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Generalised oedema in COVID-19 positive children: A case series

Experiences on COVID-19 and nutrition captured to date in Field Exchange have been at a programme level rather than at individual case management level. To fill this knowledge-sharing gap, here we feature three case reports of generalised oedema in COVID-19 positive children in India that appeared to respond to nutrition treatment



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Key messages:

- Three cases of generalised oedema were seen in COVID-19 positive children and nutrition therapy with F-75 milk formula was associated with oedema resolution in all three cases.
- As the understanding of kwashiorkor to enable preventive and therapeutic interventions evolves, it is helpful to observe that mechanisms in kwashiorkor have much in common with the phenomena of oedema associated with other conditions.

Generalised oedema is an important clinical presentation in children and systemic causes are usual, namely renal, cardiac and hepatic as well as nutritional oedema in severe acute malnutrition (SAM). In this article we present three cases of COVID-19 positive children, from Mumbai and surrounding areas, with acute generalised oedema and without other signs of malnutrition or other systemic dysfunction. This clinical feature is rare and has not been described in literature worldwide (Sarangi et al, 2020).

Case 1

A 15-month-old female child was admitted with complaints of cold, cough and fever for five days and generalised oedema. The child was admitted with a weight of 11.38kg (weight for age Z-score and mid-upper arm circumference measurements were not taken due to the presence of oedema for each case) and tested positive for SARS COV 2 by RT-PCR test. On examination, the child was irritable and had generalised oedema but her vitals were normal. The child was not breastfeeding at admission nor during treatment duration. A complete blood count showed haemoglobin (Hb) at 8.7 g/dl, a total leukocyte count (TLC) of 12,520 mm³ and elevated C-reactive protein (CRP). Urine routine microscopy and culture were normal and blood urea nitrogen, serum creatinine and liver functions, including serum proteins, were normal. The chest X-ray and echocardiogram were normal. The presumptive diagnosis was iron-deficiency anaemia with generalised oedema with COVID-19 infection. The child was managed with antipyretics and azithromycin. Nutritional therapy with F-75 milk formula was started on day three post-admission as oedema failed to resolve. The child showed remarkable improvement with oedema subsiding over the following three days post-treatment, with weight upon discharge measured at 9 kg with no oedema. No antivirals, oxygen or steroids were used.

Case 2

A three-year-old male child, weighing 15kg, was admitted, with complaints of fever for seven days, breathlessness and mild generalised oedema. The child was admitted and tested positive for SARS COV 2 by RT-PCR test. On examination, his heart rate was

112/min, respiratory rate was 44/min (on non-invasive ventilation) and blood pressure was 92/61mm Hg. A complete blood count showed Hb: 8.0 g/dl, TLC: 13,660 mm³ and elevated CRP. The chest X-ray showed bilateral consolidation and ground glass opacity. Serum proteins, renal and liver functions were normal. The echocardiogram was normal. The presumptive diagnosis was COVID-19 pneumonia with generalised oedema. The patient was managed with methylprednisolone, antibiotics and symptomatic therapy. The child showed significant improvement in their general condition but oedema did not resolve. Nutritional therapy with F-75 milk formula was started on day three post-admission. Oedema subsided within three days post-treatment. The child's weight on discharge was 13.1 kg.

Case 3

An 11-month-old male child, weighing 7.8 kg, presented with complaints of abdominal distension, scrotal oedema and bilateral pedal oedema for six days. The child was admitted and tested negative for SARS COV 2. His COVID-19 antibody response was positive. There was no icterus but significant ascites with bilateral pedal oedema present. The liver was mildly enlarged. His blood counts were normal, CRP was elevated, serum albumin was 3g/dl and total proteins were 5g/dl, while liver enzymes were normal. An echocardiogram showed a normal heart function. The infant was breastfeeding on admission and throughout treatment. The child was managed with nutritional therapy using F-75 milk formula, after which generalised oedema subsided completely within two days.

Discussion

There have been around 38.2 million cases of COVID-19 infection in India, out of which 7.33 million cases have been reported in Maharashtra with Mumbai being the epicentre with 1,023,707 cases as of 20th January 2022. Mumbai, being a densely populated city, had great difficulty in stopping the spread of COVID-19 due to an inability to maintain social distancing and universal masking. Children in general had a low rate of infection, especially those without comorbidities (Ministry of Health and Family Welfare, 2021). Infections – such as measles, whooping cough, tuberculosis and sepsis – are

known to precipitate nutritional oedema. However, as COVID-19 is a novel infection, this is the first reported case series of such an association to the best of the author's knowledge.

Oedema formation is defined as an increase in interstitial volume and depends on the balance between intravascular and interstitial hydrostatic and oncotic pressure and the permeability of the vascular wall to macromolecules (e.g., albumin). There are two rare causes, lymphoedema and myxoedema, which are not relevant to our case series. The pathophysiology of oedema formation is conceptually categorised into three groups which relate to these three factors: an increase in capillary hydrostatic pressure, a decrease in capillary oncotic pressure and an increase in vascular permeability ('capillary leakage'). An increased capillary hydrostatic pressure is an often-hypothesised mechanism for parvovirus-induced oedema formation as most published cases have reported signs of plasma expansion. Severe sepsis in children, including from viral infection, also commonly causes oedema through high-level inflammation affecting the vascular endothelium. COVID-19 (like other severe viral infections including influenza, severe acute respiratory syndrome and Middle East respiratory syndrome) is highly proinflammatory.

