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Motor dysfunction in preschool children exposed to zika virus during pregnancy and normocephalic at birth: Developmental Coordination Disorder and Minimal Neurological Dysfunction

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1. Introduction

Child motor development begins during the gestational period and extends through the first two decades, influenced by gestational, perinatal, genetic and environmental factors [1]. Sequentially, new motor skills create new learning opportunities and can instigate cascades of development far removed from the original achievement, leading to an evolutionary continuum that unfolds intensely in the first years of life but never ceases to exist [2]. The motor domain is subdivided into fine motor skills and gross motor skills. After acquiring the main motor milestones in the first two years of life, the development of motor skills is related to the individual's functionality and daily living abilities [3]. The occurrence of motor dysfunctions such as Developmental Coordination Disorder (DCD) or Minimal Neurological Dysfunction (MND) can bring harm to daily life. It may be associated with cascading impact to

cognitive, social and behavioral development [4,5]. DCD is a neurodevelopmental disorder characterized by impairments in the individual's motor performance, impacting school, professional, social and leisure activities throughout life [6,7]. The diagnosis of DCD can be made using validated instruments that demonstrate impairment in motor performance, such as the Movement Assessment Battery for Children-Second Edition (MABC-2) [8], in addition to evidence that the dysfunction causes functional impairment to the individual, through validated questionnaires, such as the Developmental Coordination Disorder Questionnaire (DCDQ) [9].

Furthermore, the onset of symptoms occur in the first years of life and deficits in motor skills are not better explained by other neurological conditions [7]. When it is impossible to meet all the criteria, the term probable DCD may be used [10]. The estimated worldwide prevalence of DCD is 5 to 6 % in children aged 5 to 11 years [7].

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ABSTRACT

The occurrence of motor dysfunctions was assessed at the age of 5 to 7 years in 61 normocephalic infants with prenatal Zika virus exposure. Traditional neurological examination, Touwen neurological examination, Movement Assessment Battery for Children-Second Edition (MABC-2) and the Developmental Coordination Disorder Questionnaire (DCDQ) were used to identify Developmental Coordination Disorder (DCD) and Minimal Neurological Dysfunction (MND). A high frequency of motor dysfunctions was found, 47 (81.0%) of MND and 15 (24.5%) of probable DCD. It is also possible to suggest some association between both conditions.



Abbreviations: DCD, Developmental Coordination Disorder; DCD-Q, Developmental Coordination Disorder Questionnaire; MND, Minor neurological dysfunction; MABC-2, Movement Assessment Battery for Children, Second Edition; SGA, small for gestational age.

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MND is a set of motor signs found in a specialized neurological examination developed by Touwen in 1979 and may indicate an underlying neurological pathology, with a greater risk of future cognitive and behavioral outcomes. The occurrence of one or two altered clusters indicates simple MND, while three or more defines complex MND before puberty [11–14]. Traditional neurological examination is often normal in children with behavioral, cognitive, or learning disorders, as well as those with established neurodevelopmental disorders [14,15].

Adverse prenatal or perinatal events, prematurity and male sex are important risk factors for these motor dysfunctions. Both DCD and complex MND may share risk factors with cerebral palsy (CP), often referred to as non-CP motor impairment [13,16,17]. Among prenatal adverse events, the occurrence of congenital infections is known to affect the neurological future of children. However, maternal inflammatory and immunological activation during pregnancy is also a wellknown environmental factor affecting child neurodevelopment [18,19]. The Zika virus (ZIKV) epidemic in Brazil in 2016 caused severe consequences in children infected during pregnancy and who developed congenital ZIKV syndrome (SCZ) [20,21]. Some studies that followed the first years of those born asymptomatic raised the suspicion that some damage could also occur in their development [21–23].

1.1. Objectives:

To describe the frequency of probable DCD and MND in preschoolaged children exposed to the ZIKV during pregnancy, born at term and without microcephaly, as well as possible associations between these motor dysfunctions.

2. Material and Mmethods:

Cross-sectional descriptive study. Of the Natural History of Zika Virus Infection in Gestation (NATZIG) cohort, 370 children met the established inclusion criteria, defined by children between five and seven incomplete years of age with a history of proven exposure to ZIKV during pregnancy and who were not born with microcephaly. They had been evaluated by the Bayley III Screening Test in their second year of life. The motor domain was considered for this study. Due to refusal or impossibility of contact, 61 children were finally included in the study and evaluated between 2022 and 2023. They were evaluated using the traditional neurological examination, Touwen Neurological Examination and MABC-2, and the questionnaire for DCD, DCDO-Brazil.

2.1. Data analysis:

The exact chi-square test (χ^2) was used to analyze possible associations between demographic and outcome variables of motor dysfunction of the sample, in addition to being used to search for possible associations between probable DCD, MND and their subcategories. To compare the percentile means in the MABC-2 motor test between two groups, the nonparametric Mann-Whitney test was used. We considered the significance level (p) to be ≤ 0.05 in all analyses.

