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Early Predictors of Poor Neurologic Outcomes in a Prospective Cohort of Infants with Antenatal Exposure to Zika Virus

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Abstract

Background & Objectives: Identify early predictors of poor neurodevelopment in infants with antenatal Zika virus (ZIKV) exposure.

Methods: Analysis of a prospective cohort of infants with antenatal ZIKV exposure confirmed by maternal and/or infant RT-PCR or IgM during the epidemic in Rio de Janeiro, Brazil. Clinical findings prior to 3 months of age were associated with Bayley-III Scales of Infant and Toddler Development conducted after 6 months of age.

Results: ZIKV exposure was confirmed in 219 cases; 162 infants were normocephalic, 53 were microcephalic, 4 had no head circumference (HC) recorded due to perinatal death/LTFU. 7 of the 112 normocephalic infants developed secondary microcephaly between 3 weeks and 8 months of age.

Among the normocephalic at birth cohort, the mean HCZ among normal, at risk, and developmentally delayed children was significantly different (ANOVA p=0.02). In particular, the mean HCZ of the developmentally delayed group was significantly lower than that of the normal group (Tukey's test, p=0.014). HCZ was more strongly associated with lower expressive language scores (p=0.04) than receptive language scores (p=0.06). The rate of auditory abnormalities

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differed among the normal, at risk, and developmentally delayed groups (Chi-squared test p=0.016), which was driven by the significant difference between the normal and at risk groups (post hoc test p=0.011, risk ratio 3.94). Auditory abnormalities were associated with both expressive and receptive language delays (p=0.02, and p=0.02 respectively).

Conclusion: Clear predictors of neurodevelopment in normocephalic ZIKV-exposed children have not been previously identified. Our findings demonstrate that smaller HCZ and auditory abnormalities in these infants correlate with poor neurodevelopment as toddlers. Language delay is the most prominent developmental concern among these children, who will require frequent auditory and speech evaluations throughout childhood.

Keywords

Neurodevelopment; Congenital Infection; Language; Speech

Introduction

Between May 2015 and December 2016, there were 707,133 reported cases of Zika virus (ZIKV) infection across 48 countries in the Americas, though this is a clear underestimate of the true disease burden[1]. In 2015, health surveillance systems in Brazil noted a 20-fold increase in microcephaly cases [2,3]. The causal relationship between congenital ZIKV infection and microcephaly was subsequently established upon review of the compelling evidence using Sheppard's teratogenicity criteria and Bradford Hill's causation criteria [4].

Vertical transmission of ZIKV results in fetal loss, intrauterine growth restriction (IUGR) and diverse neurologic abnormalities[5]. In its most severe manifestation, infants may suffer from Congenital Zika Syndrome, the features of which include microcephaly, seizures, developmental delay, auditory and visual deficits, arthrogryposis, abnormal tone and reflexes [6,2,7]. Although it is clear that children with Congenital Zika Syndrome, particularly those who are microcephalic, will very likely have neurodevelopmental delay, predictors of neurodevelopment in non-microcephalic children with confirmed antenatal ZIKV exposure have not been well characterized. The main focus of the present study is the evaluation of non-microcephalic infants antenatally exposed to ZIKV in Rio de Janeiro, Brazil with the goal of identifying early predictors of poor neurodevelopment in children who are born without stigmata of ZIKV infection, particularly microcephaly. In the first three months of life, these infants were evaluated for the presence of specific clinical findings, with associations explored between these early findings and neurodevelopmental outcomes after 6 months of age, as assessed by the Bayley Scales of Infant and Toddler Development-III[8]. We hypothesize that antenatal exposure to maternal Zika virus infection, in infants born without CZS (i.e., without microcephaly), will adversely impact language development due to the potential for hearing deficits following antenatal ZIKV infection.

Methods

Study Population:

The study was conducted at the Fernandes Figueira Institute (IFF), Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Brazil. This was a an ancillary research study

based on our prospective cohort of ZIKV-exposed infants with laboratory-confirmed ZIKV exposure followed at IFF from December 2015 to present (Clinicaltrials.gov NCT03255369) [5]. Institutional review board approvals for retrospective review of medical records were obtained at IFF/FIOCRUZ (CAAE: 52675616.0.0000.5269) and the University of California, Los Angeles.

Laboratory Testing:

Real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) (Qiagen) or IgM serology (MacElisa, CDC) was performed on mothers during pregnancy and/or infants after birth at the IFF laboratory using the protocol described by Lanciotti et al. [5,9,10] Maternal specimens were serologically tested for antibodies to HIV, cytomegalovirus (CMV), Parvovirus B19, Epstein-Barr Virus (EBV), syphilis (VDRL), and *Toxoplasma gondii*, and RT-PCR tested for Chikungunya and Dengue viruses [5].

Infant Clinical Assessments:

