to an exclusive aldosterone pathway defect. Disorders of aldosterone pathway, namely, ASD and PHA can be differentiated by aldosterone levels [3]. A decreased/ inappropriately low levels of aldosterone clinches the diagnosis of ASD [4]. The presence of low/near normal aldosterone levels favors the diagnosis of ASD type 2 [5,6]. While most common mutations are missense and nonsense, we noted a deletion in the index case. This mutation was not noted in about 1,670 variants described MGeND database and 942 variants described in gnomAD database. ASD type 2 is an autosomal recessive condition and this is the first report of a heterozygous mutation resulting in ASD type 2. The child requires lifelong mineralocorticoid replacement and continued monitoring of electrolytes and growth.

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Expanding the Neuroradiological Phenotype of 18q Deletion Syndrome

Central nervous system (CNS) abnormalities characterize several rare genetic diseases and syndromes. Case reports on rare conditions, and their uncommon findings can help to delineate their clinical phenotypes. Deletions of the long arm of chromosome 18 (18q-) (MIM 601808), occur in 1/40,000 liveborn infants [1]. The phenotype is variable, characterized by facial dysmorphisms, short stature, foot and hands deformities, congenital aural atresia (CAA), variable intellectual disability (ID), microcephaly and cerebral white matter (WM) abnormalities [1,2]. Kidney malformations, bone dysplasia, congenital heart disease, and IgA deficiency are less common [1]. Autoimmune diseases have been associated to 18q- [1].

We report a 10-years-old girl carrying an 18q22'!qter heterozygous deletion and showing dysmorphic features, juvenile idiopathic arthritis (JIA), autoimmune thyroiditis and IgA deficiency. She also developed hydrocephalus due to stenosis of aqueduct of Silvius, suggesting this might represent an expansion of the spectrum of the CNS abnormalities in 18q-syndrome.

The patient was born at term, with normal weight and length. She received percutaneous pulmonary valvuloplasty at one year for a pulmonic stenosis and has also got an interventricular septum defect.

She came to our observation at 10 years, for unsteady gait. Her height, weight and cranial circumference were normal (138.3 cm, -0.14 SD; 38 kg, +0.97 SD; 52.5 cm, +0.5 SD, respectively). Physical examination revealed: heart murmur, arthritis of the left knee, horizontal nystagmus, dysmetria at the finger-to-nose test, hyporeflexia, and unstable gait. Romberg test was negative. Psychomotor and cognitive development were normal. No data on previous cranial circumference measurements were available. Patient's parents reported unsteady gait from the very first steps. Nystagmus has always been complained as well.

Blood tests revealed increase in C-reactive protein and erythrocyte sedimentation rate, antinuclear antibody was positive with a titer of 1:640. IgA deficiency and increased thyroglobulin antibody levels, with normal thyroid hormones were also detected. JIA, autoimmune thyroiditis and IgA deficiency were diagnosed [2]. Ophthalmological evaluation revealed neither uveitis, nor coloboma. Dysmorphic features, hands and feet abnormalities were noted (**Web Fig. 1 J-O**), array CGH analysis was performed (ISCAv2 8x60K, Agilent Technologies) revealing a *de novo* heterozygous 18q22'!qter deletion of about 13.3 Mb (**Web Fig. 1P**). The brain magnetic resonance imaging (MRI) showed supra and infratentorial dismyelination of white matter, and a segmental stenosis at the third distal part of the aqueduct of Sylvius with secondary enlargement of the third and lateral ventricles (**Web Fig. 1A-H**). Follow-up brain MRI showed worsening of ventriculomegaly and subependymal transudation (**Web Fig. 1I**), so she received a successful endoscopic ventriculocisternostomy at 11 years.

Monosomy 18q is a well-recognized chromosomal abnormality comprising deletions ranging from 18q21.2, 18q21.3 to 18q22.2'!qter, that can be associated with autoimmune disease and neuroradiological findings [1,2]. We report a 18q22.2'!qter deletion in a patient presenting with rheumatological and neurosurgical issues.

