Severe hypotonia and developmental delay due to an *EBF3* pathogenic variant. Clinical implications of a molecular defect and narrative review.

Caroline Van Kerkhoven [a,b], Lutty Mumba [c], Julie Harvengt [d], Jean-Paul Misson [a,e]

[a] University of Liège, Faculty of Medicine, Liège, Belgium
[b] CHU de Liège, Department of Pediatrics, Liège, Belgium
[c] Vivalia, Hôpital D'Arlon, Department of Pediatrics and Department of Travel Medicine, Arlon, Belgium
[d] CHU de Liège, Department of Human Genetics, Liège, Belgium
[e] Vivalia, Hôpital de Libramont, Department of Neuropediatrics, Libramont, Belgium

cvankerkhoven@student.uliege.be

Keywords

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Abstract

Hypotonia Ataxia and Delayed Development Syndrome (HADDS) is a neurodevelopmental syndrome due to missense pathogenic variants of the *EBF3* gene, located on chromosome 10q26.3. In most cases, these variants appear de novo and the transmission is autosomal dominant. HADDS would affect about 200 people worldwide and is characterized by a high clinical variability in the expression of these different symptoms : severe hypotonia, failure to thrive, psychomotor delay, digestive and feeding disorders, vesicoureteral anomalies, strabismus, and moderate facial dysmorphia. Although our knowledge is still limited, the significance of these symptoms seems to depend upon the *EBF3* expression during embryogenesis. Animal studies suggest that *EBF3* plays a critical role in neuronal migration and differentiation and interacts with *CDKN1A*, *NeuroD*, and *ARX* regulation pathways. With respect to diaphragmatic and vesicoureteral dysfunction and hypotonia, *EBF3* appears to be involved in myocyte calcium metabolism. In addition, *EBF3* has recently been identified as a novel tumor suppressor gene in some cancers. Further research on the *EBF3* gene and the associated pathological pathways is needed to improve our understanding of HADDS and to provide appropriate care for such rare diseases.

Introduction

Worldwide, several million children are born each year with neurological disturbances or with congenital neurodevelopmental disorders. Historically, their diagnosis relied on clinicians' ability to recognize and associate clinical signs and compare them with previously reported cases in the literature. The development of genetic techniques has made it possible to associate certain clinical signs based on the detection of chromosomal aberrations, and more recently, through the detection of pathogenic variants at the molecular level, thus becoming diagnostic markers. Over the last two decades, advances in molecular biology have focused on studying the disorders associated with these pathogenic variants. The intention has been to study their consequences in order to understand the biochemical mechanisms behind the expression of specific clinical and biological signs specific to these syndromes.

The case we report concerns a child with a significant developmental delay and clinical signs indicative of a rare syndrome : Hypotonia Ataxia Delayed Development Syndrome (HADDS). The discovery of a pathogenic variant in molecular biology allowed us to define the diagnostic marker. Beyond the identification of this anomaly and the gene whose expression is disturbed by it, it is interesting to analyze the neurobiological disturbances susceptible to explain the different symptoms.

Case report

A Caucasian girl was born by cesarean section at 36 weeks to non-consanguineous parents with no significant medical history. Her birth weight was 2.605 kg. She was born with mild respiratory distress requiring short-term non-invasive respiratory support, followed by a few hours of monitoring in the neonatal intensive care unit (NICU). The Guthrie test was negative.

Since her birth, she has been described by her parents as a rather quiet child, not very mobile and lacking energy. Not very reactive, she does not smile or cry vigorously. In spite of a very intense psychomotor rehabilitation program, her evolution remained very slow. She was able to develop eye contact and visual exchange with smiling. Archaic and osteotendinous reflexes were present, and no acute neurological events, such as seizures, were described. Her evolution was characterized by severe hypotonia, slow weight gain and significant failure to thrive (Figure 1), pathological gastroesophageal reflux and severe feeding difficulties leading to dehydration episodes requiring hospitalization, and chronic constipation resistant to conventional treatments. No swallowing problems were reported. She was initially fed through a nasogastric tube. However, this method was quickly proved to be insufficient and justified gastrostomy placement at 18 months

Figure 1: Weight curve showing an important slow weight gain and a significant failure to thrive < P3. She was initially fed by nasogastric tube. This method quickly proved to be insufficient and justified the gastrostomy placement at the age of 18 months.

