Annals of Agricultural and Environmental Medicine 2024, Vol 31, No 2, 306–310
www.aaem.pl

CASE REPORT

A four-year-old girl with pathogenic variant in the NAA10 gene and precocious puberty – case report and literature review

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Wojciechowska K, Zie W, Pietrzyk A, Lejman M. A four-year-old girl with pathogenic variant in the NAA10 gene and precocious puberty – case report and literature review. Ann Agric Environ Med. 2024; 31(2): 306–310. doi: 10.26444/aaem/171758

Abstract

The NAA10 gene encodes N-alpha-acetyltransferase 10 which plays an important role in cell growth, differentiation, DNA damage, metastasis, apoptosis, stress response and autophagy. Defects in the NAA10 gene correlate with the diagnosis of NAA10-related syndrome (Ogden syndrome). The most common symptoms of NAA10-related syndrome are: global developmental delay, non-verbal or limited speech, autism spectrum disorder, feeding difficulties, motor delay, muscle tone disturbances, and long QT syndrome. To-date, there are about 100 patients who have been reported with this condition. The case report presents the clinical study of a girl aged 4 years and 3 months diagnosed with Ogden syndrome. She had many characteristic features of the disorder, as well as precocious puberty. This girl represents the case of a patient with p.Arg83Cys mutation in NAA10 gene as well as precocious puberty.

Key words

precocious puberty, NAA10-related syndrome, Ogden syndrome, NAA10 gene.

INTRODUCTION

NAA10-related syndrome (Ogden syndrome) is an X-linked condition associated with defects in the N-alpha-acetyltransferase 10 (*NAA10*) gene. The process of N-alpha-acetylation is a co-translational protein modification which is essential for the proper functioning of human cells [1]. It is also essential during embryogenesis and tissue and organ development [2, 3]. N-alpha-acetylation is the most common post-translation protein modification in eukaryotic cells. This process occurs during protein synthesis, which involves the transfer of an acetyl group from acetyl-coenzyme A to the protein alpha-amino group. This protein modification acts on subclasses of proteins with Ser-, Ala-, Thr, Gly-, Cys-, and Val-N termini [4]. Recent results in mice showed that the expression of *Naa10* increases in the brain regions rich in proliferating and migrating cells in the hippocampus, and in the cerebellum [5]. Lee et al. [5] reported that the phenotypes of *Naa10*-deficient mice indicate a dysregulation of genomic imprinting and developmental defects, such as partial embryonic lethality, postnatal growth retardation, brain disorders, and maternal effect lethality. However, the studies by Lyon et al. [6] were unable to replicate the reported 'maternal effect lethality'.

NAA10, located on chromosome Xq28, encodes the catalytic subunit of N-acetyltransferase A, which is expressed in most human cell types, and plays a role as an important regulator in cell growth, differentiation, DNA damage, metastasis, apoptosis, stress response and autophagy [5]. The phenotypes of the patients with pathogenic variants in *NAA10* differ from severe phenotypes in males with p. Ser37Pro mutation (described as the Ogden syndrome) to the milder phenotypes found in both males and females, called *NAA10*-related syndrome [2, 7, 8, 9]. Esmailpour et al. [10] reported a family with a mutation in the intron 7 splice donor site (c.471+2T>A) of *NAA10 and Lenz* microphthalmia syndrome. The first patients presented in the literature – deceased boys with Ogden syndrome – had many health problems, including a senile-like appearance, global developmental delay, hypotonia, structural heart defects, cardiomegaly and cardiac arrhythmias. All of them had missense variant p.Ser37Pro in the *NAA10 gene [11].* Among a wide spectrum of malformations in NAA10-related syndromes, there are common phenotypes. The heterozygous female with *Ogden* syndrome may be asymptomatic or may have the same clinical features as affected males. The characteristic features of Ogden syndrome include: postnatal growth failure, skeletal abnormalities, severely delated psychomotor development, variable dysmorphic features, cardiac abnormalities (arrhythmias or congenital heart defects), hypotonia, redundancy or laxity of the skin, cutaneous capillary malformations, genitourinary anomalies, and recurrent infections [9, 12]. Female phenotypes vary depending on X-chromosome skewing and pathogenic variants found in *NAA10 [3].*

The patient in the presented case report is a 4-year-old girl with the *de novo* variant p.Arg83Cys in the *NAA10* gene, with many characteristic features of Ogden syndrome as well as precocious puberty.

