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Developmental Phenotype of the Rare Case of DJ Caused by a Unique ADNP Gene De Novo Mutation

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Introduction

Activity-dependent neuroprotective protein (ADNP) was discovered by the Gozes laboratory (Bassan et al. 1999; Gozes et al. 1999). Initial studies suggested that this protein is secreted from glial cells in the presence of vasoactive intestinal peptide (VIP), to further mediate VIP's neuroprotective activity (Bassan et al. 1999; Furman et al. 2004). The human ADNP (hADNP) gene structure (~40 kb) includes five exons and four introns with alternative splicing of an untranslated second exon (chromosome 20q12-13.2, a region associated with aggressive tumor growth) (Zamostiano et al. 2001; Gozes et al. 2015b).

With its key regulatory functions, ADNP controls the expression of more than 400 genes during embryonic development (Mandel et al. 2007) and of thousands of hippocampal genes postnatally, impacting pathways associated with ion channels-synaptic transmission in a sex- and age-dependent manner (Amram et al. 2016). Thus, ADNP is essential for brain formation with complete knockout resulting in neural tube closure defects and embryonic death in the mouse (Pinhasov et al. 2003) and with haploinsufficiency (heterozygosity) resulting in cognitive deficits (Vulih-Shultzman et al. 2007) as well as developmental delays and motor and vocalization impediments (Hacohen-Kleiman et al. 2018).

In humans, an ADNP gene deletion was first implicated in delayed cognitive development in a case study in 2007 (Borozdin et al. 2007). Later, a syndrome with multiple body organ involvements and neurodevelopmental delay named

In memory of Professor Kevyan Mazda head of the Department of Orthopedia who passed away, and whose experience and expertise cannot be separated from his humanity, his sense of humor and his love for the children he operated on or followed for years. DJ's rare case allowed him to meet and be saved by great physicians in most of the main Parisian Child Hospitals.

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ADNP syndrome or Helsmoortel-Van der Aa syndrome was characterized (Helsmoortel et al. 2014), caused by de novo mutations in the ADNP gene (O'Roak et al. 2012) (https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=404448). Interestingly, a recent publication suggested that ADNP is one of three major genes associated with autism spectrum disorders (ASD) (Larsen et al. 2016), complementing the original estimation of the ADNP-related syndrome constituting about 0.17% of ASD cases (Helsmoortel et al. 2014).

These findings mark ADNP as one of the most frequent autism spectrum disorder (ASD)-associated genes known to date. Therefore, further understanding of the ADNP syndrome is of general interest both from a case study point of view as well as from a population perspective.

Here, we chose to present one case study and concentrate, for the first time, on its behavioral manifestations and its changes from birth to early adulthood. We report the behavioral profile and the change of an adolescent demonstrating intellectual disability (ID), ASD, and challenging behaviors carrying the c.537dupA, p.Val180Serfs*2 de novo mutation of the ADNP gene, a novel mutation not reported previously.

Methods

We retrospectively reviewed patient's charts in both pediatric and adult hospitals and both somatic (e.g. genetics, surgery) and psychiatric departments. Given the number of hospitalizations, all in Paris area and Assistance Publique—Hôpitaux de Paris (APHP), we search the electronic database using DJ's name and social security national number. We also interviewed the mother who was specifically involved in DJ's medical history since birth. In addition, we also reviewed the chart of the child ambulatory clinics located in the corresponding district of Paris where the family lived. We found that DJ has benefited from more than 20 inpatient stays including a dozen hospitalizations for heavy surgical procedures since birth. He was supported by nearly thirty university hospital departments among Kremlin-Bicêtre, Robert Debré, Necker, Trousseau, and Pitié-Salpêtrière hospitals in Paris. He received also supports from a medical mobile unit specialized in complex situations in autism, as well as treatments from several paramedical professionals as private outpatient services. Psychiatric care was coordinated at the medico-psychological center of DJ's district since he was 5 years old. In addition, he was treated in a day-care hospital specialized in autism from 6 to 9 years old in the Child and Adolescent Psychiatry Department at the Pitié-Salpêtrière hospital. Then, he had 1 month of assessment at the age of 14 years due to challenging behaviors, and was hospitalized full-time for 3 weeks in a specialized neurobehavioral unit at the age of 15 years.