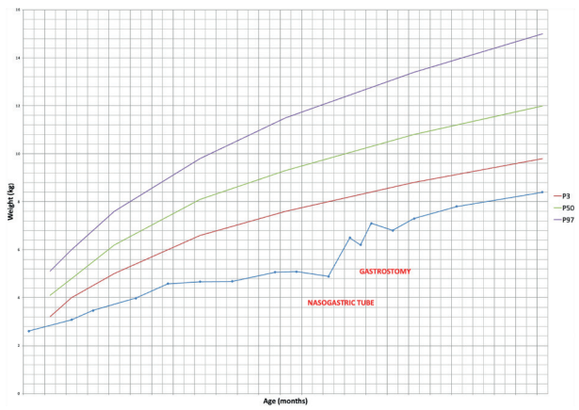
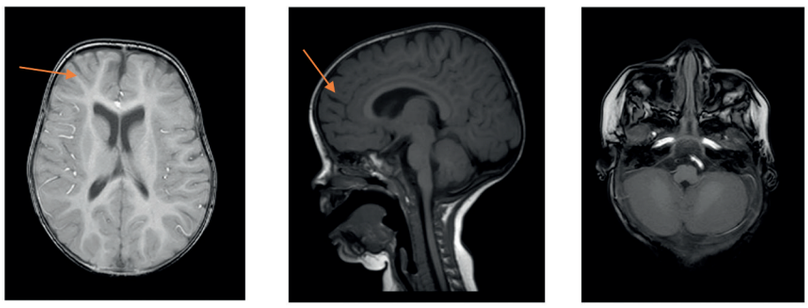


Figure 2: Brain MRI shows a discrete alteration of the cerebral gyration made of deeper sulci in the frontal area.



of age (Figure 1). She also had grade II left vesicoureteral reflux, which was responsible for recurrent urinary tract infections. Cardiac check-up was normal. A comprehensive workup was performed which allowed to rule out neuromuscular pathology, gastrointestinal pathology, malabsorption, endocrine or metabolic disorders. Her brain MRI showed a discrete alteration of the cerebral gyration consisting of deeper sulci in the frontal area (Figure 2). Routine genetic studies were also inconclusive, both fort the molecular karyotype and for any other syndromic research.

Despite a multidisciplinary rehabilitation program, her follow-up was still characterized by severe hypotonia and psychomotor retardation. At the age of 20 months, she could turn around and sit up by herself for shorts periods of time. She couldn't walk, even with assistance, but could crawl only on short distances. She had eye contact and eye tracking but did not speak. She could make only a few cries and babbles. Eight months later, she begins to say a few words such as mom and dad. She can now stand without help and presents with ataxia ; she can also take a few steps with a walker. Some dysmorphism was reported with a broad forehead and low implanted ears. She also presented with right convergent strabismus. Finally, a whole-body x-ray revealed scoliosis.

Ultimately, the association of the symptoms led to perform a whole exome sequencing. This revealed a de novo missense *EBF3* pathogenic variant c.626G>A (p.Arg209Gln).

Discussion

Hypotonia Ataxia Delayed Development Syndrome (HADDS) is characterized by the association of several major symptoms albeit of variable expression : severe hypotonia, ataxia, psychomotor delay, failure to thrive, digestive and feeding disorders, vesicoureteral anomalies, strabismus, and moderate facial dysmorphia. It was first described in Texas in 2016 (1). Specifically, HADDS is a neurodevelopmental syndrome caused by missense pathogenic variants of the *EBF3* gene located on chromosome 10q26.3.