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Received: 11.06.2023; accepted: 01.09.2023; first published: 22.09.2023

CASE REPORT

The patient is a girl aged 4 years and 3 months, born at 35 weeks of gestation as the third child of healthy, non-consanguineous, Caucasian parents. During pregnancy, her mother was diagnosed with gestational diabetes and was treated with insulin, Fraxiparine, and Disprin due to venous insufficiency. Foetal ultrasound in the third trimester showed enlargement of the brain cavities. The patient weighed 2,870 g at birth, measured 52 cm in length, and 33 cm in OFC. She received 7–7–8–9 score according to the Apgar scale. During the perinatal period, she had hypoglycaemia, was lethargic, and was diagnosed with congenital pneumonia, intracranial haemorrhage, and sensorineural hearing loss. An echocardiogram revealed an atrial septal defect type II, and cranial ultrasound showed ventricular enlargement (Evans index – 0.44). She also had global hypotonia, postural asymmetry, problems with coordination of sucking, swallowing and breathing.

During the first year of life, the psychomotor development of the patient was delayed, and her parents observed several instances of regression. She remained in a sitting position once seated, did not crawl or walk, avoided eye contact, and vocalized but did not speak. Since the fourth month of life, she has had chronic, bilateral, otitis media, and was diagnosed with moderate conductive hearing loss. At 10 months old, patient was diagnosed with premature puberty (M3P1A1 according to the Tanner scale) with breast enlargement and clitoral hypertrophy. The result of LHRH test showed elevated levels of FSH, which is characteristic for thelarche praecox. MRI results revealed a regular hypophysis morphology. An abdominal ultrasound showed that the uterus and right ovary were of prepubertal in size, and the ovarian follicles enlarged. Elevated levels of prolactin and alpha fetoprotein were also present.

At the age of 4 years and 6 months, the patient's height was 98 cm (25th percentile), and weighed 14 kg (25th percentile). Her characteristic facial features are presented on Figures 1 and 2. Although she began to walk around furniture, and despite still not speaking, her parents stated that she seemed to understand much of what was being said to her. She demonstrated emotional growth, and began to engage in cuddling. A Holter monitor test and echocardiography did not show any abnormalities. Her puberty remained M3P1A1 according to the Tanner scale, and her levels of prolactin and alpha-fetoprotein remained elevated. Therapy with Diphereline was planned.

DISCUSSION

Most human proteins are acetylated by a group of enzymes named N-terminal (Nt) acetyltransferases (NATs). So far, eight NATs have been identified and seven – NatA, NatF and NatH – are expressed in humans [13]. NatA, which is composed of catalytic subunit NAA10 and the auxiliary subunits NAA15, NAA50 and HYPK, is one of the major NATs, responsible for co-translationally Nt-acetylating nearly half of the human proteome [4]. Loss of catalytic subunit NAA10 by inappropriate expression of mutated *NAA10* is associated with different developmental defects in humans. There are several symptoms reported in the literature for patients with defects in NAA10: neonatal-onset hypotonia, brain abnormalities, dysmorphic facial features with limited subcutaneous fat, congenital heart defects (such as patent ductus arteriosus,, patent foramen ovale, ventricular septal defect, atrial septal defect, pulmonary artery stenosis), various forms of cardiac arrhythmias that may also occur prenatally (i.e ventricular tachycardia, atrial fibrillation, bradycardia, PR prolongation, repolarization delay, QT prolongation), postnatal growth restriction, inguinal hernia, cryptorchidism, and small testes in males, skeletal deformities (including scoliosis, pectus excavatum, hip dysplasia, metatarsus valgus, and relatively large halluces), varying degrees of intellectual disability, behavioural disorders (i.e. autistic features, attention deficit hyperactivity disorder, stereotypic, compulsive and obsessive behaviours, and aggressiveness), recurrent infections [9]. *NAA10* is an

