNA sequencer and the GeneMapper version 4.0 software (Applied Biosystems, Foster City, CA, USA). To assess the number of repeats, Genescan 500 ROX size standard was used (Applied Biosystems) and several samples with different DRPLA CAG allele lengths were sequenced as positive controls.

Results

The proband was a male first child, born to non-consanguineous parents of non-Asian origin (Fig. 1, individual III-1). Premature rupture of the membranes at 27 weeks of pregnancy resulted in oligohydramnios and pregnancy was closely monitored without abnormality. Birth occurred at 37 weeks of gestation by cesarean section due to delayed labor, with normal perinatal parameters (Apgar score 10/10, birth weight 2.870 kg (0.1 SD (Standard deviation)), height 47 cm (- 0.4 SD), head circumference 33.5 cm (0 SD)).

From the age of 4 months the parents noticed the absence of eye contact and visual pursuit, limited motor achievements, and feeding difficulties. The general pediatrician reported severe hypotonia and global developmental delay. The individual also exhibited abnormal movements from 4 months of age (Video section S1). The individual was finally referred to the pediatric neurologist at 10 months. Growth failure was noticed (weight 6.9 kg (_3 SD) height 70 cm (- 2.5 SD)) with microcephaly (head circumference of 42 cm (- 3.4 SD). He had normal facial features as well as normal hands and feet. Clinical examination disclosed left plagiocephaly, axial hypotonia combined to axial dystonic postures with no head control, limited spontaneous and voluntary movements, distal rigidity, increased osteotendinous reflexes in the lower limbs without other pyramidal tract signs. Close assessment of movement disorders identified bradykinesia during most of the day interrupted by several episodes of involuntary, erratic, writhing movements of his face, arms, and legs. These dyskinetic paroxysms lasted between a few minutes to several hours, no evident trigger was identified. Most of the time these movements were fluid, but rapid jerking or slow and extended dystonic postures could occasionally appear. Reduced facial expression was abruptly interrupted by mouth opening dystonia (Video section S2). Involuntary movements disappeared during sleep. Between episodes the patient did not show another kind of movement disorder. EEG recording during the episodes of involuntary movements and in calm periods without paroxysmal movements was normal and the episodes were considered as non-epileptic dyskinesia.

A gastrostomy was performed at 14 months of age. At 15 months, the individual exhibited two episodes of febrile generalized clonic seizures, lasting less than 2 minutes, during an episode of gastroenteritis. Interictal wake and sleep EEG was normal and sodium valproate treatment was initiated. Seizures did not recur. The individual never acquired the ability to control his head, grab objects, or develop language and his motor function did not improve. He died suddenly at the age of 17 months during a febrile illness.

The proband underwent a work-up at 10 months of age (detailed in Table 1). Brain MRI showed cerebral atrophy, mild atrophy of the brainstem and cerebellar vermis, thin corpus callosum, and bilateral and symmetrical globus pallidus T2-WI hyperintensities (Fig. 2).

Cerebrospinal fluid (CSF) neurotransmitters profile disclosed elevated neopterins, low levels of 5-hydroxyindolacetic acid (5-HIAA), and homovanillic acid (HVA) (Table 1).

Early developmental delay, severe hypotonia and high levels of neopterine raised the suspicion of Aicardi–Goutieres Syndrome (AGS); molecular resequencing gene panel involved in AGS (TREX1, RNASEH2B, RNASEH2A, RNASEH2C, SAMHD1, IFIH1, and ADAR) did not disclose pathogenic variant. CGH array did not show any segmental genomic copy number variations (CNVs Eight years after the proband’s death, his father aged 42 years (Fig. 1 individual II-1) was referred to the neurologist for a 5-year history of progressively

worsening ataxia, choreo-dystonic, and myoclonic involuntary movements associated to insidious impairment of executive functions and behavior (irritability, impulsiveness). Brain MRI showed cortical and pontocerebellar atrophy and white matter hyperintensities. Because of the clinical presentation, genetic testing for Huntington's disease and Huntington-like disorders was performed. Molecular analysis revealed a repeat expansion of 8 out of 61 copies of the CAG trinucleotide in the ATN1 gene and the diagnosis of DRPLA was established. Proband's stored DNA sample analysis identified a heterozygous expansion of 15 out of 98 copies of the CAG repeat, which was consistent with the diagnosis of DRPLA with a very high CAG repeat load.