Based on available information from the HADDS Foundation, *EBF3* pathogenic variants affect approximately 200 people worldwide. The incidence of *EBF3* pathogenic variants is estimated to be approximately 3 per 100 million people and affect both sexes equally (1). The *EBF3* gene is located on chromosome 10 at position 10q26.3. Each structural protein of *EBF3* is composed of a DNA binding domain (N-terminal), a transcript factor/lg-like/plexin domain of unknown function, a helix-loop-helix domain (critical for homo- and hetero-formation), and a C-terminal transactivation domain (2-5). According to the literature, the most commonly described pathogenic variants are missense variants are the most frequently described (54% of cases). Duplications (18% of cases), nonsense mutations (15% of cases), frameshifts (8% of cases), and splice-site (5% of cases) have also been described. In most cases, these variants appear de novo and result in loss of gene function. Transmission is autosomal dominant. A literature review is provided in Table 1.

According to Gene Reviews, only 42 cases of HADDS from 39 unrelated families have been identified (6). Their phenotypes are extremely variable because HADDS is characterized by a wide clinical variability with each symptom (Table 2). Moreover, no correlation could be established between the position of the affected amino acids and the clinical signs. Nevertheless, moderate facial dysmorphia, hypotonia, and ataxia were observed in 88.2%, 82.9%, and 81.5% of these patients respectively. Strabismus was described in 81% of the cases. Developmental delay was reported in 95.1% of the cases. This includes learning difficulties in reading and writing, as well as a speech delay, some children remain nonverbal. In addition, most of the time a pronunciation defect persists. Developmental delay also includes delayed motor development. MRI abnormalities were found in only 35.3% of the patients. Genitourinary anomalies and digestive disorders are described in 34-51% of the cases. Failure to thrive and/or short stature affect approximately half of the patients. Additional clinical signs such as autistic features, behavioral disorders, epilepsy, high pain tolerance, or musculoskeletal anomalies, are described in only 24-41% of the cases. Finally, it is important to note that there is a significant phenotypic overlap between patients with an *EBF3* pathogenic variants and patients with larger microdeletions in the terminal portion of chromosome 10 (7, 8).

The pathophysiology of HADDS is summarized on Figure 3. *EBF3* interacts with several cofactors involved at different stages of brain development such as *CDKN1A*, *NeuroD* and *ARX* (2, 4, 9-13). It is involved in the Cajal-Retzius migration process, the regulation of the cell cycle within the ventricular zone and their migration to the cortex as well as the differentiation of some classes of neurons. This does not lead to spectacular malformations but to subtle disturbances of neuronal organization and intracortical relations (10). The ultimate consequence is an intellectual disability and a mental retardation (14, 15). As in the central nervous system, *EBF3* interacts at muscular level with a few factors and peptides, such as myoD protein, *ATP2a1*, and *SERCA1*. These proteins are essential to maintain an proper contractility of the sarcolemma and influence $Ca^{2}+$ transport within the muscle fibers (16). The role of *EBF3* in urinary disorders remains unclear. It appears to influence similar molecular and cellular processes in sphincter contractility as they do in muscle tissue (4, 10, 11). It may involve dysregulation of several cofactors such as *ARX*, *HPSE2* and *LRIG2*, which are also involved in the Uro-Facial Syndrome (11). Disturbances in muscle contractility may also be hypothesized to explain intestinal dyskinesia and constipation. In addition, *EBF3* has recently been identified as a novel tumor suppressor gene in some cancers by inducing apoptosis (2, 4, 5). Notably, none of the HADDS cases reported to date have been associated with oncologic disease.

Figure 3: Pathophysiological mechanism of *EBF3* gene. The significance of the different symptoms of HADDS seem to rely upon the *EBF3* expression in different tissues during embryogenesis.

