

“Neurodevelopmental outcome of a child with UPD(16)mat: A case report”

Maria Novelli^{a,*}, Valeria Mammarella^a, Francesca Calandriello^{b,c}, Sara Temofonte^b, Marina Goldoni^d, Ilaria Macchiarulo^d, Paolo Versacci^e, Antonio Pizzuti^{d,f}, Jessica Petrilli^c, Carlo Di Brina^a, Barbara Caravale^b

^a Department of Human Neuroscience, Polyclinic Umberto I Hospital, Sapienza University, Rome 00185, Italy

^b Department of Developmental and Social Psychology, Sapienza University, Rome 00185, Italy

^c Centro NE.SVI, Rome 00161, Italy

^d Medical Genetics Division, Casa Sollievo della Sofferenza Foundation, San Giovanni Rotondo (FG), Italy

^e Department of Pediatrics, Obstetrics and Gynecology, “Sapienza” University of Rome, Policlinico Umberto I, Rome 00155, Italy

^f Department of Experimental Medicine, Sapienza University, Rome 00189, Italy

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ABSTRACT

Objective: UPD(16)mat is a rare genetic condition characterized by intrauterine growth deficiency and multiple congenital malformations. To the best of our knowledge, neurodevelopmental disorders have never been described in association with UPD(16)mat, nor a comprehensive neuropsychological profile of a UPD(16)mat child has never been delineated. We present a young patient diagnosed with UPD(16)mat, and provide clinical description, comprehensive neurodevelopmental, neuropsychological and neurological assessment.

Method: Neuropsychological examination included global neurodevelopment and intelligence scales, as well as specific trials for gross-motor, fine-motor and perceptual motor abilities, and language skills.

Results: The patient shows multiple congenital anomalies, including oesophageal atresia, mild bone alterations, hypospadias, persistent left superior vena cava. The neurodevelopmental evaluation demonstrates a speech disorder, signs of gross and fine motor skills difficulties, balance and visuo-motor deficit.

Conclusion: Evidence from this study indicates that UPD(16)mat may present neuropsychological and/or minor neurological abnormalities. Monitoring both the early and late neurodevelopmental outcomes during childhood is recommended for the chance of an early intervention.

1. Introduction

Uniparental disomies (UPDs) are genetic conditions characterised by the inheritance of two copies of a whole chromosome from the same parent.¹ In UPD(16)mat, two copies of chromosome 16 are inherited from the mother through different pathomechanisms, which can influence and explain the variable phenotypes of these individuals.² In fact, several clinical presentations are associated with UPD(16)mat: individuals can be almost asymptomatic or characterised by intrauterine growth retardation (IUGR), preterm birth, postnatal growth failure with low body mass index (BMI), congenital malformations and/or dysmorphism.^{2,3}

Multiple heart, vascular, skeletal and genital malformations together with facial dysmorphisms have been frequently described in subjects with UPD(16)mat, but there is not a fixed pattern of anomalies.² UPD

(16)mat has also been frequently associated with maternal hypertensive disorders during pregnancy.³ At present, neither intellectual disability nor other neurodevelopmental abnormalities due specifically to this condition has been reported.^{2,3} However, UDP can unmask a recessive disease or can be concomitant to a mosaic trisomy, being both secondary to a trisomic rescue event, and aberrant parental imprinting, so it can be linked to other genetic conditions presenting with neurodevelopmental anomalies.⁴ For example, UPD(16)mat has been found in patients with Silver–Russell syndrome, congenital disorder of glycosylation type 1a (PMM2-CDG) and mutations of FA2H/SPG35 causing hereditary spastic paraplegias.^{3–5} Therefore, it is important to carefully investigate cases of UPD(16)mat from genetic and clinical points of view to ensure early detection of any possible anomalies.

Here we describe the case of a child with UPD(16)mat associated with congenital cardiovascular anomalies, oesophageal atresia,

* Corresponding author at: Department of Human Neurosciences, Sapienza University of Rome, Via dei Sabelli 108, Rome 00185, Italy.

E-mail address: maria.novelli@uniroma1.it (M. Novelli).

