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CASE REPORT

Motor and cognitive response to intensive multidisciplinary therapy: the first reported case of congenital Zika virus syndrome

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ABSTRACT

Purpose: To provide a detailed description of the development of the first case of congenital Zika syndrome (CZS) to be reported in the literature worldwide.

Case Description: This report describes the case of a child with CZS monitored from pregnancy until four years of age, with periodic evaluations of head circumference, weight, height, motor function according to the Gross Motor Function Measure (GMFM-88), and the occurrence of comorbidities.

Outcomes: The child's birth weight and length were normal (z-score = 1.1 and −1.95, respectively), while head circumference was below the expected value (z-score = −3.15). At 48 months, head circumference reached 43 cm (z-score = −4.48). During daily home physiotherapy sessions, the child achieved developmental milestones, standing unsupported at 17 months, with a GMFM-88x score of 137. With specialist therapy, the child walked independently at 36 months and a total GMFM-66 score of 214 was achieved by 42 months. In the four years of follow-up, the child was hospitalized four times for different reasons. No convulsive seizures occurred.

Conclusions: Despite severe neurological impairment, the child's weight and height are adequate for age, with motor and cognitive function improving over the first four years of life.

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Introduction

During 2015 in northeastern Brazil, an alarming increase was recorded in the number of cases of microcephaly. In November of that same year, a fetal medicine specialist took samples of the amniotic fluid of two fetuses in whom brain abnormalities were detected at obstetric ultrasonography. In both cases, the mothers had reported exanthema during pregnancy. Reverse transcription polymerase chain reaction (RT-PCR) confirmed the presence of Zika virus (ZIKV) in the amniotic fluid. In January of the following year, Melo et al. (2020) described the ultrasound findings of these two fetuses for the first time (Oliveira-Szejnfeld et al., 2016). Those findings constituted the first steps toward understanding the role of ZIKV as a teratogenic agent. The data also suggested that microcephaly would be only one of the signs of severe brain damage caused by the infection that characterizes congenital Zika virus syndrome (CZS).

Since that landmark publication, much has been debated with respect to brain patterns (Chimelli et al., 2017); neurological condition (Saad et al., 2018); growth (Franca et al., 2018; Lage et al., 2019; Prata-Barbosa, 2019); motor, cognitive, and sensory impairment (Marques et al., 2019; Pecanha et al., 2020); and the prognoses of children with CZS (Satterfield-Nash et al., 2017). Because the present report addresses just one single case, no new information on the disease is provided here; however, there are two important peculiarities, the first being historic (i.e. this is the first case of CZS to be described) and the second that it serves to call attention to the role of intensive physiotherapy and multidisciplinary therapy implemented at an early stage. The objective of the present report was to provide a detailed description of the evolution of this first case of CZS to be reported in the literature worldwide, including imaging findings, sensory profile and aspects related to cognition and language, as well as the development of motor function, from intrauterine life until four years of age. This report also discusses the following peculiarities of this case: monitoring began before the child was born; she was submitted to neuropsychomotor interventions aimed at stimulating development from the fourth day of life; and the fact that the child's mother is a physiotherapist.

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Case description and diagnosis

The child who is described in this report was followed at a center affiliated with the Research Institute Professor Joaquim Amorim Neto which provides specialist care to children with CZS and also conducts research on the subject and monitors pregnant women with a history of exanthema. The center was designed to provide comprehensive support to children with microcephaly. The internal review board of the University Hospital Alcides Carneiro approved the protocol.

The child in question is female and has been monitored since before birth. A diagnosis of CZS was first suspected when an obstetric ultrasound was performed in the 23rd week of pregnancy. At 29 weeks, neurosonography and fetal magnetic resonance imaging (MRI) revealed fetal microcephaly and the following abnormalities: a reduction in the brain volume and in the brain sulci; calcifications in the frontal lobes and basal ganglia; dysgenesis of the corpus callosum and of the cerebellar vermis; as well as cerebellar hypoplasia and mega cisterna magna (Oliveira-Szejnfeld et al., 2016).