Feenstra, et al. [3] defined the critical regions for

microcephaly (18q21.33), short stature (18q12.1-q12.3, 18q21.1-q21.33, and 18q22.3-q23), white matter disorders and delayed myelination (18q22.3-q23), growth hormone insufficiency (18q22.3-q23), and CAA (18q22.3). There are 28 molecularly confirmed genes inside our deleted region of which *TSHZ1*, *MBP*, *NFATC1*, *NETO1* and *CYB5A* are sensitive to haploinsufficiency.

Cody, et al. [1] proposed *GALR1* as a trigger factor for short stature. Despite *GALR1* being involved in 18q deletion, our patient did not show short stature suggesting another deleted gene in the 18q22.2 region might be involved in growth deficiency.

The incidence of cardiac defects ranges from 24% to 36%, the most common represented by atrial and ventricular septal defects, pulmonary and aortic valve defects [4]. According to literature data, our patient presented pulmonic stenosis and ventricular septum defect. *NFATC1* could be involved in their etiology [4].

Our patient showed a stenotic external auditory canal. CAA incidence in the 18q deletion syndrome is 78% [5]. CAA has been associated with *TSHZ1* haploinsufficiency.

Linnankivi, et al. [3] demonstrated that IgA deficiency, present in about 25% of cases, is associated with deletions at q22.3 and at q23, as in our case. Further studies looking for candidate genes included into the critical region, responsible in developing autoimmune diseases are desired.

From a literature review of neuroradiological features of 18q deleted patients, WM poor differentiation and dismyelination represents the most common MRI findings occurring in around 66 and 62% of patients, respectively (**Web Table I**). Particularly Linnankivi, et al. [6] published on MRI findings of the largest cohort of 18q deleted subjects, identifying dismyelination in 10 of 14 individuals with 18qdel syndrome. The authors reported that it was not related with patients' cognitive function. Dismyelination seems to be more frequent in patients with terminal deletion than those with interstitial deletion. In fact, the myelin basic protein (*MBP)* gene, localized at 18q23, plays a crucial role in the formation and maintenance of CNS [6]. According to literature data our patient presented dismyelination on brain MRI. Additional reports described other MRI abnormalities including supratentorial atrophy, Chiari I malformation, porencephalic cyst, and empty sella [6] (**Web Table I**). Aqueductal stenosis has never been reported and might represent an additional feature of the syndrome. Kato, et al. [7] reported isolated and primary ventricle dilatation. The grade of ID seems to be mild in patients with deletions distal to 18q21.33 and severe in those with deletions proximal to 18q21.31 [2]. Our patient did not present ID. Among neurological issues, more than half of patients presents a certain degree of psychomotor delay, and/or dyscoordination, and/or hypotonia and/or unstable gait (**Web Table I**). Our case well recapitulates these common neurological characteristics.

On the best of available knowledge, it seems that the "typical" 18q deletion syndrome, intended as the association of short stature, delayed myelination, congenital aural atresia, feet deformities, and characteristic facial features is due to the deletion of the critical region localized to a 70.6-74.9 Mb interval within the 18q22.3 to 18q23 chromosome region [8].

Clinicians should periodically check either cranial circumference, and signs and symptoms related to potential intracranial hypertension during follow up of these patients. In case of suspicion of intracranial hypertension, a brain MRI should be promptly performed in order to diagnose and treat it.