To characterize behavioral and developmental outcomes, we used two standardized instruments: The Vineland Adaptive Behavior Scales and the Aberrant Behavior Checklist. The Vineland Adaptive Behavior Scales (VABS-II) (Kanne et al. 2011) is a behavioral scale encompassing a parent interview assessing the ability of individuals to perform daily activities required for personal and social sufficiency. It examines four specific domains: communication, daily living skills, socialization, and motor skills. The subscale scores are added up to yield an Adaptive Behavior Composite score. Although the Vineland assessment tool was not originally designed for people with ASD, studies have shown that it is relevant for this diagnosis as well. Adaptive behavior is a concept that refers to the ability of carrying out productive daily activities, necessary for personal and social autonomy. In adolescence and adulthood, three main fields of skills are explored: communication, autonomy in daily life, and social life. Each item is assessed as 0, 1, 2 points according to the regularity or the performance of each behavior. Communication refers to the skills of receptive communication (what is understood by the subject), expressive communication (what is expressed by the subject), and written communication (what is written or read by the subject). Autonomy refers to the skills of the person which are observed by the caregiver as far as personal autonomy is concerned (feeding, hygiene, dressing, and undressing oneself), family autonomy (domestic abilities), and social or community autonomy (the understanding of the dimension of time and the use of communication technology). Socialization refers to the ability of the individual to be in interaction with others (interpersonal relations), to show leisure (organization of free time) and adaptation skills (type of responsibility taken).

The results are translated into three statistical indicators comparing the skills of the tested subject with other persons: "Age equivalent" and "standard score" refer to the comparison with mainstream people. "range percentile" is the comparison with a population of people with ASD—the group which has been chosen here, in DJ case, designates non-verbal persons with ASD aged 10 years old and more.

The Aberrant Behavior Checklist (ABC-2) (Aman et al. 1985) is a checklist of symptoms aiming at assessing behavioral disorder of children and adults with ID. Fifty-eight specific symptoms are assessed. The different stages are built in comparison with a reference population following the severity criteria of ID and age. Results are to be read in percentage ranks. A high score stands for the existence of severe behavioral disorder, and a low score stands for mild or non-existing disorder. The original authors of this tool suggest that a special attention should be given when the score is above the 85% rank for the normative group. The ABC results in a total score and four subscores related to irritability, lethargy, stereotypes, and hyperactivity.

DJ was subjected to several targeted genetic tests through the years in several departments. However, given the negative results, whole exome sequencing (WES) was performed

at the age of 15.5 by the genetics department at the Pitié Salpétrière hospital and compared with the sequencing of his parents. This analysis diagnosed DJ as carrying an ADNP mutation.

Data for DJ's assessment were also collected from his mother. All materials were given with parental informed consent.

Results

Table 1 summarizes the psychiatric and developmental phenotypes using both narrative description and standardized instruments when available. Also, Fig. 1 summarizes the developmental course of both socialization and day care services dedicated to DJ. For the ease of presentation, we will detail three sections: (1) developmental and behavioral symptoms until adolescence; (2) somatic phenotype; (3) behavior and autonomy from adolescence.

Developmental and Behavioral Symptoms until Adolescence

DJ was the only child of parental couple of French and Polish descent. The pregnancy was marked by the ultrasound discovery of a single umbilical artery during the 22nd week of amenorrhea pregnancy. An amniocentesis was performed, showing a normal karyotype. The delivery took place in France during winter at late-term (43 weeks +2 days of gestation). The father was 30 years old at DJ's birth, and the mother 31 years old. There was no inbreeding and no noteworthy family history. Birth weight, length, and head circumference were, respectively, 2900 g (3rd-10th centile), 49 cm (10th–25th centile), and 33 cm (3rd-10th centile), with Apgar scores of 6–10. Hypotonia was noted at birth. Several rare and severe congenital abnormalities were discovered during the first 6 weeks of life, resulting in a polymalformative syndrome (see below).