3. Results:

Sixty-one children were included in this study. The mean age was 80 months (69 to 94 – SD 4.13); 32 (52.5 %) were female. ZIKV exposure was predominant in the second trimester of gestation (50.8 %), and none of the infants had anoxia at birth. Regarding the Bayley III Screening Test performed up to 24 months of age, 56 children (91.8 %) had been evaluated, and only one child (1.7 %) presented, at 18 months, an altered result as emerging for fine motor skills (Table 1). No findings were observed in the clinical or traditional neurological examination. Fifty-eight children underwent the Touwen Neurological Examination and all underwent MABC-2 and DCDQ-Brazil. Only ten children (16.3 %) had normal motor neurological conditions according to MABC-2 and

Table 1

Demographic and epidemiological data of the sample of children exposed to Zika
virus during pregnancy.

Variable	Results ($n = 61$)
Age (months)	80 (6984); SD 4,13
72 full months (n)	57 (93,4 %)
Sex:	
Female	32 (52,5 %)
Male	29 (47,5 %)
Socioeconomic class:	
A/B	21 (54,5 %)
C/DE	40 (65.5 %)
Complete high school graduation (main provider)	38 (62,2 %)
Gestational Trimester of Zika virus infection:	
First n (%)	13 (21,3 %)
Second n (%)	31 (50,8 %)
Third n (%)	17 (27,9 %)
Maternal comorbidities during pregnancy	9 (14,7 %)
Other vertical exposure/congenital infection	0
Gestational age at birth (weeks)	39 (3742); SD 1,13
Fifth-minute Apgar note	710
Head circumference at birth (cm)	34,3 (31,537); SD 4,5
Birth weight adequacy:	
AGA (adequate for gestational age)	52 (85,2 %)
LGA (large for gestational age)	4 (6,6 %)
SGA (small for gestational age)	5 (8,2 %)
Low birth weight	0
Bayley III Screening Test n (%)	56 (91,8 %)
Altered motor domain n (%)	
Fine motor n (%)	1 (1,7 %)
Gross motor	0

Data are expressed as means (lowest – –highest values) and standard deviation (SD) or numbers (frequencies).

Touwen neurological examination. Final motor evaluation by MABC-2 and Touwen neurological examination is presented below and in Table 2.

3.1. MABC-2 Evaluation Rresults:

Fifteen (24.5 %) children presented altered results according to MABC-2, IC 95 % (0.14; 0.37), with 12 (80 %) of them having a percentile \leq 5, or red zone, and three (20 %) having a percentile > 5 and < 16, or yellow zone. Regarding the domains evaluated, it is observed that Manual Dexterity was the most altered (80 %), followed by Balance (66 %) and Aiming and Catching (33 %). In the general sample, there was a more significant number of dysfunctions for males in Manual Dexterity (p = 0.03) and Aiming and Catching (p = 0.01), with no difference in Balance for the sexes (p = 0.2). There was no difference between the sexes for children with probable DCD for all domains. Statistically, the variables associated with probable DCD ware male sex (p = 0.04) and small for gestational age (SGA) at birth (p = 0.01).

3.2. DCDQ results:

Twelve children (19.5 %) presented with "indication or suspicion of

Table 2

Frequency of Developmental Coordination Disorder identified by MABC-2 and Minimal Neurological Disorder (MND) in Touwen Neurological Examination.

MABC-2	N (%)	Touwen exam findings	N (%)
Percentile < 16 Yellow zone	15 (24.5 %) 3 (20 %)	MND sMND	47 (81,0 %) 27 (46.5 %)
Red Zone	12 (80 %)	cMND	20 (34.4 %)
Green Zone	46 (75.4 %)	Normal	11 (19,0 %)

MABC-2: Movement Assessment Battery for Children - Second Edition; Percentile <16: altered MACB-2 result. Yellow zone: percentile between 5 and 16; red Zone: percentile lower or equal to 5; green zone: percentile greater than >15; sMND (simple MND); cMND (complex); data are presented in n (%). Source: the author. DCD" by DCDQ-Brazil, IC 95 % (0.09; 0.29). From those with altered MABC-2 results, seven (11.4 %) pointed to an "indication or suspicion of DCD", IC 95 % (0.03; 0.19). However, even though the agreement between the DCDQ-Brazil and the MABC-2 was only 46.6 %, those who presented probable DCD through the questionnaire, 12 (19.6 %), had a greater chance of having an altered MABC-2 result (p = 0.006).