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hypospadias and abnormal findings on the brain ultrasound. We focus mainly on his neurodevelopmental profile, evaluated through neurological and neuropsychological assessment during the first four years of life, comparing the results with data extracted from literature.

2. Materials and methods

2.1. Global development assessment

2.1.1. Bayley scales of infant and toddler development (BSID-III)

The BSID-III are designed to measure the developmental functioning of young children aged 1–42 months. The Cognitive, Language (Receptive Language and Expressive Language subscales) and Motor (Fine Motor and Gross Motor subscales) scales were used. Each scale provides a Composite Index Score ($M = 100$, $SD = 15$), while each subscale provides a normative-referenced Scaled Score ($M = 10$, $SD = 3$).⁶ Within each scale, children scoring below the composite score of 85 are considered clinically ‘at-risk’.^{6,7}

2.1.2. Griffiths III

Griffiths III is a developmental scale assessing the skills and abilities of children from birth to 6 years of age.⁸ It provides an overall measure of a child’s development across five areas: subscale A, ‘Foundations of learning’, which assesses critical aspects of learning during the early childhood years; subscale B, ‘Language and communication’, which measures overall language development, including expressive language, receptive language and the use of language to communicate socially with others; subscale C, ‘Eye and hand coordination’, which considers fine motor skills, manual dexterity and visual perception skills; subscale D, ‘Personal-social-emotional’, which measures constructs relating to the child’s developing sense of self and growing independence, interactions with others and many aspects of emotional development; and subscale E, ‘Gross motor’, which assesses postural control, balance and gross body coordination, among other abilities. This assessment gives standardised sub-quotient scores for each domain. Griffiths III allows one to calculate a general development (GD) quotient, which is derived using each of the measures for the five individual domains. The mean of the GD quotient and each of the subscale quotients is 100 points ($SD = 15$). A GD or a subscale quotient of ≤ 70 points (≥ 2 SD below the mean) is considered to indicate a significant delay in development, while a quotient of > 70 points indicates a mild or no delay.

2.2. Intelligence assessment

2.2.1. Wechsler preschool and primary scale of intelligence fourth edition (WPPSI-IV)

The WPPSI-IV represents a test of cognitive skills developed for children aged 2 years and 6 months to 7 years and 7 months.⁹ Two different versions are available for children from 2 years and 6 months to 3 years and 11 months and from 4 years to 7 years and 7 months; in the present study, the latter version was used. In addition to an overall intelligence quotient (IQ; $M = 100$, $SD = 15$), cognitive performance can be described in a more differentiated way by using primary and ancillary index scores. A total of 10 primary subtests are available for calculating the primary index scores. Two subtests are assigned to each scale. The Verbal Comprehension Index (VCI) is calculated from the subtests Information and Similarities. The Visual Spatial Index (VSI) is calculated from the subtests Block Design and Object Assembly. The Fluid Reasoning Index (FRI) consists of the subtests Matrix Reasoning and Picture Concepts. The subtests Picture Memory and Zoo Locations make the Working Memory Index (WMI). Furthermore, Bug Search and Cancellation are used to determine the Processing Speed Index (PSI). Ancillary indices can also be calculated for the Vocabulary Acquisition Index (VAI), the Nonverbal Index (NVI), the General Ability Index (GAI) and the Cognitive Proficiency Index (CPI), while six primary subtests are needed to determine total IQ (Information, Similarities, Block Design,

Matrix Reasoning, Picture Concepts and Bug Search). The present study includes both primary index scores. An index score between 85 and 115 points is considered to be in the normal range.

2.3. Gross motor, fine motor and perceptual motor abilities assessment

2.3.1. Movement ABC-2

Movement ABC-2 is a standardised battery used to identify motor function impairment in children. It comprises eight tasks grouped to assess three components: manual dexterity (three items), aiming and catching (two items) and balance (three items).¹⁰ Children who score below the 15th percentile are classified as children with potential motor problems (at risk or impaired). In clinical practice, this 15th percentile cut-off score is used to make diagnostic and intervention decisions.

2.3.2. Developmental test of visual-motor integration (VMI)

This standardised, norm-referenced assessment is used to explore the level of integration between visual and motor systems.¹¹ It consists of three sub-tests: complete VMI, visual and motor subtests. The mental age equivalent (in months) and the percentiles are derived from the raw scores. The cut-off score considered for clinical diagnosis is the 5th percentile.

