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HELSMOORTEL – VAN DER AA SYNDROME

Paediatrics

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ABSTRACT

Helsmoortel – Van der Aa or ADNP syndrome is a rare autosomal dominant inherited monogenic syndrome caused by de novo mutations of ADNP gene. There are very few cases reported worldwide. We are presenting a case of 8 year old male child exhibiting features of ADNP syndrome i.e. intellectual disability, autistic features, mood disorder, language developmental delay and behavioral problems. Whole genome sequencing represents heterozygous missense mutation in exon 5 of ADNP gene of variant c.1190C>T (p.Ala397Val) that results in amino acid substitution from Alanine to Valine at codon 397. The observed variant has minor allele frequency of 0.0040% in population. According to previous reported cases of ADNP syndrome, the correlation between genotype and phenotype was established. Symptomatic treatment with cognitive behavioral therapy, occupational therapy, speech therapy and nutritional support is the available treatment. Therefore, because of very few cases of ADNP syndrome present worldwide, there is need to report cases for better understanding of pathophysiology and clinical manifestation of the disease with better clinical outcome of treatment to delay progression of the disease and increasing the quality of life of patients.

Summary: The patient is presenting with ASD, intellectual disability with communication deficits and attention deficit hyperactivity syndrome. The diagnosis of the disease is made via whole genome sequencing which showed c.1190C>T, p.Ala397Val de novo mutation at exon 5 of ADNP gene that results in amino acid substitution from Alanine to Valine at codon 397, which is not reported previously.. The observed variant has minor allele frequency of 0.0040% in population. There are very few cases of ADNP syndrome present worldwide that is why there is need to report cases for better understanding of pathophysiology and clinical manifestation of the disease with better clinical outcome of treatment to delay progression of the disease and increasing the quality of life of patients.

KEYWORDS

Helsmoortel – Van der Aa Syndrome, ADNP gene, Autism Spectrum Disorder.

INTRODUCTION

Helsmoortel – Van der Aa Syndrome, is a rare autosomal dominant inherited disorder characterized by intellectual disability with autism features. This syndrome occurs due to alteration in activity dependent neuro-protective protein (ADNP) via de novo frameshift or non-sense mutation. ADNP was discovered by Gozes laboratory [1,2]. The human ADNP (hADNP) gene contains five exons and four introns. ADNP regulates various gene expressions during fetal growth and postnatal, various hippocampal genes which regulates pathway of ion channel-synaptic transmission in sex and age dependent manner [3]. According to various studies, ADNP secreted from glial cells in presence of vasoactive intestinal peptide (VIP) [1,4]. ADNP is required for brain formation and its mutation leads to cognitive defects, motor defects, developmental and speech delays [5,6]. According to recent studies, ADNP is a major gene associated with autism spectrum disorders (ASD) and constitute about 0.17% of overall ASDs [7]. Therefore, there is need for better understanding of ADNP syndrome. Here, we are presenting a case study with severe intellectual abnormality with c.1190C>T, p.Ala397Val de novo mutation at exon 5 which is not reported previously.