3.3. Touwen Neurological Examination results:

Forty-seven (81.0 %) children were classified with MND, IC 95 % (0.68: 0.90). Twenty-seven (46.5 %). IC95% (0.33: 0.60), had simple MND and 20 (34.4 %). IC95% (0.22: 0.48) had complex MND. Choreiform Dyskinesia and Coordination and Balance by the Touwen Neurological Examination were the areas of most remarkable change. Furthermore, comparing the results between the simple and complex MND groups, there was a more significant occurrence of changes for complex MND in Choreiform Dyskinesia (p = 0.00), Coordination and Balance (p = 0.01), Fine manipulation (p = 0.00) and Miscellaneous (p= 0.02). Isolated MND did not show a significant association with any variable. Complex MND with DCD (p = 0.04) and MND with DCD as cooccurrence (p = 0.05) were associated with the male sex; as well as MND with DCD as co-occurrence (p = 0.02) was associated with SGA at birth. The only child with alterations in the motor domain of the Bayley III Screening Test did not present alterations in the MABC-2 or DCDQ-Brazil; he presented with simple MND.

3.4. Associations between MABC-2 and the Touwen Neurological Examination:

The frequency of probable DCD was based on the MABC-2 for this sample. For these children with probable DCD, the frequency of MND was 73.3 % (n = 11), with 63.6 % (n = 7) of them having complex MND and 36.3 % (n = 4) having simple MND. The three children who weren't assessed by the Touwen Neurological Examination were in the probable DCD subgroup. An association was found for the occurrence of complex MND in children with probable DCD (p = 0.05) (Table 3). Regarding MND, 11 (23.4 %) patients presented probable DCD, with a higher frequency in the subgroup with complex MND (n = 7, 63.6 %), compared to simple MND, with 4 children (36.3 %). Furthermore, the mean final percentile and the mean Manual Dexterity percentile of MABC-2 were lower for complex MND (p = 0.009; p = 0.013) when compared with the simple form (Table 4).

4. Discussion:

Preschool-aged children are mostly able to cooperate with the Touwen Neurological Examination and the MABC-2 tests. Our work found a high frequency of probable DCD and MND motor dysfunctions in children who were exposed to ZIKV during pregnancy but were born without evident impairment. These results were higher than that described in many national and international series designed to assess the prevalence of those conditions, when cohorts of premature infants are not considered [24–32]. Among these studies that evaluated DCD,

Table 3

Association of Minimal Neurological Dysfunction with probable Developmental Coordination Disorder (DCD).

Towen Exam Findings	Frequency in the Probable DCD group	Frequency in the group without DCD	р
MND	11 (73.3 %)	36 (78,2 %)	0,29
sMND	4 (36.3 %)	23 (63.8 %)	0,30
cMND	7 (63.6 %)	13 (36.1 %)	0,05

p: chi-square test analysis results; statistically relevant results are shown in bold format; data are presented in n (%). Source: the author. Table 4

Results of mean percentiles in MABC-2 for the simple (sMND) and complex (cMND) Minimal Neurological Dysfunction subgroups.

MABC-2	sMND group ($n = 27$)	cMND group ($n = 20$)	р
Overall Result	46 (29)	24 (23)	0,009
Manual dexterity	41 (26)	22 (23)	0,013
Aiming and Catching	46 (27)	33 (22)	0,129
Balance	55 (33)	43 (34)	0,209

Data are expressed as means (standard deviation); *p* values were presented according to Mann-Whitney test results; results with statistical significance are in bold; MABC-2: *Movement Assessment* Battery for Children - Second Edition. Source: the author.

we highlight Mulkey (2023), who found a 6 % frequency for this disorder in preschoolers exposed to ZIKV and who were born asymptomatic [32]. The comparison between the two studies gains additional validity because they are countries of Latin origin. It is worth noting, however, that although both groups evaluated preschoolers, the Colombian children were younger (3 and 4 years old), which may have impacted the results. Later on the same group also highlighted MABC data suggesting a potential difference in gross and fine motor coordination abilities between the ZIKV-antenatal exposed preschool children and controls [33]. Erdi-Krausz et al. [34] found a DCD frequency of 22.2 %, lower but very close to that of our sample, even though the children evaluated had a history of perinatal hypoxic-ischemic encephalopathy, an important predictor of motor impairments in childhood. Their frequency of MND was also 22.2 %, reaffirming the possible co-occurrence of MND and DCD, as we found in our sample [34]. The Groningen Perinatal Project (GPP) was a Dutch follow-up project from birth to early childhood that provided information on the natural history of MND, suggesting a variation in its prevalence throughout childhood, with an increase with age until puberty, when its occurrence then decreases. For children aged six years without abnormalities at birth, the frequency of MND they found was 7 %, also lower than what we found in this series [13].

