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Multisystem Inflammatory Syndrome-Neonate: Biochemical Parameters as Early Marker of Adverse Neurodevelopmental Outcome

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Abstract

Background: Pregnant women and newborns are highly susceptible to Covid-19, manifesting as multisystem inflammatory syndrome-New-born (MISC-N) in many babies born to Covid positive mothers. The relationship between Covid-19 infection during pregnancy and neonatal neurodevelopmental outcome, if any, is unclear necessitating a follow-up study in this aspect. **Methods:** 16 babies with MIS-N, born to symptomatic Covid antibody positive mothers were enrolled. Demographic profile, treatment details and biochemical parameters were analyzed with neurodevelopmental follow-up. **Results:** 25% mothers received 2 doses of Covid vaccine; 50% had oligohydramnios and 75% received antenatal steroids. 87.5% were preterm of which 62.5% required surfactant with ventilator support and 75% required inotropic support. Significant association was found between the antibody level and D-dimer levels with the ferritin and LDH levels of the baby ($p < 0.05$); gestational age with LDH and D-dimer levels ($p < 0.05$) and Covid antibody level of the baby vs the duration of ventilator requirement (P-value-0.0009). D-dimer values of babies were positively associated with both maternal antibody and D-dimer levels. Neurodevelopmental follow-up done at 6 months of corrected gestational age showed 37.5% were normal, 37.5% hypertonic and 25% hypotonic. HINE score was below 60 in 62.5%. Development assessment using Bayley-III showed a delay in the motor domain (62.5%), cognitive domain (56.25%) and language domain (62.5%). **Conclusion:** Neurodevelopmental problems occur in babies born to Covid positive mothers and should be stratified as "high risk". Anticipatory guidance to prospective mothers for

preterm care should be given. Covid antibody titre and D-dimer levels may help to predict the NICU stay, ventilator requirement and the adverse neurodevelopmental outcomes in these babies.

Keywords

Neurodevelopment, Covid-19, Pregnancy, Multisystem Inflammatory Syndrome, Biochemical Markers, D-Dimer, HINE Score

1. Introduction

Since the emergence of the pandemic due to Covid-19 in December 2019, various strains of Covid have caused disease manifestations of varying severity to mankind. With pregnancy being highly vulnerable conditions both to the mother and the unborn, Covid-19 caused serious challenges for pregnant women like never before in human history. Covid-19 infection is highly contagious and many cases of Covid in pregnancy have been reported since its emergence [1]. Covid-19 infection causes multisystem involvement and affects various organs in our body as suggested by many recent studies. Neurological complications due to Covid-19 have been reported in many countries [2] [3]. From our previous knowledge, prenatal exposures to viruses such as zika, and rubella have been associated with long-term neurological sequelae in children [4]. Since Covid is an emerging disease and several cases of a multisystem inflammatory syndrome (MIS-N) have been reported recently in newborns and clinical data on neuro-developmental implications of Covid-19 in neonates of Covid positive mothers is limited, and the Covid virus strains keep changing with varying severity, further studies in these babies is required [5].

Past pandemics have provided a window into potential neurodevelopmental consequences in subsequent generations. For example, individuals who were fetuses during the 1957 influenza pandemic had an increased risk of being hospitalized for schizophrenia as adults [6]. The rubella pandemic of 1964 was associated with a 10 - 15-fold increase in ASD and schizophrenia in offspring [7]. The potential for neurodevelopmental morbidity in offspring exposed prenatally to SARS-CoV-2 is therefore of great concern. Given a large number of exposed individuals, even a modest increase in risk for adverse offspring neurodevelopment would still have a massive public health impact [8] [9]. In fact, a 12-month follow-up of more than 7000 deliveries in a large hospital system, including more than 200 Covid-19 exposed pregnancies, suggested that prenatal SARS-CoV-2 infection is associated with an increased risk for offspring neurodevelopmental diagnoses [10].