The child was delivered vaginally at 40 weeks of pregnancy. In the first and fifth minutes, Apgar scores were 9 and 10, respectively. Head circumference at birth was 30.5 cm, characterizing severe microcephaly. Length at birth was 46 cm and birthweight was 2,860 g, both considered appropriate for gestational age.

Computed tomography performed on the first day of life and MRI performed at 2 and 31 months confirmed the findings detected during pregnancy and also revealed delayed myelination. The child was hospitalized four times in her first 48 months of life. The first admission, at 12 months, was to investigate fever. The second was at 21 months because of tonsillitis. At 36 months, she was hospitalized to investigate suspected pneumonia and at 42 months because of a viral infection. During this same four-year period, the child also had lower urinary tract infections, respiratory allergies, and otitis, all of which involved outpatient treatment only. The child had no convulsive seizures and was prescribed no anti-seizure medications.

Intervention history

The child's mother, a general physiotherapist, began motor stimulation with the child on the fourth day of life, conducting sessions of motor physiotherapy twice daily for a total of around 45 minutes per day. The sessions included therapeutic exercises for motor function using joint mobilization, passive stretching of the upper and lower limbs and dissociation of the shoulder and pelvic girdles. The child was stimulated to achieve motor developmental milestones such as head and trunk control, rolling over, pulling herself along, and going from a seated position to all-fours. In addition, oculomotor stimulation and exercises aimed at strengthening muscles and training balance were performed. Therapy was implemented gradually taking typical motor development into consideration, and always in association with playful activities and cognitive stimuli.

The home therapy routine was maintained for 17 months during which the child was able to achieve developmental milestones such as control of the head and trunk and supported standing position. At that age, intensive physiotherapy with pediatric physical therapist specialists was initiated at the support center for children with microcephaly. This intervention consisted of sessions of motor physiotherapy lasting two hours, five times a week. In the first hour, exercises consisted of therapeutic exercises aimed at improving motor development, and maneuvers and positions based on the Bobath concept or neurodevelopmental treatment (NDT) (Knox and Evans, 2002; Raine, 2007), always taking into consideration the next level of functional activity to be achieved by the child. Specific maneuver techniques were designed to influence movement, improve the child's postural alignment, practice in developmental positions, strengthen weak muscle groups, promote improvements in muscle tone, and stimulate the practice of relevant functional task considering child age and capacity.

In the second hour of therapy, activities and therapeutic exercises were conducted in a universal exercise unit based on the PediaSuit Protocol. The suit was used to stimulate proprioception, muscle contraction, and postural control (Pedrozo, Thomas, de Oliveira, and Paiva, 2012; Scheeren et al., 2012). Therapeutic exercises were focused on joint mobility and muscle stretching and strengthening, and the practice of functional tasks considering the child's capacity. The PediaSuit protocol was not performed in its entirety due to its high energy requirement.

At the beginning of the physiotherapy sessions with the specialists, the child was unable to walk independently and used the crawling as a means of movement. In addition, she favored the right side of her body when performing functional activities, with the right side being the most active.

With the implementation of intensive, specialized intervention protocols, the child's motor skills improved and at 21 months she was able to sit by herself, unsupported, for more than 30 seconds. When she reached this motor milestone, the physiotherapy sessions were reduced to three times a week. At 28 months, after she began to walk independently, the physiotherapy protocol was changed. The new protocol consisted of 45-

minute sessions of motor physical therapy three times a week, based entirely on NDT.

Table 1 describes the child's attainment of the motor milestones during the period of home physiotherapy and after the initiation of specialist intervention compared to the typical developmental milestones described by the Brazil, Health Ministery (2016). Figure 1 shows images of the child over the treatment period.