Gestational age was measured by date of last menstrual period and serial ultrasounds during pregnancy and verified with the neonatal Ballard method exam at birth. Medical history and clinical assessments were conducted by pediatric specialists: neonatologists, neurologists, cardiologists, infectious disease specialists, ophthalmologists, geneticists, and physical therapists. Anthropometric measures at birth were obtained in all live-born infants enrolled in the study. Birth z-scores were calculated based on the INTERGROWTH-21st Project data for gestational age and sex.[11] Microcephaly was defined as a cephalic perimeter z-score of <−2 SD. Small-for-gestational-age infants were defined as infants with body-weight z-scores of <−1.28 at birth.[11] Postnatal z-scores were based on the WHO's Global Database on Child Growth and Malnutrition data.[12] Failure to thrive (FTT) was defined as fulfilling one of the following criteria; 1) Weight z-score of <−1.89, 2) Height z-score of <−1.89, 3) Weight-for-length z-score of −1 or less, or 4) Deceleration of weight-for-length z-score of −1 or more (WHO anthropometric data was used for weight-for-length variables at both time points). Ophthalmologic outcomes were based on a complete eye examination with funduscopic evaluation performed by pediatric ophthalmologist [13,14]. Auditory outcomes were based on hearing assessments evaluated through brainstem evoked response audiometry (BERA). Evoked potential assessments were performed in the dedicated clinic facility within the pediatric hospital (IFF).[5,15,16] Feeding difficulties were defined as dysphagia, altered swallowing, or altered suckling. Cardiologic abnormalities were based on echocardiograms performed by a pediatric cardiologist in the neonatal period. The most recent assessment was included for all clinical assessments, which ranged from 0 to 4 years of age.

The Bayley Scales of Infant and Toddler Development-III, a developmental tool validated cross-culturally in Brazil, was administered in Portuguese by trained neuropsychologists for children between 6 months to 3 years of age, with a median age of 18 months, and corrected for post-term age[8,17]. Three neurodevelopmental domains were assessed; cognitive, language, and motor functions[8]. Scores <−1SD to −2SD below the mean (score of 70 to <85) were defined as at risk for developmental delay (below average), and scores <−2SD below the mean (score of <70) were defined as developmental delay (very below average)[18]. The language subdomain was further divided into expressive and receptive

language wherein normal was considered a score of 10 +/− 3 [19] whereas the motor subdomain is divided into gross and fine motor functions.

Brain imaging studies were offered to all infants enrolled in the study. Screening transfontanel ultrasonography (TFUS) was routinely performed on ZIKV-exposed infants after birth. If abnormalities were detected on TFUS or physical/neurologic examination, or if infants could not have TFUS performed, further CNS imaging was performed (CT or MRI) [20].

Statistical Analysis:

Associations between clinical manifestations and Bayley-III scores were examined as 2-sided hypotheses with 5% alpha levels. Bayley-III scores were categorized as at risk or developmentally delayed as described above. Clinical manifestations were considered binomial (abnormal/normal), with the exception of Apgar scores and height, weight, and head circumference z-score which were examined continuously. Pearson's chi-squared tests were used to investigate associations between clinical manifestations and Bayley-III scores when clinical variables were considered as binomial variables. When the chi-squared test comparing the normal, at risk, and developmentally delayed groups was significant, an approach based on Fisher's exact test was utilized to identify the two groups that were significantly different from one another[21].

Odds ratios were calculated and Haldane-Anscombe corrections were used to correct for zero cells. For the continuous endpoints, analysis of variance (ANOVA) was used to test the null hypothesis that the mean value of the endpoint was the same for the normal, at risk, and developmentally delayed groups. If the null hypothesis of the ANOVA was rejected, Tukey's test was performed to identify the pair of groups that were significantly different from one another. Expressive and receptive language subsets were examined as continuous scores using T-tests and unadjusted linear regression. All analysis were performed with R[22].

Results

A total of 296 infants born during or immediately following the ZIKV epidemic were referred to IFF because of suspicion of antenatal ZIKV exposure. *In utero* exposure to ZIKV was confirmed in 219 infants (74.0%) through positive maternal and/or infant IgM serology and/or RT-PCR testing (**see** table, Supplemental Digital Content 1). Of these 219 infants, 2 died within 24 hours of birth without a head circumference being recorded, and 2 were lost to follow up at the time of birth, leaving 215 infants for whom birth data were available. Of these, fifty-three infants (24.7%) were microcephalic at birth. Among the 162 non-microcephalic infants, 112 (69.1%) had Bayley-III evaluations between 6 months and 3 years of age (Figure 1). Early clinical findings in the first 3 months of life were associated with neurodevelopmental performance after six months of age in 112 non-microcephalic children.

A total of 72 children in the group of 112 normocephalic infants (64%) were found to have average or above average Bayley-III evaluations, with scores ≥85 in all three domains. Thirty children (27%) were found to be at risk for developmental delay, scoring between

84 and 70 (between −1SD and −2SD) in at least one domain. Ten children (9%) were developmentally delayed, scoring ≤69 in at least one domain. The mean cognitive score for the 112 children was 99.9 (SD 13.3), mean language score 89.1 (SD 13.95), and mean motor score 95.4 (SD 11.8) (Figure 2). Language development was the most common neurodevelopment problem in this cohort of children. The mean expressive language score for normocephalic infants was 7.94 (SD 2.45) and mean receptive language score was 8.27 (SD 2.70) (Table 1). The age of Bayley-III performance ranged from 47 to 145 weeks with a mean age of 18 months. The 53 microcephalic infants at birth were too developmentally delayed to undergo Bayley-III testing, and as in our prior studies would have been assigned a score of 55 when included in a comparative analysis [15]. All analyses presented from here on are focused on normocephalic infants.

Of note, 7 of the 112 normocephalic infants developed secondary microcephaly between 3 weeks and 8 months of age. All of these children subsequently underwent Bayley-III assessment several months after the onset of secondary microcephaly was noted (between 9 and 31 months of age). Of these, 4 scored in the average to above average range, 2 scored in the at-risk range, and 1 had developmental delay on Bayley-III assessment. The infant with developmental delay had a TFUS performed in infancy which showed periventricular cerebellitis. One infant with secondary microcephaly had no neuroimaging performed, and the remaining five had normal TFUS in early infancy. There were 16 infants with head circumference z-scores >2 at birth. Among these, 12 resolved at follow up, 2 infants had persistent macrocephaly, and 2 were lost to follow up. Additionally, 4 infants were found to develop secondary macrocephaly between 2 weeks and 16 months of age. One of the two infants with persistent macrocephaly, and 1 of the 4 infants with secondary macrocephaly fell in the at-risk range on Bayley-III assessment. All remaining macrocephalic infants performed in the average to above average range.