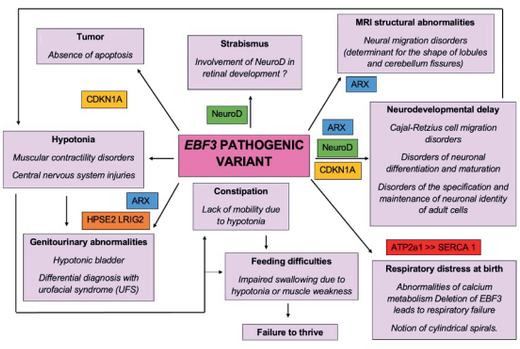


Table 1: Literature review (2-5, 7, 9-11, 13, 16-21). ***Part 1:*** EBF3 gene mutation and a maximum 4 non evaluated clinical features (included in table 2).

Ref Nr.	Individuals	Pathogenic variant	Growth	Developmental Delay	Hypotonia	Ataxia	Epilepsy	Dysmorphia	MRI	View	Genitourinary	Gastrointestinal	Others
2	**Girl** 9 years, 3 months	**c.625C>T (p.Arg209Trp)** Missense (inherited)	22kg (P3) 119 cm (<P3) HC 50 cm (P3)	Intellectual disability Motor delay Speech delay	-	+	+	+	Normal	Strabismus	-	-	-
2	**Boy** 3 years, 4 months	**c.625C>T (p.Arg209Trp)** Missense (inherited)	11 kg (<P3) 91 cm (<P3) HC 48,3 cm (<P3)	Intellectual disability Motor delay Speech delay	-	+	+	+	NE	Strabismus	-	-	-
2	**Boy** 5 years, 9 months	**c.913C>T (p.Gln305*)** Nonsense	21 kg (P50-75) 108 cm (P25) HC 51.5 cm (P25)	Intellectual disability Motor delay Speech delay	Normal with increasing age	+	-	-	Normal	Strabismus	-	Inguinal hernia	2nd and 3rd toe syndactyly
2	**Boy** 16 years, 6 months	**c.196A>G (p.Asn66Asp)** Missense	45.8 kg (P3) 168 cm (P25-50) HC 57 cm (P50-75)	Intellectual disability Motor delay Speech delay Dysarthria	-	+	-	+	Vermis hypoplasia	Strabismus	-	Gastroesophageal reflux Esophagitis	Behavioral disorders
2	**Boy** 4 years, 6 months	**c.1101-1G>T** Splice site	25,67 kg (>P97) 110,5 cm (P75)	Intellectual disability Motor delay Speech delay	+	NE	-	NE	Normal	Strabismus	-	-	-
2	**Girl** 2 years, 7 months	**c.530C>T (p.Pro177Leu)** Missense	13,3 kg (P50) 90,2 cm (P50) HC 49,7 cm (P70)	Intellectual disability Motor delay Speech delay	+	+	-	+	Normal	Strabismus	-	-	-
2	**Boy** 23 months	**c.422A>G (p.Tyr141Cys)** Missense	10,6 kg (P10) NE HC 49,7 cm (P70)	Intellectual disability Motor delay Speech delay	+	-	-	-	Normal	Strabismus	-	-	Congenital heart disease
2	**Girl** 13 years	**c.512G>A (p.Gly171Asp)** Missense	42,2 kg (P25) NE HC 51,9 cm (P10)	Intellectual disability Motor delay Speech delay	+	+	NE	+	Normal	NE	Neurogenic bladder Bilateral vesicoureteral reflux	Constipation Feeding difficulties	2nd and 3rd toe syndactyly Moderate scoliosis
2	**Girl** 25 years	**c.907C>T (p.Arg303*)** Nonsense	55 kg (P50) 167 cm (P50)	Intellectual disability Motor delay Speech delay	-	-	-	+	NE	Normal	-	-	-