Recent evidence suggests that profound immune activation seen in some infected individuals points to the possibility of the developing fetal brain being influenced by maternal and placental inflammation and altered cytokine expression [11]. Regardless of mechanism, epidemiologic studies demonstrate that

maternal infection in pregnancy, including other viral infections such as influenza, is associated with adverse neurodevelopmental outcomes in offspring, including autism spectrum disorders, schizophrenia, cerebral palsy, cognitive dysfunction, bipolar disorder, and anxiety and depression [12] [13]. Although the magnitude of these effects and strength of association varies, the consistency of such associations is difficult to ignore. As some of these disorders may not manifest until adolescence or adulthood, the true risks of maternal immune activation may not become apparent for decades. Both adults and children's subsets of individuals manifest neuropsychiatric symptoms after COVID-19 that can persist up to a year after acute illness [14]. Neuro-imaging of adults in a recent large study found region-specific morphologic changes following Covid-19 illness [15]. Further, emerging literary evidence suggests that COVID-19 may be associated with preterm delivery and other birth complications, with a recent report indicating greater severity of infection being associated with greater preterm risk [16]. Thus, converging lines of evidence point to the possibility of COVID-19 to induce persistent brain effects in children and adults, though less is known about the impact of maternal COVID-19 on the developing fetal brain.

The immature neonatal immune system may not produce sufficient SARS-CoV-2 antibodies. However, efficient transplacental transfer of immunoglobulins (Ig-G) antibodies from mother to fetus was reported in a large study cohort [17]. Though these immunoglobulins are thought to be protective against SARS-CoV-2 infection, the transplacental transfer of immunoglobulins and other inflammatory cytokines may mimic a process similar to MIS-C in older children, causing immune activation and presenting as a multisystem inflammatory syndrome in neonates (MIS-N) [18]. Sero-conversion response with both immunoglobulin-M (IG-M) and IG-G levels to SARS-CoV-2 infection was seen within 2 - 3 weeks of symptomatic infection [19] [20]. New-borns acquiring perinatal SARS-CoV-2 can also mount an antibody response, and possibility results in a late presentation similar to MIS-C seen in children [21].

Covid-19 infection induces a surge of pro-inflammatory cytokines that affect microglial functions which can be harmful to brain development, contributing to an increased risk of late onset neurodevelopmental disorders. According to a study conducted by Devika *et al.*, oxidative stress caused by Covid-19 infection in exacerbating manifestations in its pathogenesis is proven and hence this oxidative stress may affect mitochondrial functions of the developing neurons which may be structurally normal but may have problems with synaptogenesis, pruning and may slow neural migration [22]. Further, transient thyrotoxicosis induced by Covid with secondary autoimmune hypothyroidism has been reported in pregnant women, which may go undetected, impacting mechanisms of neural development such as synaptic pruning and neural circuitry formation [23].

These risk factors should be considered and the possible emergence of neuro-developmental disorders (NDD) in babies born to Covid-19 infected mothers should be kept in mind and followed up. In this context, the analysis of the

present case series is presented in its entirety.