At the time of birth, the mean head circumference z-score (HCZ) for normocephalic infants was 0.93 (SD=1.11), mean weight z-score was 0.26 (SD=0.98), length z-score was 0.27 (SD=1.21), and 7 infants (6.3%) were small for gestation age (z-score for birth weight < −1.28) (Table 1).

In the normocephalic at birth cohort, (n=112), the rate of auditory abnormalities differed among the normal, at risk, and developmentally delayed groups (Chi-squared test p=0.016), which was driven by the significant difference between the normal and at-risk groups (post hoc test p=0.011, risk ratio 3.94). Auditory abnormalities were associated with both expressive and receptive language delays (p=0.02, and p=0.02 respectively). Children with auditory abnormalities had an average expressive language score of 5.5 (SD 2.65) compared to 8.54 (SD 2.36) in children with normal hearing. Receptive language scores were 6.25 (SD 0.9) in children with auditory abnormalities, compared to 8.09 (SD2.06) in children with normal hearing.

The mean HCZ of children who performed at or above average in all three Bayley-III domains was 1.35 (SD 0.74), while the mean HCZ of children who performed <−1 SD below average was 1.15 (SD 0.82) and for those who performed <−2SD below average the HCZ was 0.63 (SD 0.33) (Table 2). The mean HCZ among these three groups (normal, at

risk, and developmentally delayed children) was significantly different (ANOVA p=0.02). In particular, the mean HCZ of the developmentally delayed group was significantly lower than that of the normal group (Tukey's test, p=0.014). The association between lower HCZ and abnormal language development appeared to be primarily driven by lower expressive scores (p=0.04, β = 0.66) as opposed to receptive scores (p=0.06) (Table 3).

Hearing was assessed in 71 children who were normocephalic at birth (63%), 6% of children had hearing deficits, all of whom had below average Bayley-III scores (Figure 3). An abnormal hearing assessment, as determined by brainstem evoked response audiometry (BERA), was associated with abnormal neurodevelopment on Bayley-III assessment (p=0.016). Children with an abnormal hearing assessment had an average expressive language score of 5.5 (SD 2.65) as compared to 8.54 (SD 2.36) in children with normal hearing assessments (p=0.02). Receptive language scores were 6.25 (SD 0.9) in children with abnormal hearing assessments, compared to 8.09 (SD2.06) in children with normal hearing (p=0.02) (Table 3).

Within the population of 112 normocephalic infants at birth, maternal trimester of infection was known in 111 cases (99%): 22 (19.8%) were infected in the first trimester, 63 (56.8%) in the second trimester, and 26 (23.4%) in the third trimester. Among normocephalic infants, seven (31.8%) infants exposed in the first trimester, 25 (39.7%) in the second trimester, and 7 (26.9%) in the third trimester were later considered to be at risk or to have developmental delay based on Bayley-III assessments; however, trimester of infection was not significantly associated with neurodevelopmental outcomes (p=0.6) (Table 2).

Sixteen of 112 normocephalic infants at birth (14.3%) were born preterm (< 37 weeks gestation). Of these, 9 had abnormal Bayley-III assessments (Figure 3). Detailed neurologic and ophthalmologic evaluations were performed in 86 of 112 normocephalic infants (69%) before 3 months of age. As seen in Figure 3, 58% (n=50) had neuromotor abnormalities, of whom 17 (34%) had subsequent below average Bayley-III assessments. Neuromotor abnormalities in infancy included nystagmus, hyperreflexia, hyperexcitability, hypertonia, hypotonia, or fovea sign of the flexor regions[5,15,16]. None of these early neurologic assessments demonstrated a significant relationship with poor neurodevelopment as toddlers. Two children were found to be on the autism spectrum, both of whom had below average Bayley-III assessments.

Echocardiography was performed in 59 children (53%); 32% (n=19) were found to have cardiac abnormalities (Figure 3); of these 42% (n=9) had below average Bayley-III scores. There was no statistically significant relationship between cardiac defects and neurodevelopment (p=0.5). Cardiologic abnormalities identified in normocephalic infants are listed in Table 4, online.

Complete eye exams were performed in 75 children (67%); 11% were abnormal. Of these, 37% (n=3) had below average Bayley-III scores. There was no statistically significant relationship between ophthalmologic abnormalities and neurodevelopment (Table 2).

Neuroimaging with transfontanellar ultrasonography, CT, or MRI was done in 90 of 112 children who were normocephalic infants at birth (80%), of these, 21% of children had

abnormal findings, outlined in Table 4. Below average Bayley-III scores were seen in 31.6% of children (n=6) with abnormal neuroimaging (Figure 3). There was no statistically significant correlation between neuroimaging abnormalities and below average Bayley-III assessments overall (p=0.86) in the 90 normocephalic children who had neuroimaging studies performed (Table 2).

Discussion

ZIKV is an arbovirus that can be vertically transmitted, leading to diverse neurologic abnormalities by damaging neural progenitor cells [5,23–25] and immature neurons [26]. Between September 2015 and June 2016, ZIKV spread rapidly through Brazil resulting in an epidemic of infants born with microcephaly and other features of CZS. A review by Moore et al. determined 5 distinct features of CZS that distinguish it from other congenital infections and genetic disorders: severe microcephaly with partial skull collapse, thin cerebral cortices with subcortical calcifications [27,28], macular scarring and focal pigmentary retinal mottling, congenital contractures, and marked hypertonia indicating extrapyramidal involvement [29,30]. Moore et al also noted “more data are needed on infants with congenital ZIKV infection who do not have microcephaly at birth” [29]. Indeed, 4 years after the outbreak, many infants with less overt manifestations of congenital ZIKV infection are exhibiting neurodevelopmental delay[16].