2.4. Language abilities assessment

2.4.1. Test for phonological assessment of child language (Prove di valutazione fonologica del linguaggio infantile [PFLI])

The PFLI evaluates the phonological characteristics of the child’s pronunciation; the phonetic and phonological differences and similarities between adult and child language; the communicative potential, in terms of phonological contrasts and phonotactical possibilities; and the developmental status of the subject, by comparing the characteristics of the child under consideration with those of normal development.¹² The test consists of a set of 90 pictures designed to collect a spontaneous language sample. The child’s speech is transcribed using the symbols and diacritics of the International Phonetic Alphabet (IPA) to analyse the phonetic inventory and the phonological simplification processes.

2.4.2. Peabody picture vocabulary test – revised (PPVT-R)

The PPVT-R is used to assess vocabulary knowledge in children and adults.¹³ Four pictures are shown for each vocabulary word. The respondent must select the picture that best illustrates the definition of the word provided and receives 1 point for each correct answer. The collected raw scores are converted to standard scores ($M = 100$, $SD = 15$).

2.4.3. Test of oral sentence repetition (Test di ripetizione di frasi [TRF])

The TRF is a sentence repetition task assessing the child’s early grammatical development, in particular morphological and syntactic aspects.¹⁴ The evaluation considers the total number of correctly repeated sentences. The raw score is converted to a z-score.

2.4.4. Language assessment battery for ages 4–12 (Batteria per la valutazione del linguaggio [BVL 4–12])

The BVL is a battery of tests used to assess speech and language production, perception and comprehension in children.¹⁵ The ability to select and produce words (lexical abilities) are assessed by administering the ‘Naming and Articulation’ subtest. The child must name a set of black and white pictures and receives 1 point for each correct answer. Raw scores are converted to z-scores.

2.4.5. Child language comprehension test (Test di comprensione grammaticale per bambini [TCGB])

The TCGB is used to assess morphosyntactic/syntactic comprehension in children, who have to choose which picture out of four corresponds to a provided target sentence.¹⁶ It verifies the knowledge of eight

Table 1
Griffiths III scores.

Subscale	Raw Score	Developmental age equivalent	Standardised score	Developmental Quotient	95 % confidence interval	Percentile
(A) The Foundation of Learning Subscale	37	37	4	72	68–76	3°
(B) The Language and Communication Subscale	53	55	13	114	110–119	82°
(C) Eye and hand coordination subscale	43	38	7	86	82–90	16°
(D) The personal-social-emotional domain	52	46	10	99	94–103	45°
(E) Gross-motor skills	39	33	2	58	54–62	<1°
Overall Performance	45	41	7	87	84–90	18°

different Italian grammatical structures: locative, inflectional, active affirmative, active negative, passive affirmative, passive negative, relative and dative. The TCGB raw score is the number of wrong answers provided by the child; its percentile is derived by comparing it with standard score curves. The normal range of variation is between the 90th (upper limit) and 10th (lower limit) percentiles. Values between the 25th and the 10th percentile are to be interpreted as borderline.

3. Results

The patient, a 4-year-old male, was conceived by healthy non-consanguineous parents. A diagnosis of IUGR associated with polyhydramnios and a single umbilical artery was made based on prenatal ultrasound. The patient was born at 36 weeks of gestation by caesarean section due to a nuchal cord. The birth length, weight and occipito-frontal circumference (OFC) were 43 cm (3rd percentile), 1730 g (< 5th percentile) and 31.5 cm (3rd–10th percentile), respectively.

He presented peculiar facial dysmorphism and multiple congenital anomalies including oesophageal atresia requiring surgical correction, mild bone alterations and hypospadias. Transthoracic echocardiography (TTE) detected the persistence of a left superior vena cava (LSVC) with suspicion of drainage into the left atrium through an unroofed coronary sinus, an atrial septal defect of the ostium secundum type and a perimembranous subaortic ventricular septal defect (VSD). His-oxygen saturation was 88 % on room air. TTE was again performed after administering an agitated saline via the left arm; it showed the appearance of microbubbles in the left atrium, confirming an unroofed coronary sinus. In the next months after the diagnosis, the VSD closed spontaneously. At the age of 2 years, the child underwent cardiac catheterisation and the LSVC was successfully closed using an Amplatzer Vascular Plug II 12 mm. Immediately after the procedure, his oxygen saturation reached 96 % on room air. His-motor development was mildly delayed, but no neurological signs emerged from the neurological examination.