2. Materials and Methods

Sixteen new-borns born to Covid positive mothers were enrolled prospectively in this study after getting informed consent at 40 weeks of gestational age. Newborn with MIS-N with proven antibody titers, Newborn with positive Covid testing for mother at delivery were included in the study. Those neonates who lacked antibodies, clinically suspected but antibody negative and other causes of sepsis were excluded from the study. The proforma designed for the same contained details about demography, co-morbidities, investigation and treatment profile of the mother, gestational age, resuscitation details, examination findings, need for intervention and its details in addition to neurobehavioral assessment and biochemical analysis. Biochemical analysis included analysis of inflammatory parameters like D-dimer, LDH, Ferritin, anti-Covid antibodies of both mother and neonates. The babies were followed up with neurodevelopmental assessment as per schedule using Hammersmith infant neurological Examination (HINE) at 40 weeks and 6 months along with formal developmental assessment using Bayley-III at six months of corrected gestational age. It includes 26 items assessing cranial nerve function, posture, quality and quantity of movements, muscle tone, and reflexes and reactions. Each item is scored individually (0, 1, 2 or 3), with a sum score of all individual items (range: 0 - 78). A questionnaire with instructions and diagrams is included on the scoring sheet, similar to the Dubowitz neonatal neurological examination. This study was performed according to guidelines of institutional human ethical committee under approval number SU/IEC/RD/005/2021. Adjustments were made for corrected gestational age in preterm babies. The results were analyzed using Graph pad Prism-8. Statistical significance of different parameters for comparison was done with Mann Whitney for non-parametric parameters. Multiple pair-wise comparisons of parameters were done with Bonferroni t-test. One way ANOVA was done to assess the significance of difference between mean of group.

3. Results

Sixteen babies with MIS-N due to Covid-19 were followed up in this study. Antenatally 4 mothers received 2 doses of Covid vaccine (25%).8 mothers (50%) had oligohydromnios. In the present study, 10 (62.5%) were girls and 6 (37.5%) were boys. The mean age of the mothers was 25.6 (22 - 34 years). 9 mothers belong to lower socio economic status and 7 belong to upper middle class status. 12 mothers (75%) had received antenatal steroids before delivery. 14 babies (87.5%) were preterm babies.10 babies were born through lower segment caesarian section (LSCS) (62.5%), 4 babies were born through normal vaginal delivery (25%), 2 baby required assisted vaginal delivery (12.5%).10 babies (62.5%) required surfactant and ventilator support. 12 babies (75%) required ionotropic support. All babies received dexamethasone for 5 days. ECHO abnormalities

were seen in 10 babies (62.5%).MRI was done for 3 babies out of whom 2 had abnormal findings in MRI.

3.1. Biochemical Parameters

The Covid antibody titer, D-dimer level, LDH, ferritin was done in the neonatal period which were found to be elevated in all babies. Mother's antibody titers and D-dimer levels were also done. These parameters were compared with gestational age and birth weight of the baby. One-way ANOVA analysis showed significant difference between mean of groups. A significant association was found between the antibody level and D-dimer level of the baby. There was association of D-dimer levels with the ferritin and LDH levels of the baby. The association between the antibody level of baby with ferritin level and LDH level was not statistically significant. There was significant association of gestational age of the baby with LDH and D-dimer (DdB) levels (Table 1).

Mann Whitney test comparison between Antibody of baby (AbB) and number of days of ventilation shows a significant P-value of 0.0009, reflecting that the difference between the 2 rank totals is less likely to have occurred by chance (Table 2). Mann Whitney test done between Covid antibody level and Birth weight (BW) of the baby showed exact P-value of 0.0002, which was statistically significant (Table 3).

Unpaired t-test of D-dimer baby with Covid antibody baby shows significance at p-value of 0.0039 ($p < 0.05$). This shows that antibody-baby had an association with D-dimer levels of Baby in t-test; however co-relational analysis did not show any linear relationship between the two (Table 4). Similarly, Antibody baby did not correlate linearly with Birth weight also, though there is association

Table 1. Multiple pair wise comparison of biochemical parameters of baby and gestational age.

Bonferroni's Multiple Comparison Test	Mean diff.	t	P < 0.05
AbB vs Gest age	813.8	2.607	No
AbB vs Fer	534.1	1.711	No
AbB vs LDH	−122.4	0.3920	No
AbB vs DdB	−1649	5.281	Yes
Gest age vs Fer	−279.7	0.8959	No
Gest age vs LDH	−936.1	2.999	Yes
Gest age vs DdB	−2462	7.888	Yes
Fer vs LDH	−656.5	2.103	No
Fer vs DdB	−2183	6.992	Yes
LDH vs DdB	−1526	4.889	Yes

(AbB: Covid antibody of baby, Gest age: gestational age, Fer: ferritin, LDH: lactate dehydrogenase, DdB: D-dimer of baby).