2	**Boy** 3 years, 5 months	**c.469_477dup (p.His157_Ile159dup)** 9pb duplication	12,4 kg (P3) 95 cm (P25) HC 51 cm (P50)	Intellectual disability Motor delay Speech delay	+	NE	-	+	Vermis hypoplasia	Strabismus	Recurrent urinary tract infection Phimosis	Constipation	-
9	**Boy** 7 years	**c.488G>A (p.Arg163Gln)** Missense	NE	Developmental delay Dysarthria	+	+	NE	+	Vermis hypoplasia, small cerebellar lobes	Strabismus	Micropenis Cryptorchidism	Dysphagia Gastroesophageal reflux	Decreased fetal movements
9	**Girl** 5 years	**c.488G>A (p.Arg163Gln)** Missense	NE	Developmental delay Dysarthria Apraxia	+	+	NE	+	Vermis hypoplasia	Strabismus	-	Feeding difficulties	Decreased fetal movements High pain tolerance
9	**Girl** 3 years	**c.488G>T (p.Arg163Leu)** Missense	NE	Developmental delay Dysarthria	+	NE	NE	+	Normal	NE	-	Dysphagia	High pain tolerance Motor stereotypes
4	**Boy** 2 years, 6 months	**c.191A>C (p.Lys64Thr)** Missense	10.890 kg (P3) HC 47 cm (P10)	Sitting at 18 months Stands on its own, do not walk. Nonverbal, he understands his parents	+	+	-	+	NE	NE	Micropenis	-	High pain tolerance No social contact Pectus excavatum Laryngomalacia
4	**Girl** 24 years	**c.244delG (p.Val82TrpfsX50)** Frameshift	68,5 kg (P85) 149,5 cm (<P3) HC 56 cm (P75)	Sitting at 9 months Walking at 2 years Speaks normally, dysarthria	+	-	-	+	Normal	Strabismus	-	-	autistic features with tics and hallucinations Hypothyroidism Scoliosis ++
4	**Girl** 10 years	**c.471C>A (p.His157Gln)** Missense	27,2 kg (P10) 131,5 cm (P10) HC 52,5 cm (P50)	Sitting at 12 months Walking at 3 years Speaks at 5 years, dysarthria, fine motor difficulties	+	NE	-	+	NE	Strabismus	Bilateral vesicoureteral reflux Neurogenic bladder Renal duplication	-	Behavioral difficulties, autism, 2nd and 3rd toe syndactyly, sleeping disorders
4	**Girl** 11 years	**c.486-1G>A (IV55-1G>A)** Splice site	30.2 kg (P10) 129 cm (<P3)	Walks with help only Nonverbal	+	+	-	+	Vermis hypoplasia	Strabismus	-	Constipation Nasogastric tube	Autistic features Headaches
4	**Girl** 11 years	**c.616C>T (p.Arg206X)** Nonsense	51,6 kg (P95) 131,4 cm (P3) HC 54,2 cm (P75)	Sitting at 4 months Walking at 14 months Speaks at 10 months, dysarthria	+	+	-	+	Delayed myelination at 2 years	Refraction error	Recurrent urinary tract infections, hydronephrosis	-	Obesity