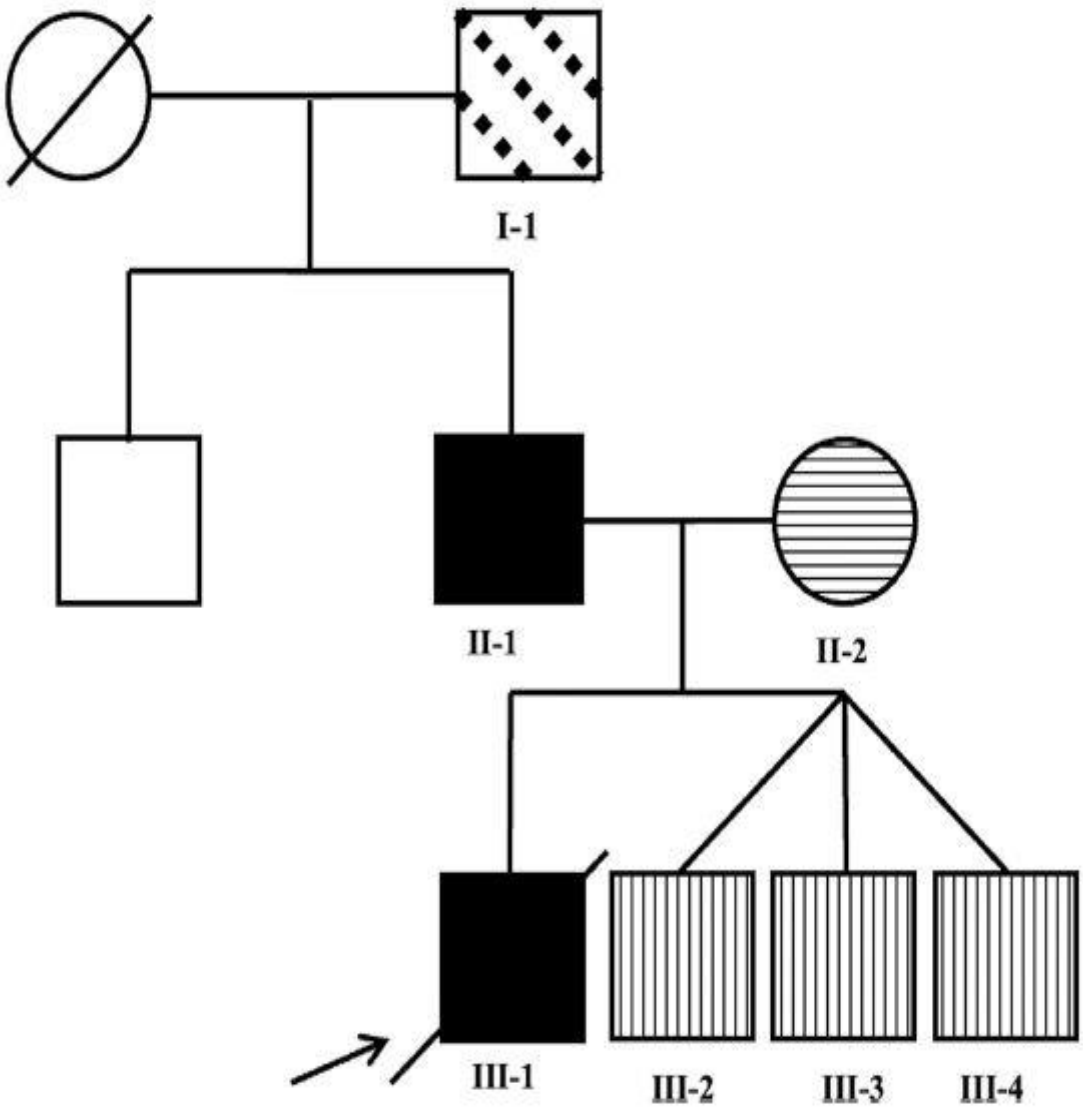

Figure 1. Family pedigree. The proband III- 1 is indicated by an arrow. Individual I-1 was reported to suffered from some level of cognitive disability, he denied neurological and molecular analysis. Individuals II:2-4 were triplet siblings born 3 years of the individual III-1. They were born after an uneventful pregnancy at 36 weeks of gestation by an elective cesarean delivery. Neonatal period was unremarkable. Individual III:2-4 exhibited a global developmental delay (walk unaided between 19 and 20 months of age, first words after 2 years of age, first sentence after 3.5 years of age) requiring physical, speech and language therapy. At last follow-up (6 years of age), the three siblings had mild cognitive disabilities and benefited of a special educational program; they never exhibited epileptic seizure; last neurological examination did not disclose any movement disorder. Fragile-X and whole exome sequencing analysis were normal; *ATN1* expansion analysis was not performed. Black symbol: individual with trinucleotide expansion consistent with DRPLA; different symbols as follows, spotted: cognitive impairment; vertical grid: neurofibromatosis type 1; horizontal grid: developmental disorder.