Table 2. Comparison between Covid antibody level of baby and duration of ventilation requirement.

Column-A Vs Column-B	AbB Vs Vent days
P value	0.0009
Exact or approximate P value	Gaussian Approximation
P value summary	***
Are medians signif. Different - (P < 0.05)	Yes

Table 3. Comparison between Covid antibody level and birth weight of the baby.

Column-A Vs Column-B	AbB Vs BW
P value	0.0002
Exact or approximate P value	Exact
P value summary	***
Are medians signif. Different - (P < 0.05)	Yes

Table 4. Comparison between Covid antibody level and D-dimer value of the baby.

Unpaired t-test	
P value	0.0039
Signif. different (P < 0.05)	Yes
Mean ± SEM of AbB	847.6 ± 114.4
Mean ± SEM of DdB	2496 ± 464.0
Difference between means	1649 ± 477.9
95% confidence interval	2674 to 623.5
R square	0.4594

between the two.

Maternal parameters were compared with baby's parameters. One-way ANOVA analysis showed significant difference between mean of groups. Significant association was found between birth weight and baby's D-dimer level. Maternal antibody level was positively correlated with baby's D-dimer value. There was positive association between maternal and baby's D-dimer levels. Birth weight was not associated with antibody level of baby, antibody level of mother, D-dimer level of mother. There was no statistical significance between maternal and baby antibody level (Table 5).

3.2. Neurodevelopmental Follow-Up

Neurodevelopmental assessment at initial visit near term for corrected age showed that persistent fisting and cramped synchronized movements were seen in 6 babies and 10 had incomplete Moro reflex. Spasticity was noted in 2 babies and 4 babies were hypotonic at first visit. Analysis of Amiel-Tison angles showed

Table 5. Pair-wise Comparison between maternal and neonatal Antibodies and D-dimer with Birth weight.

Bonferroni's Multiple Comparison Test	Mean Diff.	t	P < 0.05
BW* Vs AbB*	−845.7	2.750	No
BW Vs AbM*	−761.9	2.478	No
BW Vs DdM*	−344.1	1.119	No
BW Vs DdB*	−2494	8.112	Yes
AbB vs AbM	83.75	0.2724	No
AbB vs DdB	501.6	1.631	No
AbM vs DdM	417.9	1.359	No
AbM vs DdB	−1732	5.634	Yes
DdM vs DdB	−2150	6.993	Yes

(BW-birth weight, AbB-Covid antibody of baby, AbM-Covid antibody of mother, DdB-D-dimer of baby).

adductor angle was abnormal in 8 babies, popliteal angle abnormal in 10, dorsiflexion of feet in 2 and heal-to-ear was abnormal in 8 (Table S1).

Neurodevelopmental follow up of babies were done at 6 months of corrected chronological age using HINE, of which 37.5% (6) babies were normal, 37.5 % (6) were hypertonic and 25% (4) were hypotonic. HINE score was below 60 in 10 babies (62.5%). Only 7 (43%) had abnormal CDC grading for head control at corrected 6 months of age. Adductor angle was normal for age in 6 babies (37.5%) and above normal in 4 babies (25%) suggestive of hypotonia and below normal range in 6 babies (37.5%) suggestive of hypertonia. Popliteal angle was within normal range in 6 babies (37.5%), above normal range in 4 babies (25%), and below normal range in 6 babies (37.5%). Scarf sign was normal in 10 babies (62.5%) and abnormal in 6 babies (37.5%). Moro was persistent in 5 babies (31.5%) and ATNR was persistent in 8 babies (50%) (Table S2).