CASE REPORT

An 8 year old male child, born to non-consanguineous parents presented to us with complains of behavioral problems, hyperactivity, developmental delay and intellectual disability. On taking detailed antenatal and perinatal history from parents, patient's mother told that antenatal history during this pregnancy was insignificant as the boy was delivered via normal vaginal delivery at 38 weeks of gestation with normal birth weight of 2900 g. The father was 32 years old at the time of patient's birth, and the mother 30 years old. The family history was insignificant; as two elder siblings of the patient of age 11 and 10 years were healthy. The patient was asymptomatic until age of 4 years, when he presented with complains of hyperactivity, inattentiveness and intellectual disability. Patient's parents consulted in psychiatry department and did various tests like Malin's intelligence scale for Indian children (MISIC), Binet-kamat test (BKT), Vineland social maturity scale (VSMS), non-contrast computed tomography (NCCT) brain, echocardiogram (ECG), electroencephalogram (EEG), ophthalmologic examination etc. According to tests, the patient was restless, unable to sit at one place, language and communication were very poor, intelligence quotient (IQ) 45 and partial dependence on parents for self-care. Patient's sensory functions (vision and hearing) and motor functions (gross and fine motor) were adequate. NCCT did not show any significant abnormality. The patient was diagnosed with attention deficit hyperactivity disorder and started on methylphenidate with some improvement. At the age of 5 years, patient's parents complained of symptoms progress with poor school performance, risk taking behavior, poor sleep, stereotype behavior, difficulty in social interaction and communication, poor eye contact, echolalia, non-purposeful hands movement (absence of seizures), behavioral problems and episodic mood disorder such as angry and irritable mood were observed. After various consultations with psychiatrists and neurologists, patient did not show any improvement in symptoms. Then, the patient's parents presented to us with similar complains and we advised the parents for whole genome sequencing. In the genetic molecular test, the patient was diagnosed with Helsmoortel – Van der Aa Syndrome (HVDAS) or ADNP syndrome with heterozygous missense mutation in exon 5 of ADNP gene of variant c.1190C>T p.Ala397Val that results in amino acid substitution from Alanine to Valine at codon 397. The observed variant has minor allele frequency of 0.0040% in population. The treatment started with cognitive behavioral therapy, occupational therapy, speech therapy and symptomatic treatment. The patient is called for regular follow up every month. The patient's parents reported some improvement in the patient.

DISCUSSION

ADNP gene is the most frequent gene associated with ASD [7,8]. ADNP syndrome is very recent in concern of knowledge and correlation between genotype and phenotype features. So, it is really important to describe every case diagnosed with ADNP mutation and their follow up. Here, via this case report, we are presenting a new rare case of ADNP syndrome of a child with c.1190C>T (p.Ala397Val) de novo mutation at exon 5 of ADNP gene.

In this case report, the patient presented with ASD, intellectual disability with communication deficits and attention deficit hyperactivity syndrome. Other reported cases of ADNP syndrome also presents with, poly-malformative syndrome (distinctive facial dysmorphism, premature teething, and neurological, visual, cardiovascular, gastrointestinal, urological, musculoskeletal and immune features), and emotional dysregulation [9]. Recently a study showed premature tooth eruption as a potential strong early diagnostic biomarker for ADNP mutation [10].

The treatment of ADNP syndrome is symptomatic. Cognitive

behavioral therapy, speech therapy, occupational therapy and specialized learning programs with nutritional support, are the treatments available. Neuropsychiatric features can also be symptomatically treated.

Recent treatment advances for ADNP syndrome using novel biologically active ADNP peptides is to treat the ADNP children. NAP (NAPVSIPQ) is the shortest active snippet of ADNP [11,12]. The mechanism of action of NAP is via increasing ADNP activity at the cellular level [13]. NAP (Davunetide / CP201) has been in the clinical trials before, leading to increased cognitive scores in amnestic mild cognitive impairment patients [14]. The Gozes laboratory comprehensive assessment of NAP in ADNP haplo-insufficient mice, now paves the path to clinical trials of NAP (CP201) in ADNP children. Coronis Neuro Sciences obtained an orphan drug designation for CP201 from the United States Food and Drug Administration (US-FDA) for the treatment of the ADNP syndrome.

SUMMARY AND CONCLUSION

Helsmoortel – Van der Aa or ADNP syndrome is a rare genetic autosomal inherited disorder due to de novo mutation in ADNP gene. In the above case, patient is presenting with ASD, intellectual disability with communication deficits and attention deficit hyperactivity syndrome. The diagnosis of the disease is made via whole genome sequencing which showed c.1190C>T, p.Ala397Val de novo mutation at exon 5 of ADNP gene that results in amino acid substitution from Alanine to Valine at codon 397, which is not reported previously.. The observed variant has minor allele frequency of 0.0040% in population. Symptomatic treatment with cognitive behavioral therapy, occupational therapy and speech therapy started and called for regular follow up every month. There are very few cases of ADNP syndrome present worldwide that is why there is need to report cases for better understanding of pathophysiology and clinical manifestation of the disease with better clinical outcome of treatment to delay progression of the disease and increasing the quality of life of patients.

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