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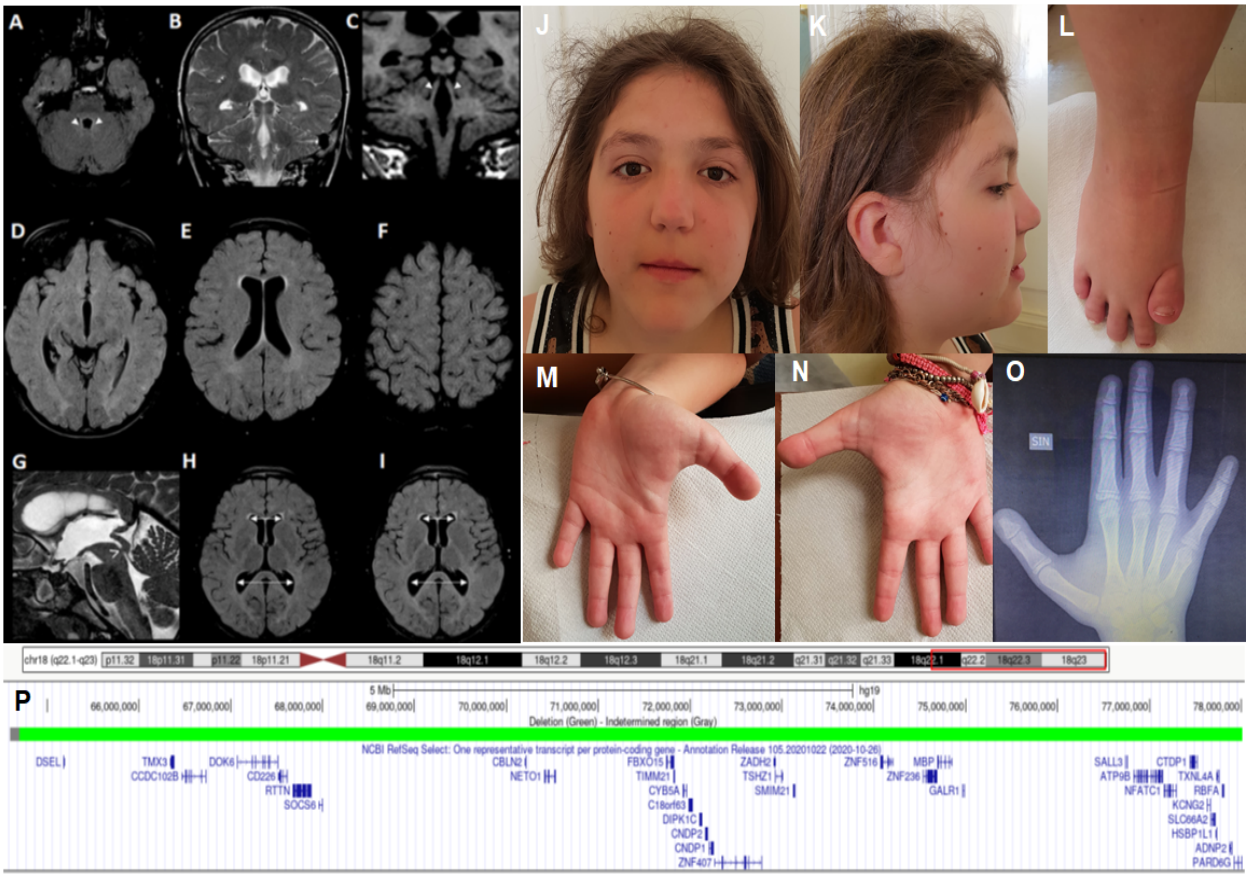

Web Fig. 1. Radiological features observed in the proband, Pictures of our proband and representation of the found deletion**.**

Brain MRIs of our patient showing bilateral high signals in the superior cerebellar peduncles (SCP) on the axial view (arrows head) and atrophy of the SCP on the coronal view (arrows head) (A-C); poor differentiation of gray and white matter due to slight hyperintensity of the periventricular and subcortical white matter (B, D-F); enlarged 3rd ventricle with expansion of both infundibular and pineal recess with normal size and configuration of the fourth ventricle (G). Aqueduct was stenotic with web (>) seen in its inferior third part. H-I: The first (H) and follow-up (I) MRI exams showed progression of the enlargement of both lateral (+) and third ventricle, secondary to aqueduct stenosis. (A, D-F, H-I: FLAIR axial image; B and C T2w and T1w coronal images at the level of the SCP; G (T2-weighted steady-state midsagittal image).

J and K pictures show squared face, mild hypertelorism, wide nasal bridge, down-slanting palpebral fissures, squared tip of the nose, smooth and long nasolabial filter, prominent chin, thin upper lip, thickened, slightly posteriorly rotated, ears with prominent antitragus. L picture shows short I metatarsus with clinodactyly. The proximal implant of the first finger of both hands with hypoplastic last phalanx and both fifth fingers clinodactyly, and shortness of fifth metacarpal are documented in pictures M and N.

X-ray of the left hand (O) shows the proximal implant of the first finger with hypoplastic last phalanx, shortness of fifth metacarpal bone, fifth finger's clinodactyly, and cone shaped last phalanges.