Longitudinal assessment and outcomes

Prior to the initiation of specialist physiotherapy, the child's weight, height, and head circumference were measured regularly to monitor growth. At 14 months of age, evaluation of motor function was implemented using the Gross Motor Function Measure (GMFM-88) (Russell et al., 1989) and the Gross Motor Function Classification System (GMFCS) (Palisano, Rosenbaum, Bartlett, and Livingston, 2007). The GMFM-88 assessment was repeated at 17, 22, 26, 30, 34, 38, and 42 months of age. The software package Gross Motor Ability Estimator (GMAE) was used to calculate GMFM-66 scores, which were analyzed according to the expected percentages, taking the GMFCS classification into consideration (Hanna, Bartlett, Rivard, and Russell, 2008).

Serial anthropometry showed progressive growth in all parameters, with only the measurements recorded for head circumference showing differences from the values expected for age. Figure 2 shows the development of the child's weight, height, and head circumference, as well as the reference values for sex and age (World Health Organization, 2006).

The child was classified as GMFCS level III prior to reaching two years of age. The GMFM-88 total score at 14 months was 116 points: 51 points for dimension A; 46 for B; 15 for C; 4 for D; and 0 for E. At 26 months, the total score was 183 points: 51 points for dimension A; 57 for B; 38 for C; 20 for D; and 17 for E. At the 42-month evaluation, the total score had increased to 214 points: 51 for dimension A; 60 for B; 35 for C; 33 for D; and 35 for E (Table 2). The GMFM-66 scores were above the 97th percentile of expected values for children classified as GMFCS level III from the fourth evaluation onwards (Figure 3A). This classification was not used in the previous evaluations due to the lack of expected normative reference values for the GMFM-66 and their respective percentiles for children under two years of age (Hanna, Bartlett, Rivard, and Russell, 2008).

Other functional domains such as cognition, receptive, and expressive language skills, fine motor fine skills, and socio-emotional and adaptive characteristics were evaluated at 17, 34 and 38 months using the Bayley Scales of Infant and Toddler Development (Bayley-III) (Madaschi, Mecca, Maced, and Paula, 2016; Marques et al., 2019) (Figure 3B). Compared to typical development, cognitive function, expressive and receptive language, and motor function were described as extremely low in this child at 17 months. At 34 months, cognitive function was classified as borderline, with the other functions being evaluated as extremely low. At 38 months, cognitive function was classified as intermediate-low, with no change from the previous evaluation for the other functions.

Sensory evaluation was performed at 44 months using the Sensory Profile Score (Pavao and Rocha, 2017). At that time and taking the scores achieved in each domain into consideration, there were no differences between the classification of auditory and oral processing in this child compared to typical development (i.e. auditory processing: 24 points – expected score between 10 and 24; and oral processing: 16 points – expected score between 8 and 24). The classification of visual and tactile processing is higher in this child compared to typical development children (visual processing: 19 points – expected score between 9 and 17; and tactile processing: 25 – expected score between 22 and 28).

Stomatognathic functions were clinically evaluated by a specialist in this field and by videofluoroscopy when the child was 37 months old. There was no evidence of risk of aspiration during feeding. However, the child had difficulty in opening her mouth when asked to and there was post-swallow residue. The evaluation also detected difficulty in sucking and chewing, early loss of contrast in the hypopharynx and a delay in the pharyngeal phase of swallowing, leading to a classification of mild oropharyngeal dysphagia. An experienced speech therapist evaluated the child at 36 months and reported that her oral language was restricted to short monosyllabic or disyllabic words, with difficulty in speech motor control and dysarthria. At that time, however, the child was able to communicate in an alternative fashion through picture exchange communication.

During the follow-up period, other professionals evaluated the child. At 26 months, an orthopedist evaluated her and found no evidence of hip dislocation or scoliosis, diagnosing her with pes planovalgus. A neurological evaluation conducted at 31 months yielded the following results: electroencephalogram with a regular and generalized background rhythm, hypotonia of the face and mouth and hypertonia of the right and left lower limbs, with signs of dystonia in the feet and left hand. At the ophthalmologic evaluation conducted at 23 months, the child was able to focus on and follow small objects with her eyes, and no

Table 1. Motor developmental milestones achieved by the child during the period of home physiotherapy and after initiating the intervention provided at the support center.