A transfontanellar ultrasound was performed in the neonatal period and then 9 months, revealing minimum hypoplasia of the corpus callosum not confirmed in the second examination and mild enlargement and asymmetry in lateral ventricles. The frontal horns of both lateral ventricles were also dysmorphic. A CT scan of the brain was performed

at 9 months of life and confirmed a mild ventricular asymmetry (IVA) and minimum ventriculomegaly without clinical or neurosurgical significance.

The neurodevelopmental evaluation performed at the age of 7 months using the BSID-III showed scores in the normal range, except for the Motor Scale that revealed a Composite Index Score of 82, below the threshold of 85.

Griffiths III, performed at 4 years of age, revealed a non-homogeneous developmental profile: the ‘Language and communication’ and ‘Personal-social-emotional’ subscales were relatively stronger compared with the other subscales (‘Foundations of learning’, ‘Eye and hand coordination’ and ‘Gross motor’), which evidenced difficulties with gross and fine motor skills. The patient had difficulties when handling concrete objects or performing pencil and paper tasks, with graphomotor tasks that require the manipulation of a pencil (including copying and drawing). The child was also unable to use universal scissors or manage other tasks requiring bilateral coordination, such as buttoning and unbuttoning. Furthermore, he exhibited difficulties in all tasks requiring motor planning, sequencing and balance (details in Table 1).

In view of the unevenness found in the profile and in relation to the fact that the performance in the cognitive area linked to learning and thought (cf. ‘Foundations of learning’) was affected by aspects related to the oculus-manual area, to get a more coherent measure of his cognitive functioning, we decided to administer a scale that could be used to measure intelligence in multiple components. Hence, we administered the WPPSI-IV to assess his cognitive ability across five areas of cognitive functioning. His-overall FSIQ was in the average range compared with other children his age (FSIQ = 94). His-WMI (107) was a strong point of his cognitive profile. Among the different subtests, his performance in ‘Drawing with cubes’ indicated weakness, a finding similar to the Griffiths III results (Table 2).

Motor evaluation revealed balance impairment: he scored at the 16th percentile for the *Movement ABC-2* (based on the total score; performed at 3.11 years), at the 37th percentile for manual dexterity, at the 50th percentile for aiming and catching and at the 5th percentile for the balance index.

The VMI test disclosed severe visuomotor difficulties (VMI percentile rank 34, visual perception percentile rank 11 and motor coordination

Table 2
Index score summary (WPPSI-IV).

Composite	Sum of Scaled Scores	Composite Score	Percentile Rank	95 % Confidence Interval	Qualitative Description
Verbal Comprehension VCI	20	101	53	93–109	average
Visual Spatial (VSI)	16	89	23	79–99	low average
Fluid Reasoning (FRI)	16	89	23	81–97	low average
Working Memory (WMI)	22	107	68	99–115	average
Processing Speed (PSI)	19	96	39	87–105	average
Full Scale IQ (FSIQ)	54	94	34	88–100	average
Composite	Sum of Scaled Scores	Standard Score	Percentile Rank	95 % Confidence Interval	Qualitative Description
Vocabulary Acquisition (VAI)	24	113	81	104–122	high average
Nonverbal (NVI)	42	89	23	82–96	low average
General Ability (GAI)	33	88	21	81–95	low average
Cognitive Proficiency (CPI)	41	102	55	94–110	average