While much of the body of work has focused on characterizing features of CZS, much less has been done to link early clinical findings with later neurodevelopment. In one study of 60 infants, 24 of whom had confirmed ZIKV exposed by IgM, first trimester maternal infection and smaller head circumference were significantly associated with the presence of abnormal ocular findings[31]. A case series of 1,501 infants demonstrated that those who were exposed during the first trimester of pregnancy to ZIKV had the lowest HCZ [32], and in Bahia, Brazil, the estimated risk of microcephaly following a first-trimester ZIKV infection was 1%–13% [33].

In the present study, we aimed to identify early predictors of future suboptimal neurodevelopment in normocephalic infants with *in utero* ZIKV exposure. We found that HCZ at birth was correlated with poor neurodevelopmental outcomes as toddlers[10]. This highlights the importance of analyzing HCZ as a continuous variable, rather than categorizing infants as microcephalic (<−2SD) or normocephalic. We also found that 6.25% of infants who were normocephalic at birth went on to develop secondary microcephaly between 3 weeks and 8 months of age. Among those with secondary microcephaly, 43% performed below average on Bayley-III assessment. Thus, parents must me counseled on the importance of regular infant follow up to reassess head circumference beyond the time of birth, as it may be a marker for more severe disease and a strong predictor of poor neurodevelopment.

Language scores across the entire cohort were profoundly lower than cognitive or motor scores, with average expressive language scores being slightly lower than receptive language scores. All infants with abnormal hearing assessments had poor language function later. In our assessment, hearing deficits in this patient population are likely the main cause

of delayed language development, to the extent that poor language development can be considered a surrogate for possible hearing deficits, and the two conditions are likely cause (hearing deficit) and effect (impaired language development). This could potentially be circumvented by implementing hearing screening for all children with ZIKV exposure, and early and aggressive intervention with hearing correction or speech therapy. While these findings may seem intuitive, it is important to note that formal audiometric evaluations are not routinely available in lower income settings, and presently these are the only predictors available to clinicians and parents of these infants.

While CZS is defined by several cardinal features, we did not identify any correlation between neurodevelopment and neuroimaging, ophthalmologic, or congenital neuromotor abnormalities in a relatively large non-microcephalic population of infants with confirmed maternal ZIKV infection in pregnancy. This may be due to the limited power of our analysis, as only 19 infants had structural abnormalities identified on ultrasound, CT, or MRI; however, a prior analysis by Moreira et al, similarly found no correlation[15]. Additionally, when microcephalic infants were included in the analysis, there was no significant correlation with congenital upper motor neuron signs, abnormal feeding, cardiologic abnormalities, or prematurity suggesting that while these may be more common in infants antenatally exposed to ZIKV, they are not necessarily markers of more severe disease.

Our cohort was a highly symptomatic population of children, likely because IFF is a referral center for congenital infections. For this reason, frequency data of clinical findings from this cohort should not be interpreted as incidence data pertaining to all infants with antenatal ZIKV exposure. That being said, the present study focused on 112 non-microcephalic infants, who were sufficiently developmentally proficient to undergo Bayley-III assessments and would not meet criteria for CZS. Within this non-microcephalic population, we still found a significant burden of disease characterized by neuromotor abnormalities (58.1%), failure to thrive (51.9%), and higher than expected rates of cardiologic abnormalities (32.2%), as well as preterm births (14.3%).

In the present analysis, approximately 1/3 of children who underwent echocardiography had cardiologic abnormalities, which was comparable to a prior study by Orofino et al. This is much higher than the rates of cardiac defects in the general population, [34,35]suggesting that cardiac defects are another sequelae of congenital ZIKV infection. Orofino et al advised that general newborn screening guidelines for cardiac ECHO be followed given that none of the cardiac defects identified required emergent surgery; however, when considering long-term management of this population, clinicians should carefully screen and have a low threshold for ECHO referral. Furthermore, in ZIKV endemic areas, the presence of cardiac defects at birth, like microcephaly, may be an indication to evaluate for ZIKV exposure *in utero*, particularly because ZIKV infection might be asymptomatic during pregnancy. We found, however, no significant correlation between cardiac defects and below average Bayley-III scores.

Potential confounders included prematurity; however, in our analysis, prematurity showed no association with poor neurodevelopmental outcomes. Other potential confounders include

socio-economic status contributing to poor infant stimulation, however the children in our cohort had similar socio-economic backgrounds, as the patient population is reflective of individuals seeking medical care in a public (free of cost) health system. As our sample size is relatively modest (112 normocephalic participants who underwent neurodevelopmental testing), performing extensive evaluation for confounders is challenging. However, we have to remember that these were all children born to mothers with laboratory proven ZIKV infection, which is a high-risk group for adverse infant outcomes. Potential confounders such as prematurity or poverty would likely further potentiate adversity in children who are already at risk

This was an analysis in which providers were not blinded to the patient's ZIKV status. As such, abnormalities may have been over reported. Additionally, our data set was limited by loss to follow up. Many parents refused Bayley-III assessments, and even fewer were evaluated by other specialties as often parents did not identify a need for additional evaluations in a seemingly normal child. Antenatal ZIKV infection is a stigmatizing diagnosis, and parents may be reluctant to pursue an evaluation that can lead to a diagnosis of neurodevelopmental delay, particularly if they were reassured that their child was not microcephalic at birth. It was not feasible to include a simultaneous control population as we were unable to definitively determine that control participants had never been exposed to ZIKV *in utero* due to short lived IgM responses and very narrow window of viral detection by RNA PCR.