In Bayley III assessment done at 6 months follow up, motor composite score was normal in 6 babies (37.5%),moderate delay was scored in 9 babies (56.25), and 1 baby had severe delay (6.25%).Cognitive composite score was normal in 7 babies (43.75%), mild delay was noted in 7 babies (43.75%), moderate delay was noted in 2 babies (12.5%). Language composite score was normal in 6 babies (37.5%), mild delay is noted in 5 babies (31.25%), moderate delay in 4 babies (25%), and 1 baby had severe delay (6.25%) (Table S3).

4. Discussion

Based on our results, out of 16 cases, 14 were premature deliveries, predominantly late preterm. This confirms the results of previous studies which state that Covid 19 infected women are susceptible to preterm deliveries. All mothers included in the study had no co-morbidities in antenatal period, 4 mothers vacci-

nated for Covid and 12 of them received 1 dose of antenatal steroid and antibiotics. Premature rupture of membranes at term and preterm are more frequent in patients with SARS-CoV-2 infection [26]. One of the possible explanations for this association is the activation of a series of mediators and biochemical pathways of inflammation in the premature rupture of membranes and premature delivery that are also found in SARS-CoV-2 infection, such as macrophages or IL-6 [27].

The effect of SARS-CoV-2 on placental tissue is already described by multiple papers; main histopathological findings are fetal and maternal vascular malperfusion and/or placental inflammation [28]. Furthermore, oligohydramnios is a sign of severe placental insufficiency. In our study 8 cases (50%) had oligohydramnios which confirms placental insufficiency which might have adverse effects on the fetus.

Controversy exists regarding whether SARS-CoV-2 can be transmitted in uterus from an infected mother to her infant before birth. However, few cases of new-borns with elevated IgM antibodies to SARS-CoV-2 born to mothers with Corona virus disease (Covid-19) have been reported [29]. In our study, Apgar score was normal for all babies at birth, Covid antibodies were elevated in all the 8 babies on day 2 of life and their inflammatory markers were elevated and they presented clinically as MISC (N). Subsequently, mother's antibodies status was checked and found to be reactive. Out of 16 babies, 10 babies required ventilatory support and 14 babies were on CPAP, 1 dose of surfactant was given to babies less than 34 weeks. Dexamethasone was given to all babies and improvement noted after 5 days course of dexamethasone. Ionotropes support for cardiogenic shock was needed for 12 babies; abnormal ECHO findings [IVS hypertrophy (1), PFO with left to right shunt (6), PDA (2), PAH with left ventricular dysfunction (1)] were noted in 10 babies. MRI brain was normal in 1 baby, one baby showed grade 4 PVL and another baby showed acute non-haemorrhagic arterial infarcts in bilateral perirolandic areas, bilateral corona radiata, bilateral posterior limb of internal capsule. 1 baby had seizures during NICU stay and is on anticonvulsants.

The HINE is an easily performed and relatively brief standardized and scorable clinical neurological examination for infants between 2 and 24 months of age, accessible to all clinicians, with good inter-observer reliability even in less experienced staff. The use of the HINE optimality score and cut-off scores provides prognostic information on the severity of motor outcome. Sequential use of the HINE allows the identification of early signs of cerebral palsy and other neuromotor disorders, while individual items are predictive of motor outcomes. According to a study, HINE score in preterm infants assessed between 6-15 months corrected age, scores above 64 predict independent walking with a walked sensitivity of 98% and specificity of 85%. Conversely, scores below 52 were highly predictive of cerebral palsy and severe motor impairments [30]. In our study, HINE scores were below 60 in 10 babies (62.5%).

Tone abnormalities were noted in 10 babies during high risk follow up. Their Amiel-Tison angles [31] were less than normal range for age in 6 babies, more than normal age range in 4 babies suggestive of hypertonia and hypotonia respectively. In a study conducted by Carl E., Lauren L, neurological manifestations including tone abnormalities were noted in neonates born to Covid mothers [32]. No abnormal sleep patterns sleep issues or excessive cry was noted in any of the babies, however follow up is needed to find neurobehavioral issues if any.