Age	Therapy characteristic	Expected milestones for a child with typical development	Milestones achieved by the child reported here
1–3 months	Home therapy, twice daily for 45 minutes Stimulation of motor developmental milestones Oculomotor stimulation	• Control of head and trunk	• Control of head and trunk
4–6 months	Home therapy, twice daily for 45 minutes Stimulation of motor developmental milestones Joint mobilization and dissociation of shoulder and pelvic girdles. Oculomotor stimulation	• Brings hands together at midline • Rolls onto back • Sits supported • Lifts head and chest when lying on stomach • Pivots	• Rolls onto back
7–9 months	Home therapy, twice daily for 45 minutes Stimulation of motor developmental milestones Joint mobilization, passive stretching and dissociation of shoulder and pelvic girdles. Oculomotor stimulation	• Sits unsupported • Maintains quadruped position • Starts crawling • Stands supported	• Sits supported • Lifts head and chest when lying on stomach • Pivots
10–12 months	Home therapy, twice daily for 45 minutes Stimulation of motor developmental milestones Joint mobilization, passive stretching and dissociation of shoulder and pelvic girdles. Exercises for strengthening muscles	• Moves from seated position to all-fours, kneeling, half-kneeling, and standing • Stands unsupported • Walks sideways • Walks independently	• Sits unsupported • Moves from seated position to supported standing position, without half-kneeling • Stands supported
13–17 months	Home therapy, twice daily for 45 minutes Stimulation of motor developmental milestones Joint mobilization, passive stretching and dissociation of shoulder and pelvic girdles. Exercises for strengthening muscles Training balance	• Gradually gains balance and reduces support base • Climbs stairs using handrails or crawling • Kneels down	• Moves from seated position to all-fours position, • Maintains all-fours position • Walks sideways • Stands unsupported
18–24 months	Specialized Physiotherapy, outpatient care From 17 to 21 months: Daily sessions of motor physiotherapy lasting two hours, five times a week. One hour based in NDT concept and one hour base in PediaSuit Protocol. Before 21 weeks: 45-minute sessions of motor physical therapy three times a week, based entirely on NDT	• Goes downstairs using handrail • Starts to jump	• Starts crawling • Climbs stairs using crawling • Kneels down
25–30 months	Specialized Physiotherapy, outpatient care 45-minute sessions of motor physical therapy three times a week, based entirely on NDT concept.	• Kicks a ball without losing balance • Is able to stand on one foot	• Walks independently • Climbs stairs using handrail
31–36 months	Specialized Physiotherapy, outpatient care 45-minute sessions of motor physical therapy three times a week, based entirely on NDT concept.	• Climbs stairs alternating leg movements • Jumps on the spot using both feet	• Walks independently • Goes downstairs using handrail

Figure 1. Images showing the child's motor development. a: One month; b: Two months, partial neck and trunk control when prone; c: Three months, neck and trunk control when prone; d: Seven months; sits supported; e: Eight months, sits unsupported; f: Eleven months, stands supported; g: Twenty months, crawls; and h: Twenty-eight months, school activities.

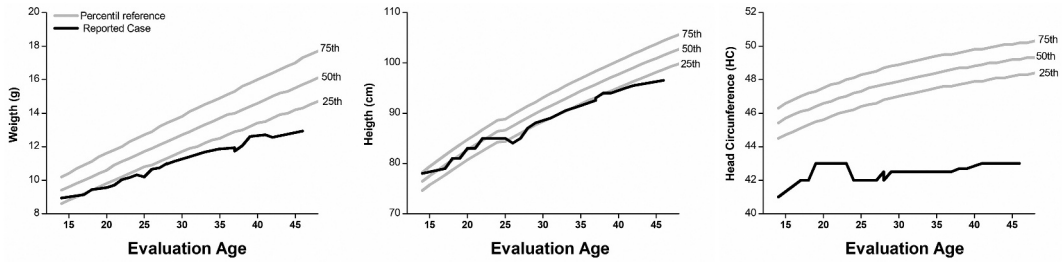

Figure 2. Weight (a), height (b), and head circumference (c) measurements throughout the evaluation period, together with the respective World Health Organization reference values for children with cerebral palsy.