DJ presented a global developmental delay with an acquisition of sitting at 16 months, of toe walking at 27 months, and no language development despite normal hearing. As an infant, he was hypotonic and had issues with suction and alimentation. He showed a lack of eye contact and social interest at 10 months, hyperreactivity to auditory or luminous input, severe eating and sleeping disorders with motor stereotypies reported by his mother in early infancy.

In later years, during childhood, he was assessed in a day-care unit specialized in rare diseases and autism. He was diagnosed with a complex neurodevelopmental disorder associating ASD, severe intellectual disability (ID), severe attention deficit hyperactivity disorder (ADHD), anxiety, emotional dysregulation, and, behavioral problems such as clutching, pushing, and head banging. DJ was on risperidone from the age of 9 to the age of 14 years with moderate behavioral improvement. The drug was stopped due to the development of gynecomastia. It was then changed to aripiprazole 5 mg daily, along with melatonin 6 mg at bedtime to improve sleep.

Mostly, DJ has received physiotherapy and then occupational therapy (psychomotor approach) since the age of 1 year and speech therapy since the age of 4 years until now, with a more recent care targeted on rehabilitation of oral-mouth-facial motor functioning. He also received applied behavioral therapy (ABA therapy) from age 8 to age 10 years and between age 14 and 15 years (see Fig. 1) (Dale and Hayden 2013; Plaud and Gaither 1996; Welch and Polatajko 2016; Yu et al. 2014).

Somatic Phenotype

DJ presented with a polymalformative syndrome and had numerous somatic dysfunctions:

Early Feeding and Gastrointestinal Problems

DJ had a congenital hypertrophic pyloric stenosis that needed surgical treatment at 1 month of life; a portal cavernoma with esophageal varices and digestive hemorrhages that required four surgeries since the age of 1.5 years including a mesocaval anastomosis at the age of 3.5 years; a glucose-6-phosphate dehydrogenase (G6PD) deficiency that required a specific diet; and a gastroesophageal reflux disease (GERD).

Neurological Problems

DJ showed hypotonia at birth; he had wide ventricles on brain MRI at the age of 2 months, with normalization of the size and position of the cisternoventricular system at the age of 18 years. Furthermore, he had a history of seizure after major vascular surgery at the age of 3.5 years.

Visual Problems

DJ had a convergent strabismus, astigmatism, and hyperopia; he also had a unilateral iris coloboma and bilateral optic nerve coloboma (coloboma is a hole in one of the structures of the eye).

Cardiovascular Problems

DJ had a patent ductus arteriosus that required a surgical ductal closure at the age of 2 months; a ventricular septal defect with spontaneous closure at the age of 11 years; a moderate left ventricular hypertrophy; and several spontaneously resolving cyanotic episodes.

Table 1 Summary of the psychiatric and developmental phenotypes using both narrative description and standardized instruments

Domain, scale		Early infancy	Toddler	Pre-School	Scholar	12 years	13 years	15 years	18 years
Domains									
Social domain	**Gaze**	No eye contact (10 months)	Severe lack of eye contact		Moderate lack of eye contact		Light lack of eye contact		
	Social interaction	No social interest (10 months)	Interest for peers but no social overtures					Interest for peers but no social overtures	
Verbal communication			No words Repeats syllables	Few recognizable syllables "ma", "pa". but no words Spontaneous vocalizations					
Receptive communication			Follows simple instructions like "come", "look"						
Non-verbal communication			Uses another person's hand as a tool. No pointing No imitation		Pointing for demand Several conventional gestures Poor imitation skills				
Sensory symptoms and repeated behaviors		Severe defensive visual reaction					Moderate defensive visual reaction		
		Visual fascination with lights			Self-visual stimulatory behavior			Look at sun reflection	
		Auditory hypersensory input	Defensive reactions such as covering his ears.		Cover his ears when he heard his name.				
			Put frequently objects to mouth				Less frequent behavior		Put his finger on his mouth and bite his clothes
			Lateral body rolling movements				Less frequent behavior		
					Spinning				
			Severe hands stereotypies					Moderate hand steretypies	
Motricity		Hypotony Oral motor dysfunction	Sitting position at 16 months Walking at 27 months	Toe walking Does not run	Toe walking Able to run Problems of posture and walking balance		Clumsy walking	Physical activities like running, swimming, horse riding	
Level of activity/attention				Severe Hyperactivity Severe attention deficit			Lethargic period during 10 months	Less hyperactive, some moments of attention	
Emotion regulation and anxiety			Severe anxiety and emotion dysregulation					Moderate anxiety and emotional dysregulation	
Sleeping		Severe sleeping disorder with compulsive stereotypy						Moderate sleeping disorder	
Eating disorder		Severe eating disorder							
Challenging Behaviors, aggression				Grips Pull hair	Grips, pull hair Punch and head-butts Throw objects				
Challenging Behaviors, self-injurious				Head banging					
Challenging Behaviors, sexuality							Masturbation Getting nude	Better assimilation of social code	
Personal daily living skills				Partial toilet control No self-dressing Eating and cleaning assistance			Regression in bowel control	Partial bowel control Dressing with partial assistance. Uses spoon and fork	
Scales									
VABS Communication					11 months			23 months	33 months
VABS Autonomy					20 months			28 months	49 months
VABS Socialization					6 months			17 months	20 months
CARS					59.5			39	
ABC irritability								90	90
ABC lethargy								90	70
ABC stereotypies								95	85
ABC hyperactivity								85	80