Table 1. Summary of the clinical work-up that was performed when the individual was 10 months of age.

Plasmatic metabolic screening: normal
Blood cell count
Liver transaminases
Creatine phosphokinases
Ammonemia
Lactate
Acid–base parameters
Thyroid hormones
Plasma amino acids
Very long chain fatty acids profile
Urinary metabolic screening: normal
Organic acids chromatography
Sialic acid
Oligosaccharides
Methylmalonic acid
Guanidinoacetate and creatine
Cerebrospinal fluid (CSF) analysis
Cerebrospinal fluid analysis: abnormal neurotransmitter profile
Cell count protein, glucose, serine and interferon levels, and glycorachia/glycemia ratio normal
CSF neurotransmitter profile
Neopterins: 199 nmol/L (normal range 8–43)
5-Hydroxyindolacetic acid (5-HIAA): 92 nmol/L (114–490)
Homovanillic acid (HVA): 138 nmol/L (295–932)
3-O-methyldopa (3-OMD): 54 nmol/L (4–50)
Brain imaging
Brain MR: brain atrophy, mild atrophyof the brainstem and cerebellar vermis and bilateral, thin corpus callosum, and symmetrical globus pallidus T2-WI hyperintensities
Brain CT scan: normal
Other investigations
Ophthalmological assessment at 10 months of age: poor eye contact, absence of pupillary light reactions, normal slit-lamp and funduscopic examination
Electroretinogram recording: normal
Brain auditory- and visual-evoked potentials: normal
Echocardiogram: normal
Skeletal radiography: normal
Genetic testing
Molecular resequencing gene panel involved in AGS (*TREX1*, *RNASEH2B*, *RNASEH2A*, *RNASEH2C*, *SAMHD1*, *FIH1*, and *ADAR*): no pathogenic variant
CGH array: normal
CAG repeats in *ATN1* gene: 15/98

Discussion

We described a child affected by a severe rapidly progressive neurological disease with early infantile onset, major developmental delay with axial hypotonia and no motor achievement, combined to a complex movement disorder characterized by dystonia-parkinsonism with episodes of oromandibular and limbs dyskinesia; the individual had acquired microcephaly, generalized febrile seizures and fatal outcome. Molecular testing following his father's diagnosis of DRPLA identified the largest ATN1 CAG expansion with a total of 98 repeats published in the literature up to now.