Table 2. Gross Motor Function Measure Scores (GMFM-88) in the first four years of life.

	GMFM-88 Score					
Age at evaluation	Dimension A	Dimension B	Dimension C	Dimension D	Dimension E	Total
14	49	34	5	4	5	97
17	51	50	18	11	7	137
20	51	55	28	18	13	165
22	51	53	33	15	14	166
23	51	53	36	16	14	170
24	51	57	35	20	14	177
25	51	56	29	18	15	169
26	51	57	38	20	17	183
27	51	58	39	29	17	194
28	51	58	36	26	23	194
29	51	59	35	29	34	208
30	45	59	36	27	34	201
34	51	58	36	27	30	202
38	51	60	38	29	27	205
42	51	60	35	33	35	214
46	51	59	35	26	27	198

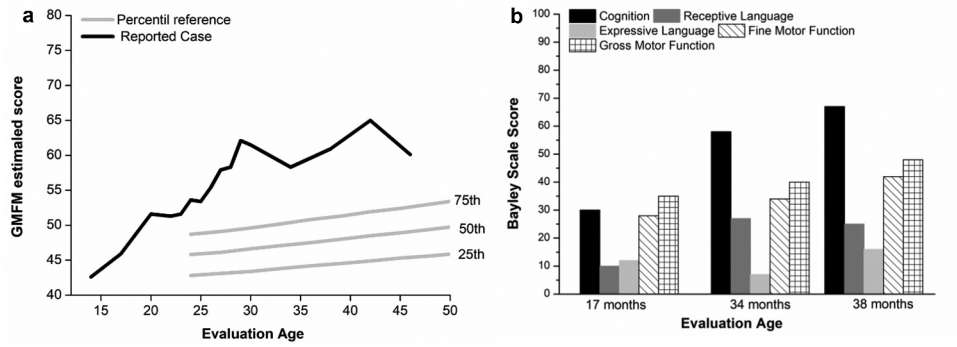

Figure 3. Score change for the a) Gross Motor Function Measure (GMFM-88) and for the b) Bayley-III per domain over the follow-up period.

abnormalities were found. Her hearing was assessed at 42 months using Brainstem Evoked Response Audiometry (BERA), with no hearing-related abnormalities being detected.

Discussion

Since 2015, the consequences of ZIKV infection to fetuses have been a subject of debate (Oliveira Melo et al., 2016; Pessoa et al., 2018). Despite the advances made, understanding the natural history of the disease and accessing protocols of rehabilitation that could encourage the neuropsychomotor development of these children have represented a major challenge to healthcare professionals in countries such as Brazil where abortion is not an option. Severe impairments to motor function have been described in children with CZS (Melo et al., 2020) and, in most cases, they are unable to stand upright or speak (Alves et al., 2018).

Some findings are noteworthy in the present case such as the GMFM-66 scores above the 97th percentile of expected values for children classified as GMFCS level III (Hanna, Bartlett, Rivard, and Russell, 2008) and the changes in the GMFM-66 score, confirming the progress made in the child's motor development over the follow-up period. In fact, only Takeuchi and Izumi (2012) reported this type of analysis in children with CZS. Of 100 children evaluated, with a mean age of 31.4 months, only two were classified as GMFCS level III. In two assessments performed six months apart using the GMFM-66, one of those children remained at the 15th percentile, while a reduction occurred from the 70th percentile to close to the 60th percentile in the other children, with the same total GMFM-66 score being maintained. Those findings suggest that, contrary to what was observed here, a deceleration in the motor development is expected for children classified as GMFCS level III (Takeuchi and Izumi, 2012).