Urogenital Problems

DJ had a unilateral cryptorchidism that required orchidopexy at the age of 1 year; a high-grade (IV) left vesicoureteral reflux that required a vesico-ureteral re-implantation at the age of 1 year; a unilateral renal hypoplasia with a chronic stage two kidney disease and high blood pressure treated with antihypertensive drug since the age of 11 years.

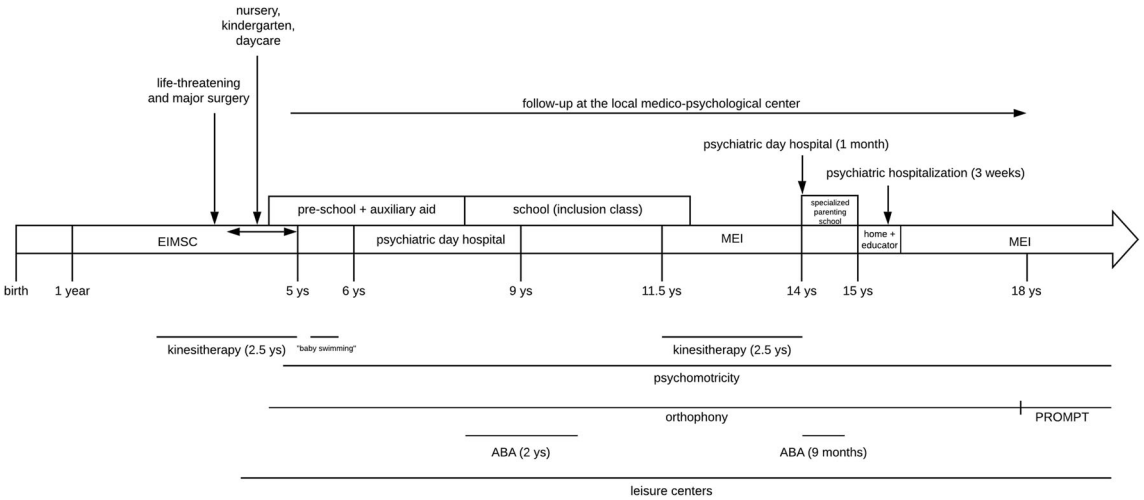

Fig. 1 The developmental course of both socialization and day care services dedicated to DJ. ABA, applied behavior analysis; ASD, autism spectrum disorders; EIMSC, early intervention medico-social center; MEI, Medical Education Institute; PROMPT, Prompts for Restructuring Oral Muscular Phonetic Targets therapy; ys, years

Infectious Problems

DJ had two chronic pyelonephritis, due to *Escherichia coli* acute pyelonephritis, during the first 2 years of life; he also showed several pulmonary diseases due to GERD during infancy and one severe pleuro-pneumopathy requiring drainage in intensive care at the age of 16 years.

Musculoskeletal Problems

DJ had bilateral genu valgum, dextroconverse lumbar scoliosis, and history of unilateral hip dislocation.