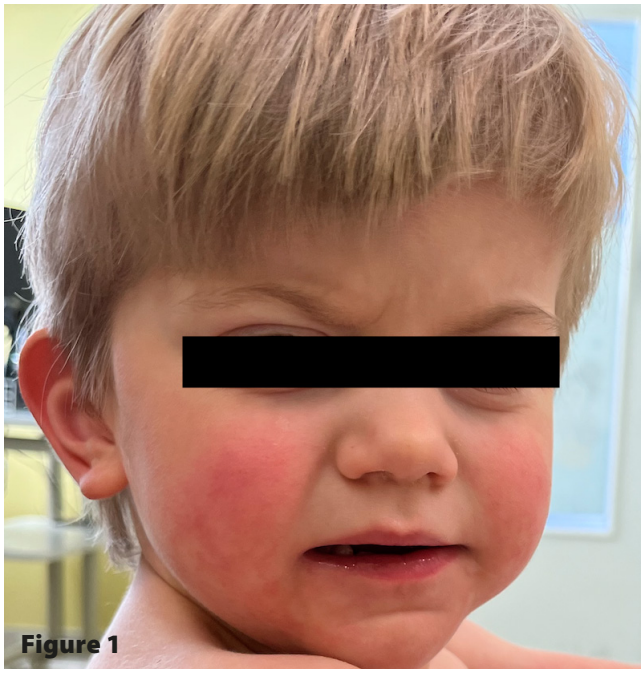
Figure 1


Figure 2

Figures 1 and 2. Note the characteristic dysmorphia: coarse facial features, prominent eyes and philtrum, thick eyelids, sparse eyebrows and large, low-set ears.

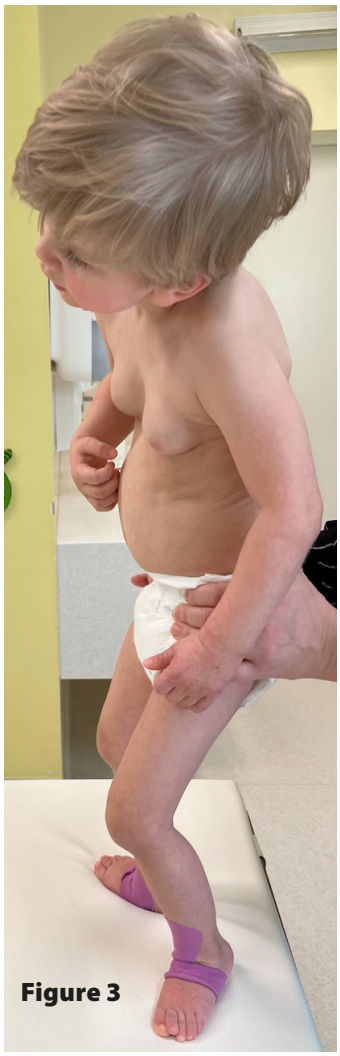
Figure 3

Figures 3, 4 and 5. Note the posture of the patient, her hand and feet. The features of premature puberty (M3P1A1 according to the Tanner scale) are also visible

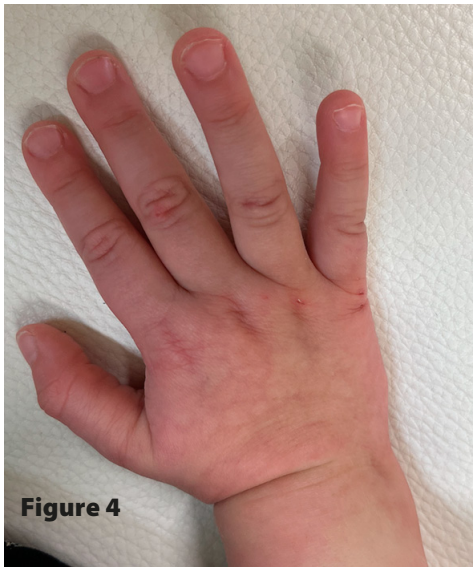
Figure 4


Figure 5

X-linked gene, and hemizygous males are more severely affected compared to heterozygous females. The phenotypes of female patients range from asymptomatic to having some of the same clinical symptoms that affect males, depending on the presumed favourable or unfavourable X-chromosome inactivation [2].

