AUCTORES
Globalize your Research

Archives of Medical Case Reports and Case Study
Sandhyabandara *

Open Access

Case Report

Multisystem Inflammatory Syndrome in Neonates; a Real Diagnostic Dilemma!

Bandara S[1], Bavanandan B[2], Karunarathna W.A.C.N[2], Attanayake J.C[3]

[1]Consultant Paediatrician, Incharge - Neonatal unit, Teaching hospital, Peradeniya, Sri Lanka.

[2]Registrar in Paediatrics, Neonatal intensive care unit, Teaching hospital, Peradeniya, Sri Lanka.

[3]Medical Officer, Neonatal intensive care unit, Teaching hospital, Peradeniya, Sri Lanka.

***Corresponding Author:** Sandhyabandara, Consultant Paediatrician Incharge Neonatology unit Teaching Hospital, Peradeniya.

Received Date: May 23, 2022; Accepted Date: June 10, 2022; Published Date: June 28, 2022.

Citation: Bandara S, Bavanandan B, Karunarathna W.A.C.N, Attanayake J.C. (2022) Multisystem Inflammatory Syndrome in Neonates; a Real Diagnostic Dilemma!. *J. Archives of Medical Case Reports and Case Study*, 6(1); DOI: 10.31579/2692-9392/128

Abstract

Neonatal multisystem inflammatory syndrome is a potentially life threatening disease entity which was described following the global crisis of SARS-CoV-2 that still demands further evidence for a conclusive diagnosis. We report a group of neonates who admitted to our neonatal intensive care unit with predominantly cardiac manifestations were treated for early onset of sepsis and subsequently for Neonatal multisystem inflammatory syndrome ended up with a good survival outcome.

Key words: neonatal multisystem inflammatory syndrome; early onset sepsis; SARS-Co-2; immune dysregulation; immune modulatory therapy

Abbreviations

IgM – Immunoglobulins M

IgG – Immunoglobulins G

MIS-C – Multisystem inflammatory syndrome in children

RT-PCR – Reverse transcriptase polymerase chain reaction

QTc – Corrected QT interval

MOD – Mode of delivery

NVD –Normal vaginal delivery

LSCS – Lower segment caesarian section

EM – Emergency

EL – Elective

HVS – High vaginal swab

GBS – *Group B streptococcus*

UTI – Urinary tract infection

POA – Period of amenorrhea

IV IG – Intravenous immunoglobulins

IV MP – Intravenous Methyl prednisolone

MRSA – *Methicillin resistant staphylococcus aureus*

EF – Ejection fraction

Introduction

COVID-19 caused by SARS-CoV-2, is a global public health crisis with the significant surge in Sri Lanka. According to the figures from Health Promotion Bureau, Sri Lanka, as of 9 may 2022, 517 million individuals were infected worldwide and six hundred thousand were infected in Sri Lanka. Initial studies showed that children were spared of severe COVID-19 [1-3]. However, recently many case reports of children experiencing a potentially life threatening multisystem inflammatory syndrome in children (MIS-C) has been explained [4-6].

MIS-C is said to be due to immune dysregulation following exposure to SARS-CoV-2 though the exact mechanism is still unclear [7]. It presents with fever with multi organ involvement, with raised inflammatory markers weeks after exposure to SARS-CoV-2 (4,5,7). MIS-C has clinical and biochemical resemblance with Kawasaki disease and severe COVID-19 cytokine storm seen in adults [8]. However, its pathophysiology is somewhat different and may be mediated by autoantibodies formed following a COVID-19 infection [9]. More than 80% of children with MIS-C have positive serology (Specific IgM and IgG antibodies) against SARS-CoV-2, but only about one third are positive for SARS-CoV-2 by RT-PCR [4,10,11].

Unlike MIS-C, where the primary infection and multisystem inflammation occur in the same subject, few case reports suggest neonatal multisystem inflammation (MIS-N) occurs secondary to maternally derived antibodies against SARS-CoV-2 which were believed to occur in the newborn through trans-placental passage [13-16].