In Bayley Scale of Infant development assessment III, categorization of developmental delay is done as follows: composite score > 85 are normal, score 70 - 84 is mild delay, and score 55 - 69 is moderate delay and score <55 is severe delay [33]. In Bayley III assessment done in our study, delay was noted in 10 babies (62.5%) in motor composite and 9 babies showed delay in cognition (56.25%), and 10 babies showed delay in language composite.

According to previous studies done in MIS-C patients, laboratory markers of inflammation such as CRP, leucocyte count, procalcitonin, ferritin appear to correlate with severity of illness [21] [34]. In a systematic review study, laboratory examination reported the following: low haemoglobin, elevated leukocytes with mainly neutrophils, which point to inflammation [35]. In our study out of 16 cases, only 6 neonates (37.5%) had elevated CRP levels. Also, 50% (8 neonates) had leucocytosis and none had leucopoenia.

A retrospective study performed in a Chinese population demonstrated that a high level of serum ferritin is an independent risk factor for severity of Covid-19. Assessing serum ferritin levels during hospitalization may be important to recognize high risk individuals with Covid-19 [36]. A small retrospective study revealed that ferritin was the last parameter to return to normal while high-sensitivity CRP normalized about 5 days before ferritin thus suggesting that ferritin is more useful in assessment of the severity, rather than monitoring the course of the disease [37]. In our study babies with abnormal neurological findings had significant elevation in serum ferritin. Elevated LDH has been with a higher risk of ARDS, need associated for intensive care and mortality [38]. All babies in our study also had elevated LDH levels.

Elevated D-dimer levels are very frequently seen in patients with Covid-19. Several meta-analyses have shown that D-dimer levels have prognostic value and correlate with disease severity and in-hospital mortality. D-dimer can be an early marker to guide management of Covid-19 patients [39]. In our study all 16 babies had high D-dimer levels. To the best of our knowledge this is the first of its kind research stating the utility of D-dimer levels as a prognostic indicator of adverse neurodevelopmental outcome in newborn babies born of Covid-19 infection.

The comparison between Covid antibody level of the baby and the duration of ventilatory requirement shows statistical significance. This may enable us to predict the NICU stay and ventilation support needed in babies with MIS-N due to Covid. One neonate had congenital pneumonia with negative bacterial culture

reports, raising the question of possible antenatal transmission.

All the babies with higher D-dimer levels and antibody levels showed abnormal neurodevelopmental outcome as measured by HINE scoring and tone abnormalities. The 10 babies with a HINE scoring below 60 have a significant possibility of developing into Cerebral palsy/adverse neurodevelopmental outcome, as shown in many previous studies [25].

This study has some limitations. Our results must be recognized as preliminary given the limited duration of follow-up. In particular, we cannot exclude the possibility that additional neurodevelopmental effects will become apparent later in life; indeed, the offspring analyzed here are younger than the age at which neurodevelopmental disorders such as autism are typically diagnosed.

5. Conclusions

Whether a definitive connection exists between prenatal SARS-CoV-2 exposure and adverse neurodevelopment in offspring is not yet known, in part because children born to women infected in the first wave of the pandemic are younger than 2 years of age. Though the sample size is small, analysis of these cases shows that neurodevelopmental problems may arise in children having MIS-N due to Covid. Covid antibody titer will help in predicting NICU stay, ventilator requirement and adverse neurodevelopmental outcomes in these babies. Preterm deliveries are common in Covid infected women. So, we suggest routine screening of all pregnant women, even if asymptomatic, for Covid, and to use antenatal steroids for lung maturity in anticipated cases. Also, babies born to Covid positive mothers should be included in high-risk newborn category and should be strictly monitored and followed up for early identification of neurodevelopmental and neurobehavioral problems and early stimulation and intervention.