Lyon et al. [14] presented the features of 56 patients with *NAA10* variants, most of whom had intellectual disability, global developmental delays, autism spectrum disorder, feeding difficulties during and after infancy, characteristic facial features with thicker eyebrows, long eyelashes, upturned nose, and broad nasal bridge, arrhythmias and elongated QT interval and poor growth. Six patients reported by the authors had precocious puberty. The study by Sandomirsky et al. [15] of 61 children with Ogden syndrome, demonstrated a high prevalence of growth failure which was due to feeding difficulties in infancy, dysphagia, GERD/silent reflux, constipation, diarrhea, bowel incontinence, eosinophilic esophagitis, cyclic vomiting syndrome, Mallory Weiss tears, abdominal migraine, esophageal dilation, and subglottic stenosis.

Ocular manifestations are found in more than half of patients [16]. Among 40 patients presented by Gupta et al. [16], the most common ocular findings were: astigmatism (n=6), hyperopia (n=4), hypertelorism (n=3), myopia (n=3), cortical vision impairment (n=3), exotropia (n=3), and anophthalmia/microphthalmia (n=3). The patient in the presented case report had astigmatism for which bright lights were a strong trigger.

Sidhu et al. [17] presented a case of 14-year-old girl with the *de novo* pathogenic variant c.247C>T, p.R83C in *NAA10* gene. The patient presented with global developmental delay, dysmorphic features, epileptic encephalopathy, and hypertension with left ventricular hypertrophy. In this case, however, the authors did not report precocious puberty

A 10-year-old girl who had the p.(His16Pro) variant in the *NAA10* gene, reported by Bader et al. [18], also had severely delayed motor and language development. And just as in the presented case report, she started to walk at the age of 4. She displayed disturbed behaviour with hyperactivity and restlessness, moderate dilatation of the ventricular system and extracerebral CSF spaces, but no arrhythmias were reported. A patient presented by Hofman et al. [19], identified with c.109 T>C p.Ser37Pro variant in the *NAA10* gene, had ventricular hypertrophy and a ventricular septal defect (VSD). A patient reported by Shishido at el. [20] with c.455_458del, p. Thr152Argfs*6 variant in the *NAA10 had* hypertrophic cardiomyopathy (HCM). To-date, the patient in the presented case report does not have any cardiac problems.

Twenty females with ID and DD have been found to harbour an *NAA10* p.Arg83Cys variant, which makes it the most commonly reported *NAA10* variant to-date [7, 12].

Maini et al. [12] reported an 18-year-old girl with the *de novo* p.Arg83Cys variant in *NAA10,* with dysmorphic facial features, severely delayed motor and language development, autistic traits, postnatal growth failure, conductive hearing loss, apical muscular VSD, mild-to moderate hypertrophic cardiomyopathy, oversized spleen and liver, accessory spleen, delayed skeletal maturation, frontal lobes and cerebellar atrophy, thin corpus callosum, dilation of the frontal horns of the lateral ventricles, and epilepsy.

In the presented case report, the patient, at the age of 5, did not exhibit symptoms of hypertrophic cardiomyopathy or signs of CNS atrophy or epilepsy. Wei et al. [21] reported a 3- year-old girl carrying the *de novo* p.Arg83Cys variant in *NAA10* who had dysmorphic facial features, developmental delay, intellectual disability, growth failure, hypertrophic cardiomyopathy. The patient also had exophthalmos, blue sclera, cutaneous capillary malformations and adenoid hypertrophy; however, precocious puberty was not reported.

Among a group of 19 female patients with the p.Arg83Cys variant in the NAA10 gene, the most common symptoms were severe psychomotor developmental delays and language impairment, together with autistic traits, postnatal growth failure, dysmorphic facial features (coarse face, prominent forehead, bitemporal narrowing, arched eyebrows, and up-turned nose), visual defects, brain anomalies with white matter hypoplasia, a thin corpus callosum, and enlarged ventricles, Half of the patients had congenital heart defects and arrhythmias, and a prevalence of hearing loss. Additionally, the patients experienced delayed skeletal maturation, sleeping problems and seizures [12]. Only one patient reported by Gupta et al. [16] with the *de novo* pathogenic missense c.247C>T p.Arg83Cys variant in the *NAA10* gene, had precocious puberty, as in the presented case report.

Table 1 compares all the features described in the above reports and in the presented case report.