Maternal antibodies pass transplacentally is a well-known fact and maternal infection with SARS-CoV-2 is not different. Multiple studies are reported transplacental transfer of anti SARS-CoV-2 IgG antibodies to neonates [17-19]. The majority (87%) of infants born to seropositive mothers had detectable IgG antibodies at birth and there was a positive correlation with maternal and infant antibody titers, regardless of presence of symptoms in the mother [18].

Few Indian case series described that these neonates mainly presented with conduction system abnormalities with structurally normal hearts. Specifically prolonged QTc with atrioventricular block or thrombosis with in the 1st week after birth [20].

We present a case series of a group of newborns who admitted to our neonatal intensive care unit over the period of 6 months (1st October 2021 to 31st march 2022) with predominantly cardiac manifestations were treated for early onset of sepsis and subsequently for Neonatal multisystem inflammatory syndrome, ended up with a survival outcome of 87.5% without major comorbidities.

Case details are summarized in table 1.

(Table 1)

Case number	Sex	POA	Parity	MOD	Birth weight	Birth asphyxia	Antenatal history	Perinatal history	Fetal scan
1	Female	37	P2C1	NVD	2.5kg	No	No	No	Normal
2	Female	39	P5C3	NVD	3.3kg	No	No	No	Normal
3	Female	41	P3C2	Assisted vaginal delivery	3.1kg	No	No	Dribbling for unknown duration	Normal
4	Female	40	P1C0	EM/LSCS	3.2kg	No	No	Moderate meconium, dribbling for 14 hours, HVS – GBS positive	Normal
5	Female	38	P2C1	EL/LSCS	3.3kg	No	No	No	Normal
6	Female	40	P1C0	NVD	2.75kg	No	No	Moderate meconium	Normal
7	Male	39	P1C0	EM/LSCS	3.85kg	No	No	Dribbling 28 hours	Normal
8	Female	30	P1C0	NVD	1.4kg	No	UTI	No	Normal

Maternal features

Of the eight mothers (all with singleton pregnancy), two (25%) were symptomatic for COVID-19 during pregnancy, six (75%) were asymptomatic. Both symptomatic mothers were tested positive for Rapid antigen test for COVID-19 during 3rd trimester. All mothers were tested for COVID – 19 Rapid antigen test during the admission for delivery and none of them detected positive. Antenatal scans were normal in all mothers and there were no antenatal complications were recorded either.

All mothers were vaccinated for COVID – 19 during pregnancy. The details of vaccination are shown in table 2.

(Table 2)

Case number	Maternal RT-PCR	Maternal RAT	Maternal Serology	Symptoms suggestive of COVID – 19 infection	Exposure History	Vaccination status during pregnancy			Serological evidence in the neonate
						1st dose	2nd dose	Booster dose	
1	Not done	Positive at 28 weeks	Not done	Yes	Yes	6 weeks	32 weeks	Not given	IgG positive (393AU/ml)
2	No	No	Not done	No	No	19 weeks	23 weeks	33 weeks	IgG positive (>400AU/ml)
3	Not done	Positive at 40 weeks	Not done	Yes	Yes	12 weeks	16 weeks	Not given	IgG positive (362AU/ml)
4	No	No	Not done	No	No	24 weeks	28 weeks	Not given	IgG positive (Titer not available)
5	No	No	Not done	No	No	18 weeks	22 weeks	Not given	IgG positive (245AU/ml)
6	No	No	Not done	No	No	22 weeks	26 weeks	Not given	IgG positive (>100AU/ml)
7	No	No	Not done	No	No	22 weeks	26 weeks	Not given	IgG positive (274AU/ml)
8	No	No	Not done	No	No	23 weeks	27 weeks	Not given	IgG positive (Titer not available)

Resuscitation at birth and post resuscitation period

Three neonates (37.5%) did not cry immediately after birth and two of them had significant respiratory distress in the delivery room. But none of them require any positive pressure ventilation in the delivery room. However all three required respiratory support in the form of nasal prong oxygen. Five neonates (62.5%) neither required resuscitation nor respiratory support in post resuscitation period.