Premature infants born to mothers with a Covid-19 infection may also have a Covid-19 infection, presumably via vertical transmission. Further studies are needed to confirm this route of transmission. The need for an extended and cautious follow-up period for asymptomatic neonates with Covid-19 should be kept in mind, as symptoms may appear secondarily with rapidly severe respiratory symptoms that may require prolonged respiratory support.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary Table

Table S1. Neurological assessment at initial visit.

Pull to sit	Ventral suspension	prone	Scarf sign	Adductor angle	Popliteal angle	dorsiflexion	Heel to ear	tone	Neuro behaviour	MORO	ATNR*
Head lag	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	80	100	45	100	Normal	N	+	+
Head Lag	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	80	100	45	100	Normal	N	+	+
Head lag	Head down, back curved, limbs hang straight	No head lift	Crosses midline	90	150	45	150	Hypotonia	N	partial	+
Head lag	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	70	80	45	90	Spasticity of all limbs	Excessive cry	partial	+
Head lag	Head down, back curved, limbs hang straight	No head lift	Crosses midline	100	110	45	120	hypotonia	N	partial	+
head lag	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	70	70	45	80	normal	N	partial	+
Head lag	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	80	90	45	100	normal	N	partial	+
Head lag +	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	70	90	45	90	Normal	N	+	+
Head lag	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	80	100	45	100	normal	N	+	+
Head Lag	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	80	100	45	100	normal	N	+	+
Head lag	Head down, back curved, limbs hang straight	No head lift	Crosses midline	100	160	45	150	Hypotonia	N	partial	+
Head lag	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	60	80	45	80	Spasticity of all limbs	Excessive cry	partial	+
Head lag	Head down, back curved, limbs hang straight	No head lift	Crosses midline	110	110	45	120	hypotonia	N	partial	+
head lag	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	70	70	45	80	normal	N	partial	+

Continued

Head lag	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	80	90	45	100	normal	N	partial	+
Head lag+	Head down, back curved, limbs slightly flexed	No head lift	Does not cross midline	70	90	45	90	Normal	N	+	+

*ATNR-Asymmetric tonic neck Reflex.

Table S2. Follow up at corrected 6 months age.

Name	Pull to sit Head control-CDC Grade	prone	Adductor angle	Popliteal angle	Scarf sign	dorsiflexion	tone	DTR	MORO	ATNR	NEUROBEHAVIOUR	HINE
B/O A	4	Lifts head and chin upbears weight on elbow	100	110	Elbow cross midline	45	normal	+	disappeared	disappeared	normal	63
B/O B	4	Lifts head and chin upbears weight on elbow	100	110	Elbow crosses midline	45	normal	+	disappeared	disappeared	normal	65
B/O C	2	Lifts head momentarily	130	140	Elbow crosses midline	40	hypotonia	-	disappeared	disappeared	normal	50
B/O D	1	No head lift	60	80	Elbow not cross midline	45	Hypertonia	++	persistent	present	normal	45
B/O E	3	No head lift	120	140	Elbow crosses midline	45	hypotonia	-	partial	present	irritable	51
B/O F	4	Lifts head and chin up , Does not bear weight on forearm	60	80	Elbow does not cross midline	40	hypertonia	++	Disappeared	present	normal	57
B/O G	5	Lifts head and chin upbears weight on elbow	100	110	Elbow cross midline	45	normal	+	disappeared	disappeared	normal	64
B/O H	2	No head lift	50	80	Not cross midline	45	hypertonia	++	present	present	irritable	48
B/O I	4	Lifts head and chin upbears weight on elbow	100	110	Elbow cross midline	45	normal	+	disappeared	disappeared	normal	65
B/O J	4	Lifts head and chin upbears weight on elbow	100	110	Elbow crosses midline	45	normal	+	disappeared	disappeared	normal	64
B/O K	2	Lifts head momentarily	140	150	Elbow crosses midline	40	hypotonia	+	disappeared	disappeared	normal	49
B/O L	1	No head lift	60	80	Elbow not cross midline	45	Hypertonia	++	persistent	present	normal	44
B/O M	2	No head lift	130	140	Elbow crosses midline	45	hypotonia	+	disappeared	present	irritable	50
B/O N	4	Lifts head and chin up , Does not bear weight on forearm	60	80	Elbow does not cross midline	40	hypertonia	++	disappeared	present	normal	56