In conclusion, the patient described exhibits many clinical features previously described in females with the p.Arg83Cys variant in *NAA10, as well as central precocious puberty, which* expands the *NAA10* clinical phenotype. Therefore, it is recommend that patients diagnosed with the *NAA10-related syndrome should* undergo a precise medical follow-up, particularly for neurodevelopment, cardiac disease, including HCM, ocular abnormalities, and scoliosis. Due to the risk of *precocious puberty, the patients* should also be under the care of paediatric endocrinologists

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Table 1. Comparison of the features of the presented patient with the features of other reported patients

Characteristic Features of NAA10 Mutation (Ogden Syndrome)	Our Patient female	Patient No. 2 female [12]	Patient No. 3 female [18]	Patient No 4 female [22]	Patient No. 5 female [16]	Patient No 6 female [17]	Patient No. 7 female [8]	Patient No. 8 male [8]	Patient N. 9 female [23]	Patient No. 10 male [24]	Patient No. 11 male [19]	Patient No. 12 male [2]	Patient No. 13 male [2]	Patient No. 14 male [25]	Patient No. 15 male [25]
X-linked recessive	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
X-linked dominant	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Short stature	+	+	+	-	+	-	+	+	-	+	-	+	+	+	+
Postnatal Growth Failure	+	+	+	-	+	-	+	+	-	+	-	+	+	-	+
Prominent forehead	+	-	-	-	+	-	-	+	-	-	-	-	-	-	-
Wrinkled forehead	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-
Depressed midface	+	-	-	-	+	-	-	+	-	+	-	+	+	-	-
Coarse facial features	+	+	+	-	+	-	+	-	-	+	-	+	+	-	+
Prominent philthrum	+	+	-	-	-	-	-	+	-	+	+	+	+	-	-
Large ears	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-
Low-set ears	-	+	-	-	-	-	-	-	-	+	-	+	+	-	+
Prominent eyes	-	-	-	-	-	-	-	+	-	-	-	-	-	-	+
Downslanting palpebral Fissures	-	-	+	-	+	-	-	+	+	+	-	+	+	-	-
Thick eyelids	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Epicanthol folds	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sparse eyebrows	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Flared nares	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypoplastic alae nasi	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Short columnella	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-
Broad nasal bridge	+	+	+	-	-	-	+	-	-	+	+	-	-	-	-
Flat nasal bridge	-	-	-	-	+	-	-	-	-	-	+	+	-	-	-
Protruding upper lip	-	-	-	-	-	-	-	-	+	-	-	-	-	+	-
Thin upper lip	-	+	-	-	-	-	+	-	-	+	-	-	-	-	-
High-arched palate	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-
Dental abnormalities	-	-	+	-	-	-	-	-	-	+	-	+	+	-	-
Ventral septal defect	-	+	-	-	-	-	-	-	-	-	+	-	-	-	+
Atrial septal defect	+	-	+	-	-	-	+	-	-	-	+	-	-	-	-
Arrythmias	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-
Torsade de pointes	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Premature ventricular contraction	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-
Premature atrial defect	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Supraventricular tachycardia	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-
Pulmonary artey stenosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cyrptochiridism	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inguinal hernia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Delayed closure of fontanels	-	+	-	-	-	-	+	-	-	+	-	-	-	-	-
Scoliosis	+	+	+	-	-	-	-	-	-	+	-	+	+	-	-
Broad great toes	+	-	+	-	-	-	-	+	-	-	-	-	-	-	-
Cutis laxa	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-
Redundant skin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cutaneous capillary malformations	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fine hair	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Long eyelashes	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Minimal subcutaneous fat	+	-	+	-	-	-	-	-	-	+	-	-	-	-	-
Delayed psychomotor development	+	+	-	+	+	+	+	+	-	+	-	-	-	+	-
Hypotonia	+	+	-	-	+	+	+	+	+	+	-	-	-	-	-
Cerebral atrophy	-	+	-	-	-	+	-	-	-	-	-	-	-	-	-
Autistic features	-	+	-	-	-	+	-	+	-	-	-	-	-	-	-
Sterotypic behaviours	-	+	-	-	-	-	-	+	-	-	-	-	-	-	+
Recurrent infections	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-