Clinical presentation

The most common presentation involved the cardiovascular system. Three had rhythm disorders (37.5%) and all of them presented with prolonged QTc interval. One infant also had an episode of persistent unexplained tachycardia. Hypotension was seen in four neonates. Cardiac dysfunction (Septal hypokinesia, dilated cardiac chambers and low ejection fraction) in 2D Echocardiography was seen in 87.5% of neonates. One neonate had slightly prominent right coronary in the 2D Echocardiogram and another one had thin rim of pericardial effusion. One had normal 2D-Echocardiogram.

Table 3 summarizes the general characteristics and other clinical presentations

(Table 3)

Characteristic	Variables	Percentage	Total number of cases assessed
Maternal symptoms	Symptomatic Asymptomatic	25% 75%	8
Trimester when the mother had COVID	1st trimester 2nd trimester 3rd trimester	0% 0% 100%	2
Maternal exposure to COVID patients	Exposure No exposure Unknown	25% 0% 75%	8
COVID Vaccination status 1st dose 2nd dose Booster dose	 1st Trimester 2nd trimester 3rd trimester 1st Trimester 2nd trimester 3rd trimester 1st Trimester 2nd trimester 3rd trimester	 25% 75% 0% 0% 25% 75% 0% 0% 100%	 8 8 1
Mode of delivery	NVD Assisted vaginal delivery EL/LSCS EM/LSCS	50% 12.5% 12.5% 25%	8
Gestational age at birth	<28 weeks 28 – 32 weeks 32+1 – 36+6 weeks >37 weeks	0% 12.5% 0% 87.5%	8
Birth weight	>3.5Kg 2.5Kg – 3.5Kg 1.5Kg – 2.5Kg < 1.5Kg	12.5% 75% 12.5% 0%	8
Multiplicity	Singleton Twin	100% 0%	8
Age at presentation	<24hours 1 – 5 days >5days	37.5% 50% 12.5%	8
Organ system involvement	Cardiac Hematologic	87.5% 75%	8 8

	Respiratory	50%	8
	Gastrointestinal	25%	8
	Neurologic	12.5%	8
	Cutaneous	0%	8
	Renal	12.5%	8
	Fever/Temperature instability	50%	8
	Antenatal Complications	0%	8
Cardiac manifestations	Bradycardia	0%	8
	Unexplained tachycardia	12.5%	8
	Hypotension & shock	50%	8
	Prolonged QT interval	37.5%	8
	Dilated cardiac chambers	75%	8
	Dilated coronary arteries	12.5%	8
	Tricuspid regurgitation	0%	8
	Mitral regurgitation	0%	8
	Pericardial effusion	12.5%	8
	Intracardiac thrombosis	0%	8
	Persistent pulmonary hypertension	12.5%	8
Respiratory manifestations	Respiratory distress	25%	8
	Pleural effusion	12.5%	8
Gastrointestinal manifestations	Feed intolerance	12.5%	8
	Ascites	25%	8
Renal manifestations	Acute renal failure	12.5%	8
CNS manifestations	Convulsions	12.5%	8

Four of eight neonates (50%) had at least one indication for intra partum antibiotic prophylaxis to prevent early onset sepsis (21,22). Two of them had dribbling for more than 18 hours, one had high vaginal swab positive for *group B streptococcus* in current pregnancy and one neonate born prematurely at 30 weeks of gestation in whom the mother had symptomatic culture negative urinary tract infection during antenatal period.

As five of eight neonates had positive blood cultures (one positive for MRSA and four positive for *klebsiella pneumoniae* – 62.5%) and all of them had blood pictures positive for possible early onset bacterial sepsis (left shift with neutrophil toxic changes) with elevated inflammatory markers we have considered early onset of sepsis as the primary diagnosis and commenced intravenous antibiotics according to the local guidelines. Neonates who developed circulatory compromise (50%) were effectively managed with intravenous inotropes.