Dysmorphic Abnormalities

DJ had several hand and foot abnormalities and facial features including unilateral transverse palmar fold, wide and flat feet, epicanthus, telecanthus, erasing of orbital margins, protrusion of metopic, plagiocephaly, thick and supplied eyebrows, low implanted low-set ears, short nose, and anteverted nostrils. He also presented a premature primary tooth eruption, totaling 11 teeth at 9 months, and fully erupted dentition at 1 year of age.

Notably, DJ had no endocrine problems such as early puberty (reached since he was 12 years old) or growth abnormalities. At the age of 18 years, the body mass index (BMI) was 19.8 kg/m^2 (37th percentile).

Behavior and Autonomy from Adolescence

At the age of 15.5 years, DJ was hospitalized during 3 weeks in a neurobehavioral unit for challenging behaviors as he exhibited hetero-aggressive gestures at home and inappropriate sexual behaviors (Guinchat et al. 2015). At that time, he had no socialization for 5 months and was almost permanently at home, which led to maternal exhaustion. ASD severity as measured by the Children Autism Rating Scale (CARS) had improved compared with the score during childhood (Table 1), but clinical impairment was very significant. A cognitive and functional developmental evaluation (VABS) found a severe ID and severe adaptive behaviors (Vineland-II adaptive age equivalent to 17 months in areas of socialization, 23 months in communication, and 28 months in autonomy). A behavioral and functional analysis of disruptive behaviors (focusing on the identification of variables that influence the occurrence of challenging behaviors) was conducted. Three types of problematic behaviors were identified: (1) hetero-aggressive gestures (pushes, grips, head-butts, punches); (2) self-aggressive gestures (biting the top of his t-shirt, giving moderate intensity head banging against the walls); and (3) sexualized gestures (friction, masturbations). Functional analysis identified two precipitating factors: (1) hetero-aggressive actions occurred with family members in cases of close physical contexts or verbal, motor, and/or tactile overstimulation. No hetero-aggressive gestures toward peers or staffs were observed. (2) Self-aggressive actions occurred in two circumstances: after a blood test, and at the time of separation at the end of his mother's visits. However, for sexualized gestures in common living spaces, we found no particular context.

These observations allowed discussing the interest of focused work on separation-individuation for DJ. The full-time hospitalization itself constituted a separation experience (with visits three times/week and return home during weekends). Psychoeducational mediation work was conducted with the family to establish a proper distance in accordance with the affective but also the empowerment needs of DJ. An approval has been requested from the Departmental House of Disabled Persons (DHDP), so that DJ could benefit from respite stays

90 days/year with specialized organizations, in concert with the search for a new specialized medico-educational establishment. A new genetic analysis was carried out in 2013, including whole exome sequencing (WES), as the initial research dating back more than 10 years did not use up-to-date techniques. The analysis discovered a c.537dupA, p.Val180Serfs*2 de novo mutation of the ADNP gene and protein, that was absent in the parents.

At admission, DJ was given aripiprazole 5 mg daily, along with melatonin 6 mg at bedtime. He was also on antihypertensive drug (acebutolol 200 mg/d) for nephrogenic hypertension. A change to bumetanide 2 mg/d was tried for antihypertensive purposes, but also to reduce the severity of autistic manifestations (Lemonnier et al. 2017). However, bumetanide was not maintained for a long time after discharge due to the appearance of a diurnal enuresis. During hospitalization, the blood test revealed disturbed urinary functions, including hyperuricemia with values of 636 μmol/L, slight hyperammonemia with values of 68 μmol/L, and normal prolactinemia with values of 24.8 micrograms/L while being treated with aripiprazole. Mild eosinophilia (eosinophilia defined as > 500 polynuclear eosinophils/mm^3 and < 1500/mm^3) was present between 1000 and 1500/mm^3 according to prior blood counts. The rest of the biological tests were normal (hemostasis, hepatic assessment, albuminemia, lipid balance, fasting glucose, CRP, TSH, phosphocalcic balance, vitamin D, B9, and B12).

Outcome and Patient Perspectives

After 2 years, aripiprazole was replaced by mirtazapine to reduce inappropriate sexual behaviors (Naguy et al. 2018). Currently, DJ receives mirtazapine 15 mg/d and cyamemazine 50 mg/d as psychotropic treatment.