In conclusion, while microcephaly has become the most infamous sequela of congenital ZIKV infection, the spectrum of disease encompasses much more subtle manifestations as well. This study demonstrates that all infants antenatally exposed to ZIKV are at risk for developmental delay in addition to cardiologic defects and FTT and should be carefully followed for these conditions. Congenital cardiac findings in infants born to mothers in endemic areas should raise suspicion for antenatal ZIKV exposure and should prompt a diagnostic work-up for this pathogen. The findings of this study also suggest that normocephalic infants with smaller HCZ at birth or auditory abnormalities are most at risk for developmental delay and require close monitoring such as audiometry and speech evaluations throughout early childhood. Conversely, the absence of these findings may act as reassurance to clinicians and parents in a field that otherwise has very few prognostic indicators. These early clinical indicators allow for identification of high-risk children who would benefit from expedited interventions, particularly in low- and middle-income settings where prioritization of targeted efforts is necessary. Finally, perinatal screening for congenital ZIKV infection should be indicated in endemic areas so that children with confirmed exposure can be followed by a multidisciplinary team and assessed for these risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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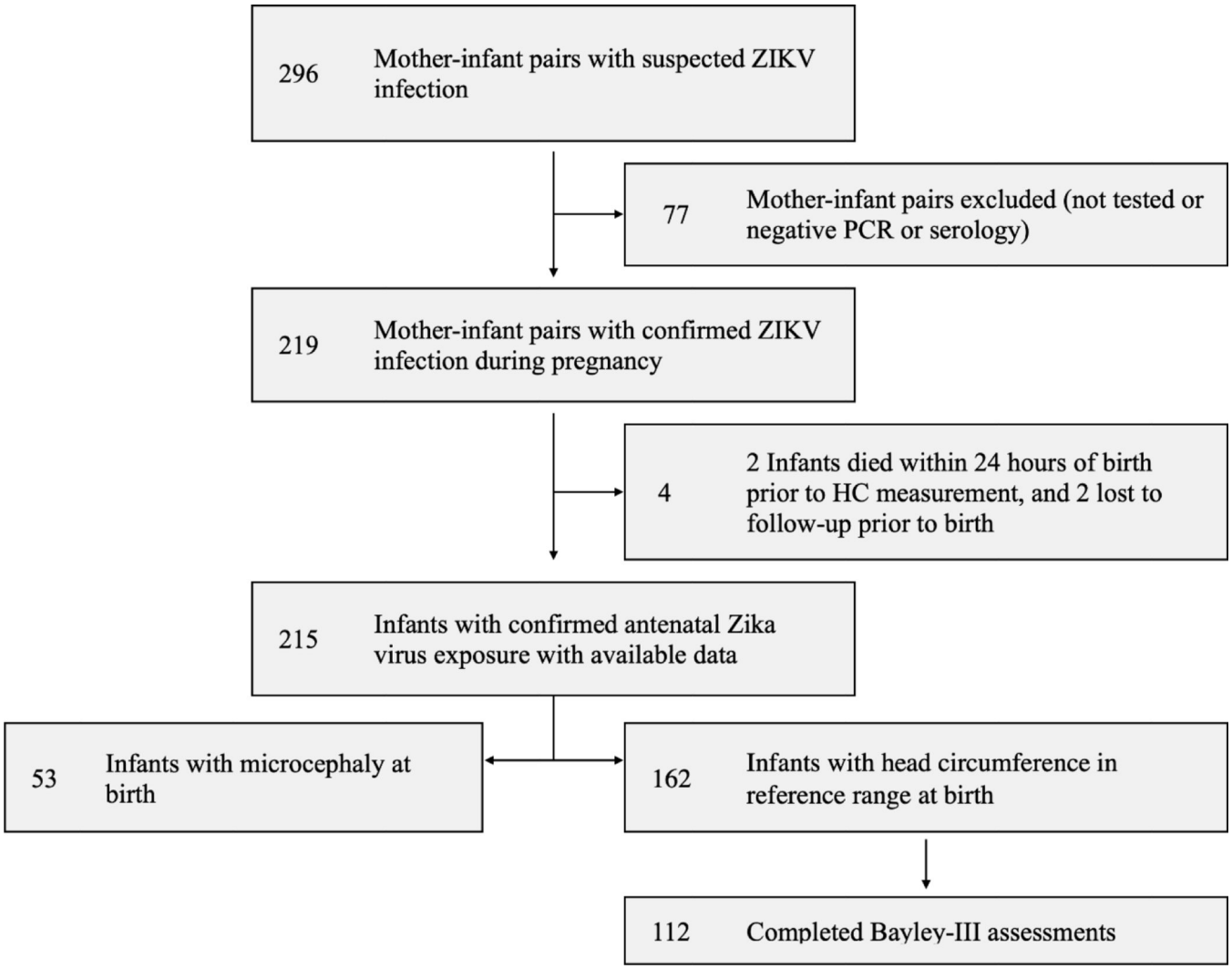