4	**Boy** 15 months	**c.626G>A (p.Arg209Gln)** Missense	8 kg (<P3) 72,2 cm (P3)	Sitting at 9 months No walking at 12 months, babbling at 8 months, but no words at 12 months	+	+	+	+	Abnormal	Strabismus	Micropenis	-	No social smile Decreased fetal movements
4	**Girl** 4 years	**c.1402_1414del13 (p.Thr46Profs*10)** Frameshift	14,7 kg (P50) 104 cm (P50) HC 47,2 cm (P10)	Sitting at 8 months Walking at 2 years Speaks at 4 years (begins to say words at 2 years)	-	+	-	-	Normal	-	Recurrent urinary tract infection	-	Hypertonia of the hips
3	**Girl** 2 years	**c.487C>T (p.Arg163Trp)** Missense	Height (< P3) Weight & HC (P25)	Developmental delay Sitting at 12 months Do not walk at 2 years 2-3 word's sentences at 2 years	+	-	NE	+	Normal	Strabismus	Urethra stenosis Bicornuate uterus	-	Pectus excavatum
5	**Boy** 13 years	**c.488 G>C (p.Arg163Pro)** Missense	Height (< P3) HC (P75-90)	Stands with support at 2 years Walking at 5 years and 8 months Speech = 50 words at 6 years ½ Dysarthria Intellectual disability (IQ 71) – special school	+	+	-	+	Vermis atrophia	Strabismus	Left cryptorchidism	-	High-pitched voice, pectus excavatum
5	**Boy** 7 years	**c.530 C>T (p.Pro177Leu)** Missense	Normal height Normal weight HC (P50-75)	Sitting at 9 months Stands with support at 19 months Walking at 2 years Speaks at 20 months, (speech delay), dysarthria Normal school	+	+	-	+	Normal	Strabismus	-	-	High pain tolerance Behavioral difficulties
5	**Boy** 8 years, 4 months	**c.355 + 1 G>C** Unknown pathogenic variant	Height & Weight (<P3) Microcephaly	Stands with support at 2 years Walking after 4 years Speaks at 3 years (speech delay) Normal school	+	+	NE	+	Normal	Strabismus	-	-	Smalls toes and fingers
5	**Girl** Unknown age	**c.579 G>T (p.Lys193Asn)** Missense	Short stature Normal HC	Head support at 2 years Sitting at 30 months Stands with support at 4 years, do not walk Speech : < 20 words at age 10 Special school	+	-	+	+	Normal	Strabismus	Bilateral vesicoureteral reflux	Feeding difficulties	-
5	**Girl** 8 years, 5 months	**c.280_283del (p.Glu94Lysfs*37)** Frameshift	Short stature Small weight Small HC	Sitting at 12 months Waking at 2 years, 8 months Speech : a few sentences, echolalia and dysarthria Special school	+	+	Febrile seizures	+	Subtle cortical dysplasia	Strabismus	Neurogenic bladder, bilateral vesicoureteral reflux Recurrent urinary tract infections	Constipation Feeding difficulties	-