Vineland was repeated at late adolescence (18 years old) (adaptive age equivalent to 20 months in areas of socialization, 33 months in communication, and > 4 years in autonomy). Interestingly, these scores showed an overall skills improvement since early adolescence (15 years old), mainly in familial autonomy, from an adaptive age equivalent of 2 years and 4 months to 4 years and 1 month. Some improvement was also noticed in communication (mainly in the receptive type) from adaptive age equivalent 23 to 33 months. Besides, the results indicated a global positive evolution in these years in three of the four main subscales of ABC, with a decrease in lethargy in particular, as well as in hyperactivity and disabling stereotypies (Table 1). At the age of 18 years, DJ can designate three parts of his body, show pictures with known objects. He is able to listen to longer stories, starts to respond to demands heard a while before and can produce some communicative gestures in a clearer way. He can make demands and makes efforts to verbally answer with short sentences. In written communication, DJ can identify some letters of the alphabet. He has also improved in autonomy. He is able to put a pair of trousers with an elastic belt as well as to get undressed. He can use the bathroom, though help is needed. As for hygiene, he can wash his face, shampoo his hair and control the temperature of the water. Concerning family autonomy, DJ participates more, putting his plate and cutlery in the sink, participating in the preparation of meal. He can help with simple daily tasks, such as picking up and putting away his belongings as well as putting away objects once an activity is over. His behavior is adapted when he travels by car, he can listen to music on a cell phone.

Through long-term institutional care and familial investment, DJ's condition substantially improved. At the age of 18 years, DJ is supported in a medical education institute (MEI) and participates in holiday stays. He mostly uses nonverbal communication but vocalizes on some occasions and presents less challenging behaviors and greater motor skills such as running, swimming, and horse riding, which he seems doing with great pleasure. For picture of DJ, please see Fig. 2.

Discussion

Extensive knowledge concerning the ADNP syndrome is very recent. Furthermore, ADNP is one of the most frequent ASD-associated genes known to date (Helsmoortel et al. 2014; Larsen et al. 2016). Precise understanding of the ADNP-related syndrome is of general interest both from a case study point of view as well as from a population perspective. Existing case studies mostly concentrate on participants of younger ages compared to the current longitudinal study. Specific promising correlations have been found between genotype and phenotype of the study cohorts (Pascolini et al. 2018; Van Dijck et al. 2019; Arnett et al. 2018). In light of these elements, it is interesting to describe each new case of the ADNP mutation, as well as the development throughout the years of older carriers of the mutation. Herein, we conducted the first ADNP midterm follow-up case study and described the developmental course of a young male carrying a c.537dupA, p.Val180Serfs*2 de novo mutation of the ADNP gene and protein, a novel rare mutation not previously reported in the databases of genomic mutations and not belonging to ADNP gene mutational hot spots (HGMD at http://www.hgmd.cf.ac.uk; Van Dijck et al. 2019).

Our proband shared typical clinical findings of ADNP syndrome, including a polymalformative syndrome (distinctive facial dysmorphisms, premature teething, and neurological, visual, cardiovascular, gastrointestinal, urological, musculoskeletal and immune features), syndromic ASD, and severe ID including nonverbal communication, emotional dysregulation, and challenging behaviors (Gozes et al. 2017b; Van Dijck et al. 2019). He also presented asymptomatic G6PD deficiency. This condition, inherited in an X-linked recessive

Fig. 2 DJ's photographs at 3 years and 8 months and at 16 years and 8 months

pattern, occurs worldwide (Nkhoma et al. 2009). However, association between ADNP syndrome and G6PD deficiency is so far unique and never been previously reported.

Recently, Gozes et al. (2017b) discovered premature tooth eruption as a potential strong early diagnostic biomarker for ADNP mutation. DJ presented premature teething but was lately diagnosed with WES, as no description of ADNP syndrome existed yet. Moreover, the presence of a sole umbilical artery during pregnancy is also noted. DJ is part of the oldest individuals with an ADNP syndrome currently described in the world (Gozes et al. 2017b; Van Dijck et al. 2019). As the main limitation of previous studies was the relatively young age of their study cohorts, our follow-up study allowed to define the developmental path from birth to early adulthood of an ADNP young man.