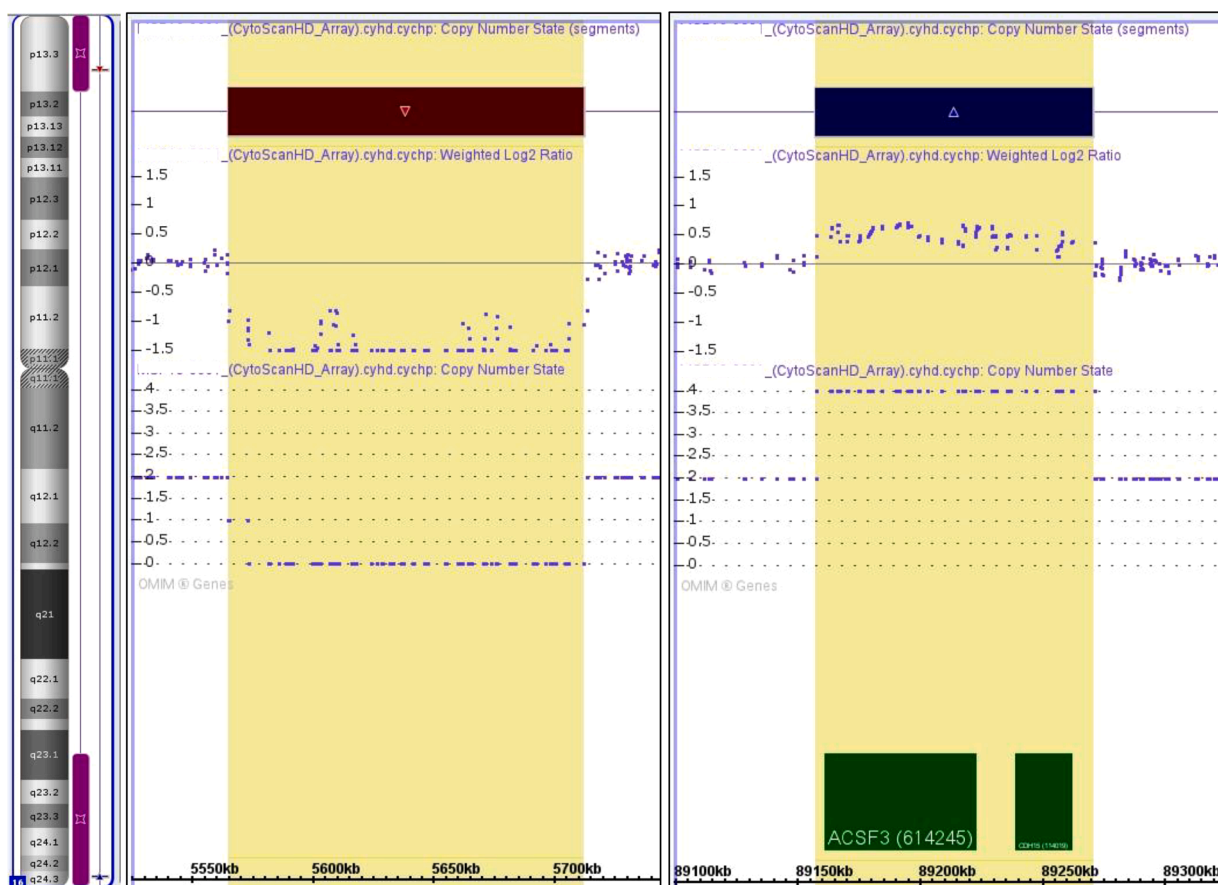


Fig. 1. SNP array of the index patient.

SNP-array results. Left panel: schematic representation of chromosome 16 with localization of the Regions of Homozygosity (ROH; purple bars) and of Copy Number Variants both mapping within the ROHs (red dash: microdeletion; blue dash: microtriplication). Middle panel: graphic representation of the genome region including the homozygous microdeletion 16p13.3 (brown bar; Copy Number State = 0). Right panel: visual representation of the genomic region 16q24.3 affected by triplication (blue bar; Copy Number State = 4) and OMIM genes included. From *Chromosome Analysis Suite software (ChAS; version 4.3; ThermoFisher Scientific)*

percentile rank not evaluable). At that time, his neurological examination revealed slight reduction in strength and mild hypotonia. At present, his neurodevelopmental profile is characterised by specific and selective motor difficulties but normal cognitive abilities.