It is not the purpose of this study to assume that the occurrence of these motor dysfunctions is higher in children exposed to ZIKV during pregnancy compared to the general population. This is a small sample, determined in part by family adherence to follow-up and without a control group with the same socio-economic characteristics. Even though gestational exposure to ZIKV raised fears in families about future outcomes, and this could have had adherence implications, after a few years of the initial risks, it is possible that those children who attended for evaluation were precisely those who already had, in the family view, some general difficulty in terms of development, behavior or learning. This possibility may have overestimated our frequency data. Furthermore, it is important to consider that participants were evaluated in the first two years following the Coronavirus (COVID-19) pandemic. The pandemic years limited these children to a period of greater confinement at home, with extensive exposure to screens, fewer sports practices and reduced opportunities to experiment with free movement, all of which have a major impact on neurodevelopment [35].

Risk perinatal events occurring in the first trimester of gestation were more associated with worse outcomes in the NATZIG cohort [36]. Minor dysfunctions in the motor domain may be associated with adverse events in the second or third trimester of gestation due to the greater vulnerability of the cortical-striate-thalamic-cortical and cerebellum-thalamiccortical pathways, circuits that play a role not only in the sensory-motor aspects of motor programming but also in the planning of movement, in the selection of programs and in motor memory [17]. In our sample, although the predominance of ZIKV infection was in the second trimester, there was no significant association of the occurrence of probable DCD or MND with the trimester of exposure. As well as literature data, however, male sex and SGA have been related to motor dysfunction in this work [37–39].

The results of the Bayley III Screening Test in the sample, as reported

in the literature, showed that its predictive value for motor problems at preschool age is questionable since it would not identify a large proportion of these problems, especially when cerebral palsy is ruled out [40–42].

In addition, as to the profile of motor damage, alterations in manual dexterity and coordination and balance and the presence of choreiform dyskinesia were highlighted in those children with probable DCD or MND [43,44]. The emphasis on changes in manual dexterity in the motor profile of children with probable DCD and complex MND, in comparison with the simple form, raises reflections on the value of this ability as a hallmark of the child's motor competence. The development of fine motor skills is directly related to the maturation and myelination of the corticospinal tract, which undergoes continuous refinement throughout childhood, stabilizing in adolescence [45]. This maturation is the product of endogenous and exogenous factors, but recent studies demonstrate that the architecture of the white matter is highly malleable in childhood and prone to the influence of motor experience [46]. For this sample, there was a high frequency of MND in children with probable DCD, with a predominance of the MND complex form. In children with complex MND, the frequency of probable DCD was also higher than in the simple form. In addition, children with MND had lower final percentile and Manual Dexterity averages by MABC-2 compared to children without MND. Few published studies highlight the occurrence of DCD and MND, seeking possible associations between these conditions [33,47-49]. Like our work, both studies suggested that children with MND have lower motor performance as measured by MABC and an association with probable DCD. In contrast, the occurrence of probable DCD by MABC would have a greater association with complex than simple MND.

The small sample size of this work is one of its main limitations, in addition to the absence of a control group and the evaluation restricted to the motor domain.

MND reaches its peak shortly before the onset of puberty and, similarly, the school-age period is when the highest prevalence of DCD occurs [13]. As such, the children evaluated in our center are being reevaluated during school age for motor performance and subtle motor neurological dysfunction, as well as for cognitive and behavioral outcomes. Regarding future studies, we believe that in addition to clinical evaluations, functional magnetic resonance imaging (fMRI) could provide a better understanding of the networks related to DCD. A systematic review in neuroimaging and DCD showed that resting-state functional connectivity studies revealed large and significant effects for connectivity in specific areas potentially involved in the process of motor learning, motor control, and cognitive control, which are key areas of interest in the study of the neurobiology of DCD [38,50,51].

Since literature suggests that a significant percentage—50 % to 70 %—of children with DCD may continue to face these challenges during adolescence and adulthood, we believe that early intervention and follow-up assessments are essential for mitigating potential long-term effects. By focusing on motor enrichment, cognitive development, and behavioral support, we can provide children with the best opportunities for success as they transition into adolescence and adulthood [38].

5. Conclusion:

Our work found a high frequency of probable DCD and MND, non-CP motor dysfunctions, in children who were exposed to ZIKV during pregnancy but were born without evident impairment. The assessment of the motor domain using the Bayley III screening test showed no association with motor findings at preschool age. Manual Dexterity by MABC-2 and choreiform Dyskinesia and Coordination and Balance by the Touwen Neurological Examination were the areas of greatest alterations. Furthermore, it is possible to suggest that there is some association between probable DCD and complex MND, and the fact that this last condition can be identified by a specialized neurological examination can provide the child neurologist with yet another diagnostic tool.

Ethics approval and consent to participate consent

All procedures were in compliance with research policies and were approved by the Institutional Committee on Human Research.

CRediT authorship contribution statement

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Author statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs Signed by all authors as follows:

Consent for publication

The correspondent author has read and understood the publishing policy and submits this manuscript in accordance with this policy.

Declaration of competing interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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