5	**Girl** 4 years, 8 months	**c.554 + 1 G>A**	Normal weight Normal height Microcephaly	Head support at 18 months Sitting at 2 years Do not stand up Do not walk Do not speak Special school	+	+	+	-	Normal	Nystagmus	Bilateral vesicoureteral reflux Renal dysplasia Recurrent urinary tract infections	-	-
5	**Boy** 14 years	**c.616 C>T (p.Arg206*)** Nonsense (inherited)	Normal weight Normal height Normal HC	Sitting at 8 months Stands with support Walking at 18 months Speech : first words at 19 months Normal school	+	+	-	+	Normal	Normal	-	-	Behavioral difficulties
5	**Girl** 9 years	**c.616 C>T (p.Arg206*)** Nonsense (inherited)	Normal weight Normal height Normal HC	Sitting at 8-9 months Walking at 16 months Speech : first words after 2 years, ten words after 2 years ½ Normal school	+	+	-	+	Normal	Normal	-	-	Behavioral difficulties
11	**Girl** Died at 17 years old	**c.626 G>A (p.Arg209Gln)** Missense	Short stature ++ Microcephaly	Developmental delay Do not walk Speech : 2 words at 3 years	+	NE	NE	+	Normal	NE	Bilateral vesicoureteral reflux Neurogenic bladder Recurrent urinary tract infections Died from acute renal failure	Constipation	2nd and 3rd toe syndactyly, Atrioventricular defect DD with orofacial syndrome (UFS)
16	**Boy** 18 years	**c.616C>T (p.Arg206*)** Nonsense (inherited)	NE	Developmental delay Intellectual deficiency Sitting at 13 months Walking at 27 months Speaks normally at 18 years, no mental retardation	+	+	-	+	NE	Strabismus	Neurogenic bladder	Feeding difficulties	Laryngomalacia Recurrent otitis Autistic features Scoliosis Muscle cramps Muscle biopsy at the age of 3 (cylindrical spirals)
7	**Girl** 34 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (de novo)	Normal height Normal HC	No development delay but clumsy Walking at 15 months No ID	+	-	NE	+	Normal at 34 years	Strabismus	Vesicoureteral reflux Recurrent urinary tract infections	-	Tremor Behavioral difficulties Vertigo
7	**Girl** > 16 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (inherited)	Normal height Normal HC	Developmental delay Walking at 24 months No ID	+	+	NE	+	Normal	Strabismus	-	-	Tremor Behavioral difficulties Congenital calcaneovalgus Pes planus
7	**Girl** > 16 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (inherited)	Normal height Normal HC	No motor delay (walking at 14 months) but clumsy Speech delay No ID	-	+	NE	NE	NE	Strabismus	Renal cyst Recurrent urinary tract infections	-	Tremor Behavioral difficulties Vertigo
7	**Girl** 5-15 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (inherited)	Normal height Normal HC	Developmental delay Walking at 21 months No ID	+	+	NE	NE	NE	Strabismus	-	-	Tremor Behavioral difficulties Pes planus
7	**Girl** 5-15 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (inherited)	Normal height Normal HC	Developmental delay Walking at 20 months No ID	-	+	NE	+	Normal	Strabismus	Smaller right kidney Recurrent urinary tract infections	-	Tremor Pes planus Proximal radius abnormalities
7	**Girl** 1-5 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (inherited)	Short stature Normal HC	Motor delay No speech delay No ID	+	+	NE	NE	Normal	Strabismus	Recurrent urinary tract infections	-	Tremor Pes planus
7	**Girl** 5-15 years	**c.625C>T (p.Arg209Trp)** Missense	Normal height Normal HC	Developmental delay Walking at 22 months No ID	+	+	NE	NE	Vermis hypoplasia	Strabismus	-	-	Tremor Pes planus
7	**Girl** 5-15 years	**c.1183C>T (p.Arg395Ter)** Missense (inherited from mosaic mother)	Normal height Normal HC	Motor delay Walking at 18 months No speech delay No ID	+	+	NE	NE	Normal	Strabismus	-	-	Tremor Pes planus
7	**Boy** < 2 years	**c.530C>T (p.Pro177Leu)** Missense	Normal height Normal HC	Developmental delay No walking at 17 months	+	+	NE	NE	Abnormal	-	Hydrocele testis	Feeding difficulties Vomiting	Respiratory distress at birth Weak cry
GY	**Girl** 2 years, 4 months (may 2021)	**c.626 G>A (p.Arg209Gln)** Missense	8,800 kg (< P3) 78 cm (< P3) HC 49 cm (P85)	Speech : few words Sits, moves on all fours, stands while holding on a chair, can take a few steps with a walker, thumb-index grasp, turns pages in a book	+	+	-	+	Large sulci Vermis atrophia	Strabismus	Bilateral vesicoureteral reflux Neurogenic bladder Recurrent urinary tract infections	Feeding difficulties Nasogastric tube, gastrostomy Constipation Gastrointestinal reflux	Sleeping disorders Hyperacusis