Figure 1.
Flowchart of Participant Recruitment

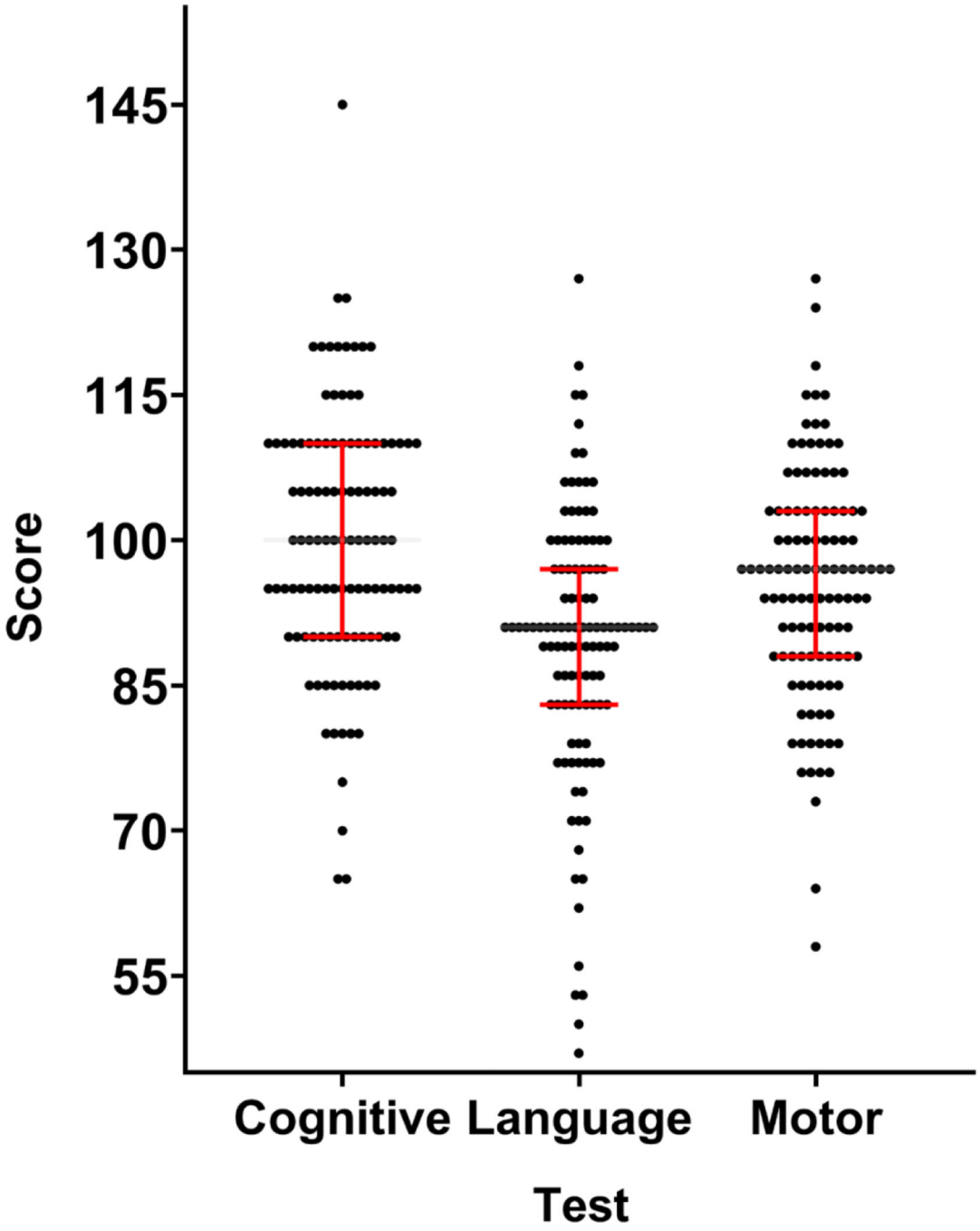

Figure 2.
Distribution of Bayley-III scores across 3 functional domains in 112 infants normocephalic at birth.