Differences in the neuropsychomotor development of children with CZS can be related to the severity of the brain damage. What is noteworthy in the case described here, however, is the fact that this child had significant brain lesions, perhaps not as severe as in other children with CZS but lesions that cannot be considered mild (i.e. frontal agyria, reduced brain volume, and cerebellar hypoplasia) (Figure 4). Furthermore, head circumference remained below that expected for age between birth and four years of age. In addition, these findings show that from two years of age onwards the motor function of the child in question progressed to above that expected for her GMFCS classification level (Hanna, Bartlett, Rivard, and Russell, 2008). Comparisons prior to two years of age were impossible since studies giving reference curves for the GMFM-66 and their reference percentiles for children with different GMFCS levels were proposed only for those over two years of age (Hanna, Bartlett, Rivard, and Russell, 2008; Rosenbaum et al., 2002).

How then do we explain how a child with severe neuroimaging findings can achieve developmental milestones such as walking unsupported? Possible hypotheses that could explain why severe disability may have been avoided include 1) The absence of convulsive seizures and the fact that no anticonvulsants were required. Motor and cognitive developmental delays have been associated with the occurrence of convulsive seizures, particularly in the first years of life (Lee et al., 2018; Luat, Behen, Chugani, and Juhasz, 2018; Melo et al., 2020; Vargha-Khadem et al., 1992); 2) The absence of severe dysphagia, which is common in children with CZS and can have a negative effect on the growth and motor development of children with neurological damage (Leal et al., 2017); 3) The absence of any visual or hearing impairments, possibly favoring the maintenance of balance despite the cerebellar hypoplasia. Postural control and motor development in children is strongly affected by visual and auditory stimuli (De Kegel et al.,