Continued

B/O O	5	Lifts head and chin upbears weight on elbow	100	110	Elbow cross midline	45	normal	+	disappeared	disappeared	normal	65
B/O P	2	No head lift	60	80	Not cross midline	45	hypertonia	++	present	present	irritable	49

DTR-Deep tendon reflex, ATNR-Assymetric tonic neck reflex, HINE-Hammersmith Infant Neurological Examination; *CDC Grading for head holding (assessed at completed 4 months) grade 0: no head holding at all, grade 1: head erect and steady momentarily, grade 2: supine-lifts head when pulled up by arms, grade 3: prone elevates self by arms-chest raised, grade 4: holds head steady while normally moved, grade 5: head balanced always. (Interpretation for CDC grading—grade 3, 4, 5—normal for that age) [24]; **HINE SCORE: Scores below 40 predict non-ambulant cerebral palsy, 40-60-ambulant cerebral palsy [25].

Table S3. Development assessment with Bayley-3 at 6 months.

Sl. no	Motor				Cognition			Language				Socio-Emotional		GAC	
	comp	%ile	Age eq:		comp	%ile	Age equivalent	comp	%ile	Age eq		comp	%ile	comp	%ile
			GM	FM						RL	EL				
B/O A	100	50	5m 20d	6m	95	37	5m 20d	103	58	5m 10d	5m	90	25	88	23
B/O B	97	42	5m 10d	5m 20d	90	25	5m 20d	97	42	5m	4m 20d	95	37	93	32
B/O C	55	0.1	3m 20d	3m 10d	75	5	4m 10d	77	6	4m 20d	4m 10d	80	9	78	7
B/O D	64	1	4m	3m 20d	85	16	4m 20d	71	3	4m	3m 20d	75	5	77	6
B/O E	61	0.5	3m 20d	3m 10d	70	2	3m 10d	68	2	3m 20d	3m 10d	70	2	73	4
B/O F	64	1	4 m	3m 20d	70	2	3 m 10 d	71	3	4m	3m 20d	75	5	77	6
B/O G	103	58	6 m	6m 10d	100	50	6m	97	42	5m	4m 20d	90	25	90	25
B/O H	58	0.3	4m	3m 20d	60	0.4	3m 20d	56	0.2	3m 10d	3m	60	0.4	57	0.2
B/O I	100	50	5m 20d	6m	102	52	6m 10d	100	45	5m 20d	5m 10d	90	25	93	32
B/O J	95	40	5m	5m 10d	90	25	5m 10d	97	42	5m	4m 20d	93	32	95	37
B/O K	55	0.1	3m 20d	3m 10d	70	3	4m 20d	70	3	4m 10d	4m	80	9	78	7
B/O L	60	0.5	4m 10d	4m	72	4	5m	70	3	4m 10d	4m	70	2	70	2
B/O M	64	1	4m	3m 20d	60	0.4	3m 20d	56	0.2	3m 10d	3m	80	9	57	0.2
B/O N	58	0.3	4m	3m 20d	70	3	4m 20d	60	0.5	3m 20d	3m 10d	60	0.4	62	0.5
B/O O	97	42	5m 10d	5m 20d	95	37	5m 10d	97	42	5m 10d	5m	90	25	93	32
B/O P	50	>0.1	2m 20d	2m 10d	58	0.3	3m	52	0.1	3m	2m 20d	58	0.3	60	0.4

*Comp-composite, %ile-percentile, Age eq:-age equivalent, GM-gross motor, FM-fine motor, RL-receptive language, EL-Expressive language, GAC-General Adaptive Composite.