Language evaluation showed adequate lexical and grammatical skills (BVL 4–12 Naming: z-score +1 SD/+1.5 SD; PPVT-R: Standard Score 97; TRF: z-score +0.33 SD; TCGB: 50th–75th percentile). He showed marked difficulties on the expressive level based on the PFL in relation to phonetic-phonological aspects (total score < 5th percentile at 48 months). Specifically, the child presented an incomplete consonant inventory (39.13%), consisting of nine stable (/m/, /n/, /p/, /t/, /k/, /b/, /g/, /j/, /w/) and five unstable phonemes, with specific difficulty in articulating affricate and fricative consonant. Therefore, it is not possible to analyse the phonological simplification processes. The most represented syllabic structure in the words produced is disyllabic with two different consonants. The child's speech intelligibility is very low. While this does not interfere or limit the use of language for narrative and conversational purposes, it makes it unintelligible within a social interaction with unfamiliar people.

- SNP-array analysis (HD Cytoscan chip; Thermo Fisher Scientific, Waltham, MA) showed a 147 kb homozygous 16p13.3 microdeletion (0 copies) and a 114 kb 16q24.3 microtriplication (4 copies), both segregated from the mother. Region of homozygosity (ROH) analysis showed two ROHs of 7 and 13 Mb on chromosome 16 suggestive of the presence of UPD(16). The genotyping analysis by SNP-array of the proband and his parents followed by calculation of Mendelian

error on chromosome 16 allowed to verify the presence of maternal UPD(16). The possible presence of a residual mosaic trisomy 16 was evaluated on 100 cells by karyotype analysis and fluorescence in situ hybridisation, using a probe mapping to chromosome 16 (N0619A23)(Library 32 K; BACPAC Resources, Oakland, CA). The maternal loss and gain were localized within the ROHs, at 16p13.3 and 16q24.3 respectively, and the maternal isodisomy of these genomic regions justified the homozygous state of the microdeletion and the presence of two extra copies of the 16q24.3 segment (Fig. 1). The CNVs were classified as variants of unknown clinical significance (VOUS) according to ACMG/ClinGen guidelines¹⁷

4. Discussion and conclusion

UPD(16)mat is a rare genetic condition and its clinical phenotype has only been vaguely characterised, ranging from severe to mild presentations.² We have described an additional case of the phenotypic characterisation of UPD(16)mat and have delineated the clinical and neuropsychological profiles.

Complex cardiac defects alongside other organ abnormalities were detected at birth. Furthermore, motor difficulties and mild neurological signs were also seen from the first months of life, and then confirmed during successive follow-up visits, together with severe clumsiness and visual-motor impairment were detected. The general intellectual functioning was characterised by a specific deficit in the visuo-constructive abilities that resulted in a weakness in the child's profile. Focusing on linguistic competence, the child showed an adequate receptive level

against marked difficulties on the expressive level, in relation to phonetic-phonological aspects.

Several cases of (UPD) 16 mat have been reported over time, but data with respect to the neuropsychological profile are scarce. Psychomotor developmental delay or intellectual disability of varying degrees is reported in some of these children,³ although it seems to be an inconstant feature. Globally, as in our personal case, developmental delay/IQ does not appear to be a distinctive characteristic of the clinical picture. Differently, speech and language abnormalities were reported in (UPD) 16 mat patients. Mild delay of speech development was also sporadically observed by Scheuvers R,² and also related also to trisomy 16 mosaicism.¹⁸

Finally, this case it is the first report of an unroofed coronary sinus among the cardiac malformations associated with UPD(16)mat. Our findings, along with data from the literature,^{2,3} confirm the need to extend follow-up through childhood.

Informed consent

Both parents have signed an informed consent to the visit and the carrying out of the assessment, agreeing to the dissemination of the results of the evaluation.

CRediT authorship contribution statement

Maria Novelli: Conceptualization. **Valeria Mammarella:** Conceptualization. **Francesca Calandriello:** Data curation. **Sara Temofonte:** Data curation. **Marina Goldoni:** Data curation. **Iliaria Macchiarulo:** Data curation. **Paolo Versacci:** Data curation. **Antonio Pizzuti:** Validation. **Jessica Petrilli:** Supervision. **Carlo Di Brina:** Visualization. **Barbara Caravale:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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