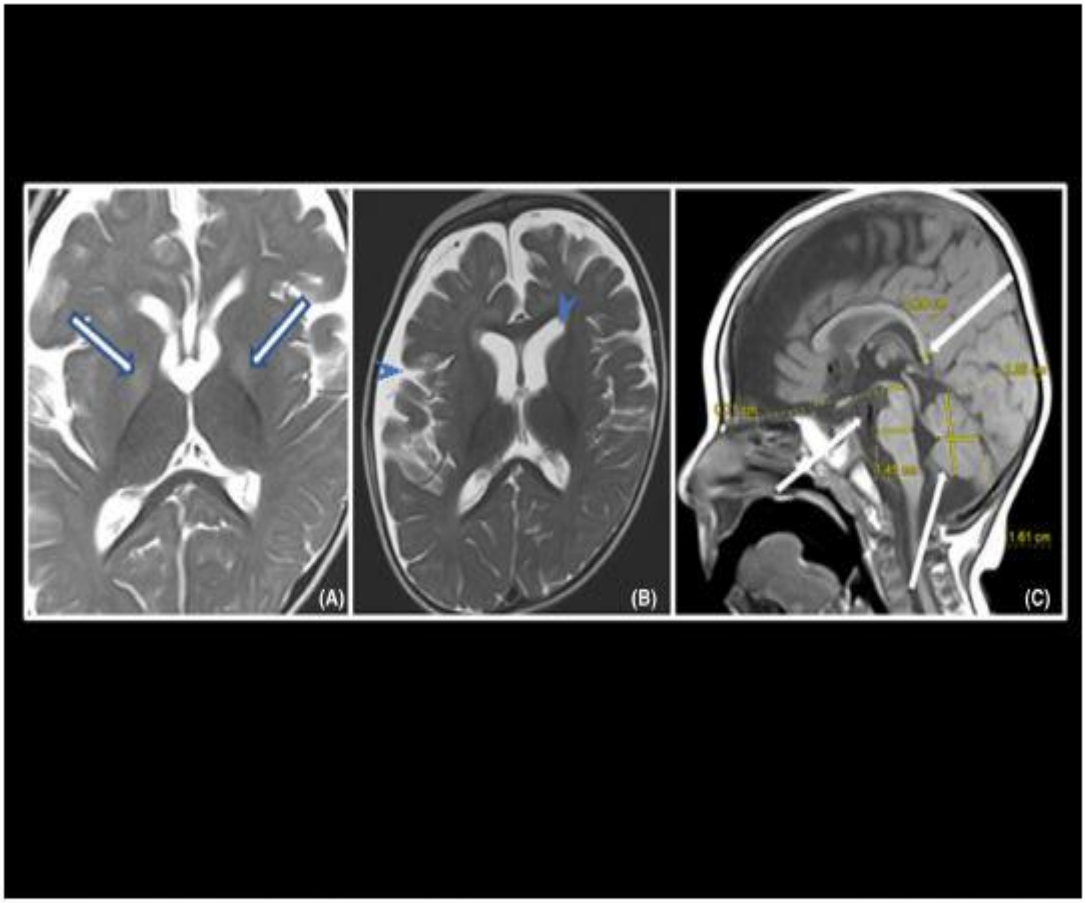

Figure 2. Brain MRI at the age of 10 months showed (A) subtle bilateral and symmetrical globus pallidus hyperintensities (Axial, T2-WI, blue line arrows) (B) enlargement of the ventricles and subarachnoid spaces associated to diffuse brain atrophy (Axial, T2-WI, arrow heads), and (C) thin corpus callosum and mild atrophy of the brainstem and cerebellar vermis (Sagittal, T1-WI, white arrows).

DRPLA have been mainly described in the Asian population, and it represents the most frequent cause of childhood-onset cerebellar ataxia in Japan.5 Neonatal or infantile DRPLA onset has only been reported in seven cases so far6–12 (Table 2) with a phenotype characterized by early developmental delay, regression of developmental milestones, and myoclonic or generalized tonico–clonic epileptic seizures, with variable age at onset and pharmaco-resistance. Abnormal movements were also common, including dystonia, chorea, myoclonus, and oral dyskinesia. The clinical presentation of our individual was mainly characterized by developmental delay with movement disorders; epilepsy was limited to two febrile seizures, but the individual was noteworthy by his very short life span compared to other cases,6–12 and this short life span is consistent with established correlation between CAG repeat load and early death1 (Table 2). Abnormal MRI findings were common to these neonatal or infantile-onset cases, especially cerebral, cerebellar, and brainstem atrophy; basal ganglia T2 hyperintensities has also been reported in infantile-onset cases6–12 as well as in late-onset cases.13 As in our case, most of the earlyonset cases inherited their expansion from their father; and unlike in our family, the individuals were referred mostly while the parental diagnosis was already established.6–12

Table 2. Individuals with a genetic confirmation of infantile-onset DRPLA and infantile onset (≤ 1 year of age).

		Reported individuals with a genetic confirmation of DRPLA and onset ≤1 year of age						
Features	Our report	7,8		9	10	11	12	13
Individual	II	II	I2	II	F2-2	I3	PIV-6	II
Origin	Non-Asian	Asian	Asian	Non-Asian	Asian	Asian	Asian	Asian
# Repeats	98	93	90	66	63	88	82	76
Clinical phenotype								
Age at onset	First months	6 months	4 months	2 months	Newborn	12 months	6 months	12 months
Age at report/death	1 year 5 months[a]	6 years[a]	15 years[a]	12 years 8 months	15 years[a]	NA	13 years	4 years
Developmental delay/regression (age)	+	+/1 year	+/8 months	+/9 years	+/11 years	+	+/6 months	+
Acquired microcephaly	+	NA	NA	+	NA	NA	NA	NA
Dysphagia	+	+	+	NA	+	NA	+	NA
Ataxia	–	–	–	+	NA	NA	+	NA
Dystonia	+	+	+	NA	NA	NA	NA	+
Chorea	–	+	+	NA	+	NA	NA	NA
Myoclonus	–	–	–	+	+	NA	+	NA
Oral dyskinesia	+	+	+	NA	+	NA	NA	NA
Deep tendon reflexes	+++	+++	+	+++	NA	NA	NA	+++
Seizures (age at onset)	+(1 year 3 months)	+(2 years 7 months)	+(1 year 8 months)	+(2 months)	+(newborn)	+(NA)	+(6 years)	+(4 years 5 months)
Seizures type	Generalized clonic	Tonic	GTC	GTC Myoclonic Atonic drop attacks Atypical absence	Neonatal seizures Myoclonic	NA	NA	Myodonic
Radiological findings								
Age at MRI	10 months	2 years	2 years	11 years	NA	NA	10 years	4 years
Cerebral atrophy	+	+	+	+	NA	NA	+	+
Cerebellar atrophy	+	+	+	+	NA	NA	+	+
Brainstem atrophy	+	+	+	+	NA	NA	+	+
Deep white matter hyperintensity	–	–	+	+	NA	NA	NA	–
Delayed myelination	–	+	+	+	NA	NA	NA	–
Basal ganglia T2 high signal intensity	+	+	–	–	NA	NA	NA	+