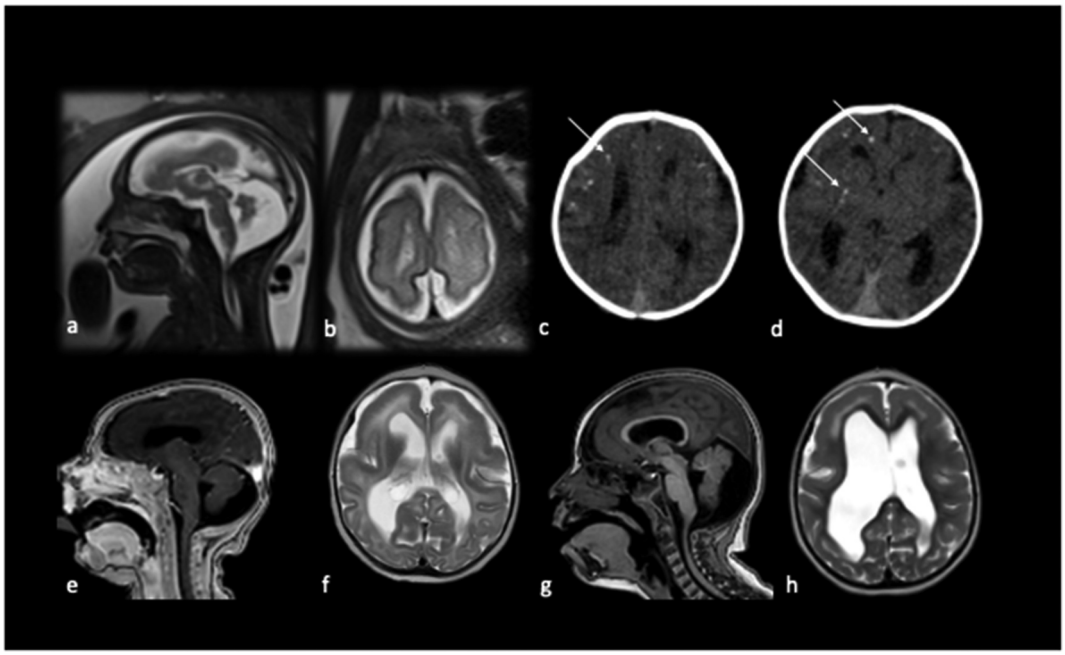

Figure 4. a) Fetal magnetic resonance imaging (MRI) – sagittal plane (reduced brain volume, hypoplasia of the cerebellar vermis); b) Fetal MRI – axial plane (microcephaly, reduced brain volume, delayed cortical development, interhemispheric fissure enlargement); c) Computed tomography (CT) – axial plane (subcortical calcifications – arrow); d) CT – axial plane (subcortical calcifications and calcifications in the basal nucleus – arrows); e) Neonatal MRI – sagittal plane (reduced brain volume, hypoplasia of the cerebellar vermis); f) Neonatal MRI – axial plane (reduced brain volume, agyria in the frontal lobe, ventriculomegaly); and g) MRI at three years of age – sagittal plane.

2016; Liao and Hwang, 2003; Vidranski and Farkas, 2015); 4) The early initiation of physiotherapy is associated with constant motor stimuli at different positions during daily activities. Motor stimulation with directed physiotherapy from the first months of life onwards may have encouraged the neural connections that occur in the first years of life (Hadders-Algra, 2018; Morgan et al., 2016); and 5) The mother's education level. Better education levels in the mother are associated with better opportunities of environmental stimuli, which can reflect directly on the child's neuropsychomotor development (Defilipo et al., 2012); 6) A combination of all of the above.

The final two points, however, should be evaluated with caution. In the case of the child described here, home physiotherapy was not conducted by parents with no knowledge of the principles of rehabilitation but by a mother who is a trained physiotherapist and who had prepared herself for a child with developmental delays since the second half of pregnancy. The findings suggest that motor stimulation based on the precepts of rehabilitation and initiated in the first days of life could have made a difference in this case. Early intervention and transfer of therapeutic benefits to the home environment are essential to maximize neuroplasticity and minimize deleterious modifications in the musculoskeletal system and growth in children with neurological disorders (Farjoun et al., 2022; Novak et al., 2017). Considering that intensity and repetition are also critical to rehabilitation and that improvement is more likely if tasks are practiced at home for at least 20 minutes a day (Herskind, Greisen, and Nielsen, 2015; Morgan et al., 2021), the time expended in motor stimulation during first months of life was likely critical for the outcomes achieved in this case.

Unfortunately, this is not a common situation for children with CZS, who are, in their vast majority, children of women from poor educational and socioeconomic backgrounds (Melo et al., 2020) with jobs not related to physiotherapy. This case does not mirror the actual situation for most children insofar as access to specialist therapies is concerned. Therapy in this case was initiated on the fourth day of life and performed for two hours daily, leading us to reflect on lost opportunities for other children. The role of the family is also a consideration. Could this child have achieved the same outcomes if her parents had been well educated but if her mother were not a physiotherapist?

The principal limitation of the present report lies in its methodology since this report refers to one single case. The description of this one case, however, adds

important information with respect to the development of children with CZS since this child was monitored from pregnancy onwards. She appears to have benefited from the motor stimulation provided by her mother from the fourth day of life onwards followed by intensive physiotherapy provided by a multidisciplinary specialist team. These findings raise various questions regarding the impact of intensive multidisciplinary care on children, not only those with CZS, beginning on the first days of life. Indeed, even in the case, in which the child has severe microcephaly, agyria, calcifications, reduced brain volume, and hypoplasia of the cerebellum and cerebellar vermis, she managed to achieve unexpected developmental milestones such as walking. A new study is being conducted to compare neurodevelopment in a greater number of cases of CZS according to the severity of brain damage and access to treatment; however, most of those children only began intensive therapy after two years of age.

Conclusions

In conclusion, despite the severe neurological impairment in this first case of CZS to be described worldwide, the child is defying prognoses, with an improvement in motor function beyond the normative values in the literature for her GMFCS classification level over the first four years of life. This finding could be related to the constant stimuli provided by specialists in a treatment environment and by the child's mother, a physiotherapist, suggesting the importance of initiating intensive rehabilitation programs from the first days of life.

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Disclosure statement

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