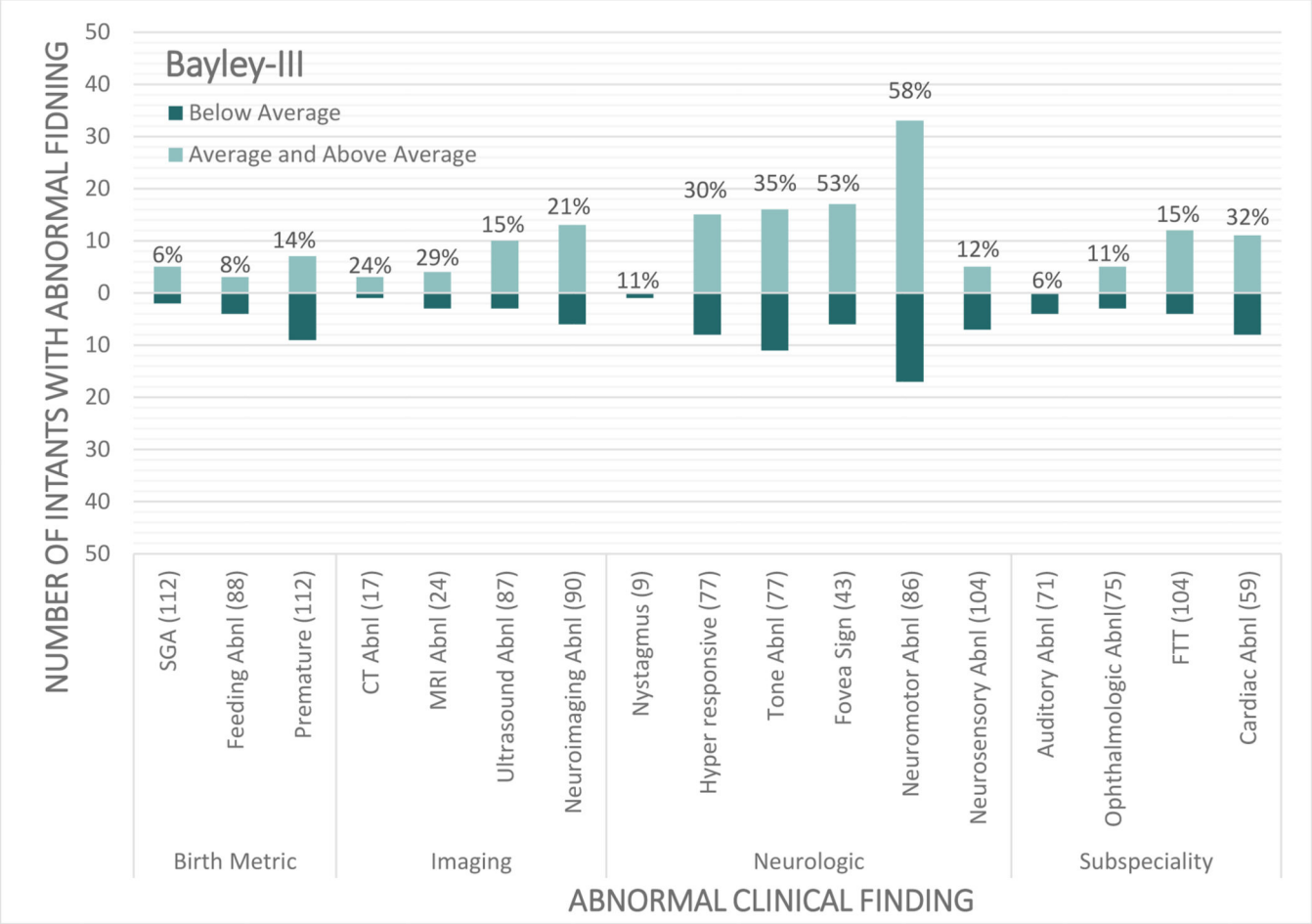

Figure 3.

Bayley-III results according to clinical findings identified in the first 3 months of life for normocephalic infants at birth (N=112)

Table 1.

Characteristics of ZIKV-exposed infants at birth including demographics, neurodevelopmental and neurosensory assessments (n= 168)

A. Demographics at birth

	Normocephalic* (n=112)		Microcephalic (N=53)	
	n	%	n	%
Infant sex				
Female	60	54	25	47.2
Male	52	46	28	52.8
Preterm infants				
<37 to ≥ 35 weeks	9	8	1	1.89
< 35 weeks	7	6.3	5	9.43
SGA	7	6.3	30	56.6
	Mean (SD)		Mean (SD)	
Head circumference z-score	0.93 (1.11)		−1.30 (1)	
Weight z-score	0.26 (0.98)		−3.56 (0.88)	
Heigh z-score	0.27 (1.21)		−1.09 (1.37)	

B. Bayley-III neurodevelopmental assessments at 7–42 months of age (n=112)

		Normal		−1 to −2 SD		≤ −2	
	Mean (SD)	n	%	n	%	n	%
All		72	64	30	27	10	9
Cognitive	99.9 (13.3)	103	92	7	6.25	2	1.79
Language	89.1 (14.0)	79	70.5	24	21.4	9	8.04
Expressive	7.94 (2.45)						
Receptive	8.27 (2.70)						
Motor	95.4 (11.8)	95	84.8	15	13.4	2	1.79

C. Other neurosensory assessments

	Abnormal	
	n	%
Hearing	4	5.63
Vision	8	10.7

*Infants were categorized as normocephalic based on birth head circumference measurements. Seven of these 112 infants went on to develop secondary microcephaly.

Table 2.

Association between infant findings at birth and Bayley-III overall developmental outcomes for 112 normocephalic children.

Early Life Clinical Indicator		**Total within each category**	**Normal Development N = 72**	**At risk for developmental delay (< −1 SD ≥ −2 SD) N = 30**	**Developmentally Delayed (<−2SD) N = 10**	
		N / # evaluated (%)	**N (%)**	**N (%)**	**N (%)**	***p*−value**
Trimester of Pregnancy	1st	22 / 112 (19.6)	15 (68.2)	5 (22.7)	2 (9.1)	0.6
	2nd	63 / 112 (56.3)	38 (60.3)	20 (31.7)	5 (7.9)	
	3rd	26 / 112 (23.1)	19 (73.1)	4 (15.4)	3 (11.5)	
	Unknown	1 / 112 (0.9)	0 (0)	1 (100)	0 (0)	
Premature		16 /112 (14.3)	7 (43.8)	7 (43.8)	2 (12.5)	0.11
SGA		7 / 112 (6.3)	5 (71.4)	2 (28.6)	0 (0)	0.69
Cardiac Abnormalities		19 / 59 (32.2)	11 (57.9)	5 (26.3)	3 (15.8)	0.5
Feeding Difficulties		7 / 88 (8.0)	3 (42.9)	4 (57.1)	0 (0)	0.11
FTT		16 / 104 (15.4)	12 (75.0)	2 (12.5)	2 (12.5)	0.39
Ophthalmologic Abnormalities		8 / 75 (10.7)	5 (62.5)	2 (25.0)	1 (12.5)	0.98
Auditory Abnormalities		4 / 71 (5.6)	0 (0)	3 (75.0)	1 (25.0)	0.016
Neurosensory Abnormalities		12 / 92 (13.0)	5 (41.7)	5 (41.7)	2 (16.7)	0.2
Excess skin on neck or Beak deformity		24 / 43 (55.8)	18 (75.0)	5 (20.8)	1 (4.2)	0.9
Neuroimaging Abnormalities		19 / 90 (21.1)	13 (68.4)	5 (26.3)	1 (5.3)	0.86
Neuromotor Abnormalities		50 / 86 (58.1)	33 (66.0)	13 (26.0)	4 (8.0)	0.9
Continuous Variables		**All Mean (SD) N = 112**	**Normal Mean (SD) N = 72**	**At Risk Mean (SD) N = 30**	**Developmental Delay Mean (SD) N = 10**	**p**
Apgar 1 (N=106)		8.26 (1.14)	8.29 (2.52)	8.37 (1.22)	7.8 (1.4)	0.39
Apgar 5 (N=106)		9.01 (1.17)	8.97 (2.82)	9.10 (0.71)	9.0 (0.67)	0.92
Weight z-score (N=103)		0.81 (0.61)	0.85 (0.58)	0.78 (0.70)	0.59 (0.46)	0.43
Head circumference z-score (N=112)		1.23 (0.76)	1.35 (0.74)	1.15 (0.82)	0.63 (0.33)	0.02
Height z-score(N=104)		0.95 (0.80)	0.91 (0.72)	1.09 (1.01)	0.82 (0.56)	0.48