–, feature/sign not present; +, feature/sign present; GTC, generalized tonic-clonic; NA, not available.
[a]Death.

Cerebrospinal fluid neurotransmitters profile has not been reported before in individuals with infantile-onset DRPLA. Atrophin-1 is a nuclear transcriptional corepressor which interacts with key proteins critical for neural progenitor cell survival, proliferation, and neuronal migration.14 Neuropathological findings of DRPLA include combined degeneration of the dentatorubral and pallidoluysian systems and white matter damage. Accumulation of expanded polyglutamine stretches have been demonstrated in the neuronal nuclei resulting in neuronal toxicity.15 Increased CSF neopterin levels may reflect an inflammatory response related to cellular damage occurring within the central nervous system and related to the disease process, as postulated in other trinucleotide repeat expansion diseases such as Huntington's disease and other adult-onset neurodegenerative disorders.16,17

Decreased levels of CSF homovanillic acid suggested secondary dopaminergic depletion, as observed in several neurological disorders especially those with degenerating process.18 The dopamine depletion profile was very concordant with the bradykinetic-dystonic phenotype of the individual. Although bradykinesia have been occasionally reported in juvenile or adult-onset DRPLA cases,6,19 dystonia parkinsonism was not reported in previously published infantile-onset cases6–12 (Table 2); it is well admitted that parkinsonian signs are difficult to assess and may be underdiagnosed especially in infants.20 Given the limited number of previously reported patients with infantile-onset DRPLA,6–12 it is difficult to draw conclusions on the phenotypic spectrum of infantile ATN1- DRPLA; as the legal guardians of the reported individual did not agree to perform further genetic testing, we cannot rule out other contributing genetic causes in his complex phenotype. However, the phenotype of our patient shares many common features with previous cases, including parkinsonian features, and we suggest that DRPLA may be added to the growing list of genetic causes of infantile parkinsonism, especially in the context of developmental delay or regression; whether the spectrum of infantile DRPLA involves dopamine depletion will be highlighted by neurotransmitters' analysis in newly diagnosed cases.

Recently, a high prevalence of individuals carrying intermediate or pathological ranges of polyglutamine disease-associated alleles among the general population has been reported.21 Trinucleotide repeat expansion analysis is not included (or covered by insurance) in the genetic workup of infantile or childhood-onset neurodegenerative movement disorders, especially in the absence of a significant familial history and the role of polyglutamine defect is probably underrecognized.22 Our case highlights that polyglutamine diseases should be considered, even in infantile onset neurodegenerative diseases without family history.
However, polyQ detection raised ethical issues; delineation of the spectrum of polyglutamine defects in infants and children will be necessary meanwhile novel techniques for genome-wide evaluation of repeat expansions are under development and validation.23

Acknowledgments

We thank the individuals and their family for sharing video and clinical information and for their trust in our work and care. We thank Doctor Lagavulin for his helpful discussions.

Author Contributions

Arthur Coget, Nicolas Leboucq, Maud Blanluet, Pierre Meyer, Marie-Claire Malinge, Marie-Céline François-Heude, Mathis Moreno, David Geneviève, Cecilia Marelli, analysis and editing of final version of the manuscript. Vincent Procaccio analysis, writing, editing of final version of the manuscript. Heidy Baide-Mairena: analysis, writing the first draft, editing of final version of the manuscript. Agathe Roubertie: design, analysis, writing, editing of final version of the manuscript.

Conflict of Interest

Authors have no conflict of interest to declare.

Funding Information

None.

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