Table 1: Literature review (2-5, 7, 9-11, 13, 16-21). ***Part 2:*** EBF3 gene mutation with less than 4 evaluated clinical features.

Ref Nr.	Individuals	Pathogenic variant	Growth	Developmental Delay	Hypotonia	Ataxia	Epilepsy	Dysmorphia	MRI	View	Genitourinary	Gastrointestinal	Others
10	**Boy** Unknown age (first visit at 5 months)	**c.512 G>A (p.G171D)** Missense	NE	Developmental delay	+	+	NE	+	Abnormal cerebellum	NE	NE	NE	NE
17	**Boy** 4 years, 8 months	**c.872 T>A (p.L291*)** Nonsense	NE	Motor delay Speech delay, dysarthria Do not go to school	NE	+	-	-	NE	NE	-	Feeding difficulties	-
18	**Unknown gender** Unknown age	**c.232 C>T (p.Gln78*)** Nonsense	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	Autistic features
16	**Girl** 31 years (mother of individual 31)	**c.616C>T (p.Arg206*)** Nonsense	NE	Developmental delay Walking at 2,5 years Speech delay	+	NE	NE	+	NE	NE	NE	NE	Scoliosis Muscular weakness with cramps Muscle biopsy at the age of 31 (cylindrical spirals)
19	**Girl** 6 years	**c.318C>G (p.Asn106Lys)** Missense Consanguineous family	NE	Developmental delay Intellectual deficiency Speech delay	NE	+	NE	NE	NE	NE	NE	NE	NE
20	**Unknown gender** Unknown age	**Unknown mutation** Missense	NE	Developmental delay Intellectual deficiency	NE	NE	NE	NE	NE	NE	NE	NE	Autistic features
13	**Girl** 11 years	**De novo 600 kb deletion at 10p26.3** 3 genes : MGMT, EBF3 & GLRX	NE	Developmental delay Head control at 12 months, sitting at 18 months, walking at 30 months No words at 3 years	+	NE	Suspicious	+	Normal	Strabismus	No renal abnormalities Urinary tract infection	Gastro-intestinal reflux	Small weight birth (< P3) Pes planus Recurrent otitis Autistic features
21	**Girl** 5-15 years	**Deletion ?**	Normal height Normal HC	Developmental delay No walking at 17 months No ID	+	+	NE	NE	Superior part of vermis dysplasia	-	-	NE	Tremor Behavioral difficulties Pes planus

Table 2: Prevalence in the literature of clinical signs observed in HADDS.

	Prevalence in the literature
Hypotonia	82,9%
Ataxia	81,5%
Developmental delay - Intellectual deficiency - Motor delay - Speech delay	95,1%
Moderate dysmorphia	88,2%
Epileptic seizures	24%
Autistic features and/or behavioral disorders	29,2%
Abnormal RMI	35,3%
Strabismus	81%
Failure to thrive and/or short stature	51,4%
Genito-urinary abnormalities - Recurrent urinary tract infections - Vesicoureteral reflux - Neurogenic bladder - Renal disorder - Micropenis - Phimosis - Cryptorchidism - Bicornuate uterus	51,2%
Gastrointestinal disorders - Gastro-esophageal reflux/dysphagia - Feeding difficulties - Constipation - Inguinal hernia	34,1%
Musculoskeletal abnormalities - Syndactyly 2nd/3rd toe - Scoliosis - Pectus excavatum - Muscle weakness/cramps - Pes planus	41,5%
Heart defects	<5%
Pathogenic variants - Missense - Nonsense - Duplication - Frameshift - Splice-site	 54% 15% 18% 8% 5%

Currently, there is no cure for HADDS. Only symptomatic treatments can improve the quality of life. Multidisciplinary care involving psychologists, speech therapists, physical therapists, and occupational therapists is essential. Assessing the prognosis of HADDS patients remains challenging due to the recent discovery of this syndrome (1).

Conclusion

HADDS is an extremely rare genetic syndrome in which the principal symptoms of severe hypotonia, ataxia, global developmental delay, strabismus, failure to thrive, and muscular dysfunction appear to be linked to a pathogenic variant of the *EBF3* gene. Other clinical manifestations have been reported with a large inter-individual variability. Further research on the *EBF3* gene and the associated pathological pathways is needed to improve our understanding of HADDS and provide appropriate care in such rare diseases.

Conflict of interest

All authors declare no conflicts of interests.

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