Premature defined as GA <37 weeks

SGA = Small for Gestational Age

FTT = Failure to Thrive

Neuroimaging Abnormalities on CT/US/MRI

Neuromotor Abnormalities = abnormal tone, abnormal reflexes, nystagmus, arthrogryposis/fovea sign

Neurosensory = auditory or ophthalmologic abnormalities

Table 3.

Associations between birth factors and expressive and receptive language outcomes on Bayley-III for normocephalic children (N=112)

			Expressive			Receptive		
Early Life Clinical Indicator	**Abnl?**	**N**	**Average**	**SD**	**p**	**Average**	**SD**	**p**
	1	22	8.18	3		7.68	2.87	
	2	63	8.32	2.3	0.92	8.06	2.24	0.81
	3	26	8.27	3.4		7.88	2.6	
Trimester of infection (N=112)	Unk	1						
	No	96	8.48	2.61	0.06	8.05	2.37	0.14
Premature (N=112)	Yes	16	7	2.97		7.25	2.89	
	No	105	8.21	2.73	0.37	7.9	2.4	0.36
SGA (N=112)	Yes	7	9.1	2.12		8.7	1.81	
	No	40	8	2.69	0.12	7.97	278	0.46
Cardiac Abnormality (N=59)	Yes	19	7	2.83		7.47	2.44	
	No	81	8.23	2.74	0.74	7.93	2.44	0.63
Feeding Difficulties (N=88)	Yes	7	8.57	2.44		8.14	2.79	
	No	88	8.16	2.79	0.75	7.99	2.55	0.66
FTT(N=104)	Yes	16	8.44	2.13		7.62	1.71	
	No	67	8.24	2.75	0.53	7.82	2.64	0.79
Ophthalmologic Abnormality (N=75)	Yes	8	7.5	2.98		7.25	1.98	
	No	67	8.54	2.36	**0.02**	8.09	2.06	**0.02**
Auditory Abnormality (N=71)	Yes	4	5.5	2.65		6.25	0.9	
	No	92	8.49	2.61	**0.04**	8.18	2.51	**0.04**
Neurosensory Abnormality (N=104)	Yes	12	6.83	2.91		6.92	1.73	
	No	19	8.11	2.35	0.17	8.11	2.21	0.39
Excess skin on neck or Beak deformity (N=43)	Yes	24	9.08	1.77		8.5	1.72	
	No	71	8.23	2.68	0.61	7.87	2.42	0.74
Neuroimaging Abnormality (N=90)	Yes	19	8.16	1.92		8.16	1.95	
	No	36	8.39	2.88	0.96	8.25	2.68	0.53
Neuromotor Abnormality (N=86)	Yes	50	8.42	2.48		7.92	2.17	
Continuous Variables			**beta**	**std error**	**p**	**beta**	**std error**	**p**
Apgar 1 (N=106)			0.2137	0.2342	0.36	0.18	0.21	0.38
Apgar 5 (N=106)			−0.08	0.23	0.73	−0.08	0.2	0.68
Weight z-score (N=103)			0.18	0.42	0.67	0.13	0.38	0.74
Head circumference z-score (N=112)			0.66	0.33	**0.04**	0.57	0.3	0.06

Early Life Clinical Indicator	Abnl?	N	Expressive			Receptive		
			Average	SD	p	Average	SD	p
Height z-score(N=104)			0.07	0.32	0.8	−0.11	0.29	0.7

Table 4.

Abnormal neuroimaging and cardiac findings identified in normocephalic children

Normocephalic (N=19)
Intracranial hemorrhages grades I to III (N=10)
Intracerebral calcifications * (N=3)
Hypoplasia of the vermis and left parietal abnormalities (N=1)
Arachnoid cysts / Mega cistern magna (N=3)
Asymmetric cerebral hemispheres with loss of brain volume (N=1)
Hydrocephaly (N=1)
Prominent intraventricular spaces (N=1)
Fusion of metopic sutures (N=1)
* Right thalamus x1, periventricular x2
Abnormal Cardiologic Findings (N=19)
Bicuspid aortic valve (N=1)
Tricuspid insufficiency (N=2)
Septal Defects (N=3)
Pulmonary stenosis (N=1)
Aortic-pulmonary shunt (N=1)
PFO * (N=14)
PDA * (N=1)

* Preterm infants with PFO or PDA were classified as normal