The higher incidence of cardiac manifestations among this group of neonates which is quite unusual to explain only by early onset of sepsis, urged us to consider cardiac markers and 2D Echocardiography to exclude possible infectious or inflammatory myocarditis in them. Surprisingly all of them had elevated troponin I values for age related ranges with 2D Echocardiographic changes suggestive of ventricular dysfunction after the 1st week of life while on treatment with appropriate antibiotics according to the antibiotic sensitivity test.

As new cases with asymptomatic COVID-19 infections being soaring up during that period in our country we have also considered Multisystem inflammatory syndrome in new born (MIS-N) induced by trans placental passage of COVID-19 antibodies as an alternative diagnosis.

To further confirm the diagnosis, investigations done according to the current guidelines for MIS-N practiced in Sri Lanka (Table 4) [23].

(Table 4)

Investigations	Percentage	Total number cases assessed
Neutrophilic leukocytosis	0%	8
Thrombocytopenia	75%	8
Elevated C reactive protein	87.5%	8
Elevated Serum ferritin	50%	2
Elevated Pro-calcitonin	100%	2
Elevated Lactate dehydrogenase	87.5%	8
Elevated D-dimers	100%	8
Elevated liver enzymes	87.5%	8
Elevated Creatinine	12.5%	8
Elevated INR	75%	8
Elevated troponin I	100%	8
Hyponatremia	12.5%	8

Positive blood culture	62.5%	8
Positive CSF analysis	25%	4
Blood picture compatible with sepsis	100%	8

Anti-SARS-CoV-2-IgM antibodies were not done in all the neonates because it is not readily available in Sri Lanka, and IgG antibodies (cut-off-index (COI) > 1 considered reactive) were positive in all neonates.

The neonates were treated with IVIG (2g/kg over 24 to 48 hours), methylprednisolone (10mg/kg over 30 minutes for 5 days), aspirin (1-5mg/kg/day) and anti-failure treatment (Furosemide and Captopril). The neonates have also been covered with 14 – 21 days of intravenous antibiotics. Normalization of QTc and remarkable improvements in ventricular functions on subsequent 2D Echocardiograms were observed following immune modulatory therapy.

Table 5 summarizes the cardiac manifestations and the treatment given.

(Table 5)

Case number	Clinical presentation	Day of presentation	Troponin I	QTc (>0.47 - prolonged)	2-DECHO	Treatment given
1	Persistent tachypnea since birth	Day 1	93pg/mL on day 10	0.40 seconds	Dilated left ventricle with mild septal hypokinesia (EF – 53%)	IVIG IV MP Captopril Furosemide Aspirin Prednisolone
2	Fever	Day 2	63.2pg/mL on day 15	0.50 seconds	Mildly prominent left ventricle (EF – 70%)	IVIG IV MP Aspirin Prednisolone
3	Fever	Day 8	93.9pg/mL on day 19	0.42 seconds	Mild fullness of left ventricle (EF – 65%)	IVIG Aspirin Prednisolone
4	Poor feeding	Day 2	195pg/mL on day 20	0.41 seconds	Fullness of left ventricle with mild septal hypokinesia (EF – 69%) Prominent right coronary artery	IVIG IV MP Aspirin Prednisolone Furosemide spironolactone
5	Persistent pulmonary hypertension	Day 2	75.5pg/mL on day 12	0.48 seconds	Mild fullness of left ventricle (EF-76%)	IVIG IV MP Aspirin Prednisolone
6	Respiratory distress	Day 1	89.2pg/mL on day 32	0.43 seconds	Global hypokinesia, mild ventricular dysfunction Thin rim of pericardial effusion (EF-45-50%)	IVIG IV MP Captopril Furosemide Aspirin Prednisolone
7	Fever	Day 3	111.4pg/mL on day 24	0.48 seconds	Hypokinetic inter ventricular septum (EF – 48%)	IVIG IV MP Captopril Furosemide Aspirin Prednisolone
8	Very prematurity	Day 1	80.5pg/mL	0.42 seconds	No evidence of myocarditis and coronary arteritis (EF – not available)	IVIG IV MP

The only premature baby in this group eventually succumbed due to acute kidney injury related complications. Those term neonates who survived (87.5%) were discharged with aspirin, oral prednisolone and anti-failures and put on follow up at clinic on regular intervals to modify the drug management according to the repeat 2D-Echocardiograms in liaison with pediatric cardiology team.