P, University of California Santa Cruz (UCSC) graphic view of the de novo 18q22.2'!qter deletion identified in the proband. The green bar corresponds to the minimal aberration length, while the flanking grey bars indicate the 5' and 3' breakpoint boundaries as determined using ISCAv2 8x60K microarray. The identified deletion of about 13.3 Mb includes 28 genes.

Web Table I Neurological and Neuroradiological Findings in Index Patient and OtherPatients With 18q Deletion Reported In Literature

	Bekiesiæska-Figatowska et al., 2001	Zannolli et al., 2003	Verrotti et al.,. 2004	Hausler et al., 2005	Linnankiwi et al., 2006														Netzer et al., 2006	Kato et al., 2010	Tanaka et al., 2012	Tada et al., 2014	Tassano et al., 2016	This paper	n/Tot (%)
					1	2	3	4	5	6	7	8	9	10	11	12	13	14							
Type of deletion	NA	18q21.31-qter	q21>qter	q22.1	q22.3	q22.3	q22.3	q21.33	q21.33	q21.32	q21.3	q21.31	q21.1	q21.32 q22.3	q21.32 q22.3	q21.32 q22.3	q22.2 q23	q21 q22.3	q21.23	q21.2.q21.33	q21.33	q21.3	q22.3 q23	18q22 →qter	
Size of deletion	NA	45cM	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	17 Mb	9.6 Mb	NA	NA	2.5 Mb	13.3 Mb	
Inheritance	NA	S	S	S	Mat	Mat	S	S	S	S	S	S	S	Pat	Pat	S	S	S	S	NA	Pat	S	S	S	17S-2Pat-3Mat/22
Sex	F	M	F	F	M	M	F	F	F	F	M	F	M	M	F	M	M	M	F	F	M	M	M	F	
Age at last examination (yrs)	3.5	9.5	0.6	2	2.8	12	36	3.1	6	4.3	23	34	44	3.8	2.7	33	0.7	6	21	18	6	5	2	11	median age 12 (0.6-44)
MRI findings																									
WM hyperintensity	-	Y	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	Y	Y	Y	-	6/24 (25)
WM poor differentiation	-	-	-	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	-	Y	-	-	16/24 (66,6)
Porecephalc cyst	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/24 (4)
Ventricles dilatation	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	-	Y	3/24 (12,5)
Chiari I malformation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	1/24 (4)
Empty Sella	Y	-	-	-	-	-	-	-	-	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	2/24 (8,3)
Dismyelination	-	-	-	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	-	-	-	-	Y	15/24 (62,5)

Hypomyelination	-	-	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/24 (4)
Stenosis of aqueduct of Sylvius	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	Y	1/24 (4)
Neurological findings																									
Epilepsy	-	-	Y	-	-	-	-	-	-	-	-	-	Y	-	-	Y	-	-	-	-	-	-	-	-	3/24 (12,5)
Nistagmus	-	-	-	Y	Y	Y	Y	-	-	-	-	Y	Y	-	-	-	Y	-	-	-	-	-	-	Y	8/24 (33,3)
Psychomotor delay	Y	Y	Y	Y	Y	Y	-	Y	Y	Y	Y	Y	Y	-	-	-	Y	Y	Y	Y	-	Y	Y	-	18/24 (75)
Dyscoordination	-	-	-	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	Y	-	Y	-	Y	-	-	Y	15/24 (62,5)
Unstable gait	-	-	-	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	Y	-	Y	-	-	-	-	Y	14/24 (58,3)
Hypotonia	-	-	Y	Y	Y	Y	-	Y	Y	Y	-	Y	Y	Y	-	-	-	Y	Y	Y	-	-	Y	-	14/24 (58,3)
Aggressive behaviour	-	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/24 (4)
Hyporeflexia	-	-	Y	Y	Y	-	Y	Y	Y	Y	-	Y	Y	-	-	-	Y	-	-	-	-	-	Y	-	11/24 (45,8)

F: Female; M: Male; Yrs: Years; NA: Not available; Y: Yes; -: No; S: Sporadic; Mat: Maternal; Pat: Paternal; WM: White matter.