We can assume that the wide ranges of deficits in major organ systems and surgical procedures may have been extremely disabling for DJ and family functioning and may have hindered DJ's early cognitive and motor development. DJ benefited from early and continuous care. During adolescence, he engaged in challenging behaviors. The individualized work done in the neurobehavioral unit on these behaviors of concern allowed a notable breakthrough (Guinchat et al. 2015; Cravero et al. 2017). Thereafter, DJ was able to go back

to a medical educational institute and improved his receptive communication and autonomy skills. These results highly suggest that non-verbal ASD individuals carrying this rare ADNP mutation can further progress in several salient areas, even in late adolescence, when appropriate care is provided.

Future Perspectives

Treatment Using Novel Biologically Active ADNP Peptides

From a scientific point of view, we strive to have tailored drugs to treat the ADNP children, early enough to avoid confounding developmental delays. In this respect, we have been developing NAP (NAPVSIPQ), the shortest active snippet of ADNP (Bassan et al. 1999; Gozes et al. 2003). NAP increases ADNP's activity at the cellular and whole animal level in terms of cellular protection as well as synaptic plasticity (Merenlender-Wagner et al. 2010; Gozes 2011a, b; Sharma et al. 2011; Sokolowska et al. 2011; Gozes et al. 2014; Magen and Gozes 2014; Oz et al. 2014; Gozes 2016; Ivashko-Pachima et al. 2017; Sragovich et al. 2017; Zhang et al. 2017; Hacohen-Kleiman et al. 2018; Mollinedo et al. 2019).

Clinical Development

The ADNP active neuroprotective snippet, NAP (INN: davunetide), current name CP201, has been in clinical trials before, showing a very clean toxicology profile in trials including more than 500 patients as well as efficacy, namely, increased cognitive scores in amnestic mild cognitive impairment patients (Morimoto et al. 2013) and protection of functional activity of daily living in cognitively impaired schizophrenia patients (Javitt et al. 2012). The Gozes laboratory comprehensive assessment of NAP in ADNP haploinsufficient mice (Hacohen-Kleiman et al. 2018) now paves the path to clinical trials of NAP (CP201) in ADNP children. Coronis NeuroSciences (coronisns.com) has obtained an orphan drug designation for CP201 from the United States Food and Drug Administration (US-FDA) for the treatment of the ADNP syndrome and has also successfully completed a pre-US-FDA's Investigational New Drug (IND) meeting.

Conclusion

The complex syndrome of non-verbal ASD, ID, and polymalformative syndrome we described stresses the importance of gene sequencing and early diagnosis of young children with the ADNP or the Helsmoortel–Van der Aa syndrome.

This case of severe syndromic ASD highlights global developmental delay, with emphasis on behavioral manifestations and developmental path of specific de novo mutation of ADNP not described before.

This case suggests that improvements may be achieved over time when both somatic and psychiatric intensive multidimensional and integrative care is provided.

Since DJ's major disability is his inability to speak, further understanding of ADNP's association with language development may possibly pave the way to new discoveries.

The more we research the ADNP protein and gene, in a variety of ways including that of detailed descriptive case reports of patients with mutations of this gene (Gozes et al. 1999; Magen and Gozes 2014; Gozes et al. 2015a), the better we will gain a valuable understanding of this unique autistic syndrome. While some previous case reports followed ADNP child development (e.g., Gozes et al. 2015a, 2017a), this is the first longitudinal study evaluating the Vineland-II and the ABC questionnaires' results, paving the path to a better understanding of the disease natural history, toward rational clinical development.

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Compliance with Ethical Standards

Ethics Statement This study was approved by the Tel Aviv University ethics committee. The study is of descriptive nature. Informed consents were given for all data by the respective parents.

Conflict of Interest Professor Illana Gozes is the Chief Scientific Officer of Coronis Neurosciences developing CP201 for the ADNP syndrome. CP201 use in the ADNP syndrome is under patent protection exclusively licensed from Ramot at Tel Aviv University to Coronis Neurosciences. No other author reports a conflict of interest.

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