Discussion

According to the proposed inclusion criteria for neonatal multisystem inflammatory response syndrome (MIS-N) secondary to maternal SARS-CoV-2 exposure or infection, presence of a positive blood culture excludes the diagnosis of MIS-N [23]. However there were no convincing evidence to describe the cardiac manifestations that we have observed in this group of neonates, caused by sepsis alone.

Presence of IgG antibodies against COVID-19 in high titers (>100AU/L) and significant improvement observed clinically, biochemically and in

follow up 2D-Echocardiograms with immune modulatory therapy further suggest an underlying inflammatory process could be due to MIS-N caused by trans-placental passage of antibodies following symptomatic and asymptomatic COVID-19 infection in the mothers during pregnancy. Thus, we believe that the immune dysregulation caused by multisystem inflammatory syndrome may increase the susceptibility to acquire early onset sepsis in newborns and both these entities may coexist in a given time. But we require further evidence to support our observation.

Conclusion

The diagnosis of neonatal multisystem inflammatory syndrome following SARS-CoV-2 infection or exposure during antenatal period, is a diagnostic dilemma that demands further studies to understand the underlying pathological mechanism and to decide on crucial immune modulatory therapy in mixed presentations as in our case.

References

1. Gupta, S.; Malhotra, N.; Gupta, N.; Agrawal, S.; Ish, P. (2020). The curious case of coronavirus disease 2019 (COVID-19) in children.J. Pediatr. 222, 258-259.
2. Brodin, P. (2020) Why is COVID-19 so mild in children? Acta Paediatr.109, 1082-1083.
3. Rawat, M.; Chandrasekharan, P.; Hicar, M.D.; (2020). Lakshminrusimha, S. COVID-19 in Newborns and Infants-Low Risk of Severe Disease: Silver Lining or Dark Cloud? Am. J. Perinatol. 37, 845-849.
4. Whittaker, E.; Bamford, A.; Kenny, J.; Kaforou, M.; Jones, C.E.; Shah, P.; Ramnarayan, P.; Fraisse, A.; Miller, O.; Davies, P.; et al. (2020). Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA J. Am. Med. Assoc. 324, 259-269.
5. Verdoni, L.; Mazza, A.; Gervasoni, A.; Martelli, L.; Ruggeri, M.; Ciuffreda, M.; Bonanomi, E.; D'Antiga, L. (2020). An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: An observational cohort study. Lancet, 395, 1771-1778.
6. Belhadjer, Z.; Meot, M.; Bajolle, F.; Khraiche, D.; Legendre, A.; Abakka, S.; Auriau, J.; Grimaud, M.; Oualha, M.; Beghetti, M.; et al. (2020). Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic.Circulation. 142, 429-436.
7. Davies, P.; Evans, C.; Kanthimathinathan, H.K.; Lillie, J.; Brierley, J.; Waters, G.; Johnson, M.; Griffiths, B.; du Pre, P.;Mohammad, Z.; et al. (2020). Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: A multicentre observational study. Lancet Child Adolesc. Health 4, 669-677.
8. Nakra, N.A.; Blumberg, D.A.; Herrera-Guerra, A.; Lakshminrusimha, S. (2020). Multi-System Inflammatory Syndrome in Children (MISC) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management.Children 7, 69.
9. Consiglio, C.R.; Cotugno, N.; Sardh, F.; Pou, C.; Amodio, D.; Rodriguez, L.; Tan, Z.; Zicari, S.; Ruggiero, A.; Pascucci, G.R.; et al. (2020). The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell 183, 968-981.e7.
10. Godfred-Cato, S.; Tsang, C.A.; Giovanni, J.; Abrams, J.; Oster, M.E.; Lee, E.H.; Lash, M.K.; et al. (2021). Multisystem Inflammatory Syndrome in Infants<12 months of Age, United States, May 2020–January 2021.Pediatric Infect. Dis. J. 40, 601-605.
11. Godfred-Cato, S.; Bryant, B.; Leung, J.; Oster, M.E.; Conklin, L.; Abrams, J.; Roguski, K.; Wallace, B.; Prezzato, E.;Koumans, E.H.; et al. (2020). COVID-19-Associated Multisystem Inflammatory Syndrome in Children-United States, March–July 2020. MMWR Morb. Mortal. Wkly. Rep. 69, 1074-1080.
12. McCarty, K.L.; Tucker, M.; Lee, G.; Pandey, V. (2020). Fetal Inflammatory Response Syndrome AssociatedWith Maternal SARS-CoV-2 Infection. Pediatrics.
13. Divekar, A.A.; Patamasucon, P.; Benjamin, J.S. (2021). Presumptive Neonatal Multisystem Inflammatory Syndrome in Children Associated with Coronavirus Disease 2019. Am. J. Perinatol.
14. Khaund Borkotoky, R.; Banerjee Barua, P.; Paul, S.P.; Heaton, P.A. (2021). COVID-19-Related Potential Multisystem Inflammatory Syndrome in Childhood in a Neonate Presenting as Persistent Pulmonary Hypertension of the Newborn. Pediatric Infect. Dis. J.40, e162-e164.
15. Kappanayil, M.; Balan, S.; Alawani, S.; Mohanty, S.; Leeladharan, S.P.; Gangadharan, S.; Jayashankar, J.P.; Jagadeesan, S.;Kumar, A.; Gupta, A.; et al. (2021). Multisystem inflammatory syndrome in a neonate, temporally associated with prenatal exposure to SARS-CoV-2: A case report. Lancet Child Adolesc. Health 5, 304-308.
16. Shaiba, L.A.; Hadid, A.; Altirkawi, K.A.; Bakheet, H.M.; Alherz, A.M.; Hussain, S.A.; Sobaih, B.H.; Alnemri, A.M.; Almaghrabi, R.;Ahmed, M.; et al. (2021). Case Report: Neonatal Multi-System Inflammatory Syndrome Associated With SARS-CoV-2 Exposure in Two Cases From Saudi Arabia. Front. Pediatr. 9, 652857.
17. Zeng, H.; Xu, C.; Fan, J.; Tang, Y.; Deng, Q.; Zhang,W.; Long, X. Antibodies in Infants Born to MothersWith COVID-19 Pneumonia.JAMA J. Am. Med. Assoc. 2020.
18. Flannery, D.D.; Gouma, S.; Dhudasia, M.B.; Mukhopadhyay, S.; Pfeifer, M.R.; Woodford, E.C.; Triebwasser, J.E.; Gerber, J.S.;Morris, J.S.;Weirick, M.E.; et al. (2021). Assessment of Maternal and Neonatal Cord Blood SARS-CoV-2 Antibodies and Placental Transfer Ratios. JAMA Pediatr.
19. Atyeo, C.; Pullen, K.M.; Bordt, E.A.; Fischinger, S.; Burke, J.; Michell, A.; Slein, M.D.; Loos, C.; Shook, L.L.; Boatin, A.A.; et al. (2021). Compromised SARS-CoV-2-specific placental antibody transfer. Cell 184, 628–642.e10.
20. Clark, B.C.; Sanchez-de-Toledo, J.; Bautista-Rodriguez, C.; Choueiter, N.; Lara, D.; Kang, H.; Mohsin, S.; Fraisse, A.; Cesar, S.;Sattar Shaikh, A.; et al. (2020). Cardiac Abnormalities Seen in Pediatric Patients During the SARS-CoV2 Pandemic: An International Experience. J. Am. Heart Assoc. 9, e018007.
21. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002; 51:1e22.
22. Prevention of Group B Streptococcal early-onset disease in newborns: ACOG committee opinion, number 782. Obstet Gynecol 2019; 134:1.
23. Sri Lanka College of Paediatricians, Management of Multisystem Inflammatory Syndrome in Children (MIS-C). Colombo: Sri Lanka College of Paediatricians; 07/2021. 23.