Sodium retention causing oedema can be primary (due to a defect in renal sodium excretion) or secondary (due to the response of normal kidneys to an actual or sensed low effective circulating volume). Secondary causes of sodium retention, for example due to heart failure, nephrotic syndrome or liver cirrhosis, were ruled out in all our patients. Increased capillary permeability could be a cause due to free radical release from oxidative stress, a hypothesis of Michael Golden for oedema related to SAM (Golden, 2002).

Infection is almost ubiquitous in kwashiorkor – which is also referred to as nutritional oedema or oedematous malnutrition and is characterised by the presence of bilateral pitting oedema and dyspigmentation of the skin and hair – and is



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frequently precipitated by an infection such as measles. The body's defence against invading organisms is to produce free radicals in sufficient quantities to kill the organisms. The body relies upon its own protective mechanisms to limit the extent of self-damage and to repair the unavoidable damage after the organism is killed. Thus, stimulated leucocytes, specifically neutrophils, produce large quantities of superoxide and hydrogen peroxide which they release into the surrounding medium. This is compounded by a deficiency of Type 2 nutrients in malnourished patients which act as scavengers of free radicals and lead to the development of oedema. Primary sodium retention is possible as in parvovirus B19 infection, and in SAM cases we see severe curtailment of the sodium-potassium pump leading to interstitial oedema (Vlaar et al, 2014). A new hypothesis has emerged which talks of Bradykinin release as a cause of interstitial oedema (Garvin et al, 2020).

Conclusion

The presence of generalised oedema is a red flag sign in a COVID-19 positive patient. Based on our experiences of case management of child COVID-19 cases with generalised oedema, nu-

trition therapy with F-75 milk formula was associated with oedema resolution in all three cases. We therefore suggest that therapeutic nutrition treatment accompany medical case management and encourage other frontline practitioners to report on their experiences.

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Postscript

Generalised oedema in COVID-19 positive children: Comment

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Although the diagnosis of kwashiorkor malnutrition requires only nutritional oedema in settings where malnutrition is common, it is a syndrome characterised by multiple signs. When it is not clear that the

oedema is indicative of kwashiorkor, medical professionals look for verification through other signs or markers.

In 1967, a colloquium of researchers and clinicians familiar with kwashiorkor came together from multiple regions. Based on their com-

bined observations, the only sign they could all agree on was that oedema resolved quickly upon improvement of the diet (McCance and Widdowson, 1968). In kwashiorkor, bilateral pitting oedema typically starts in the feet and sometimes the face, gradually increasing

through the lower legs, hands and arms (Holt et al, 1963). Often the torso remains clear of oedema. In odd circumstances such as the three case studies described above, the diagnosis is complicated, and it may be useful to look beyond the sole criteria of bilateral pitting oedema for other clues.

Other visible signs of kwashiorkor are, roughly in the order that they are often observed, irritability, lethargy, fatty enlarged liver, loss of pigment in the skin and hair, hair that is brittle and falls out, and skin lesions – typically ‘flaky paint’ dermatosis or skin darkening. A hallmark feature of kwashiorkor is also low serum albumin along with electrolyte imbalances (Di Giovanni et al, 2016). Children with kwashiorkor very often have a distended abdomen due to the fatty liver but ascites (fluid in the peritoneal cavity) is not a characteristic of kwashiorkor. Although kwashiorkor can be found in people of all ages, it is by far most common in children under six years old and rarely found in infants under six months old.

The onset of kwashiorkor can be slow, with multiple signs other than oedema appearing and resolving slowly over time then reappearing until the child descends into overt kwashiorkor. Onset can also be much more rapid, such as in conflict whereby the child’s environment and diet are suddenly deplorable and the child becomes both psychologically and physically stressed. Rapid onset can also follow illness such as measles in children who are already nutritionally compromised with signs generally appearing as the illness clears. When onset is sufficiently rapid, signs such as skin and hair changes may not have time to develop but lethargy/irritability, fatty liver and oedema are usually present. Kwashiorkor has also been anecdotally described as occurring after starting anti-retroviral therapy (ART) in human immunodeficiency virus (HIV)-infected children, possibly because ART imposes metabolic stress (Prendergast et al, 2011).

Although the biological mechanisms behind the development of kwashiorkor remain an enigma, the oedema usually clears within a few days and the child’s general nutritional status improves with the stabilisation of electrolytes and a diet providing low doses of high-quality protein, such as found in the F-

75 milk formula mentioned in the case studies. During the resolution of oedema there is little or no change in serum albumin, suggesting other causes are corrected by feeding, antibiotics and medical care during the stabilisation phase.

COVID-19 is a novel illness about which we know very little, especially in paediatric cases. Therefore, the diagnosis of kwashiorkor malnutrition in these case studies requires some consideration.

Although both children in Cases 1 and 2 presented with oedema that cleared during the administration of F-75 milk formula, the oedema was described as general, unlike the distinct bipedal pitting oedema seen in kwashiorkor. Serum proteins were described as normal, although albumin values were not given, and neither had any other signs associated with kwashiorkor. The child in Case 3 presented with bipedal pitting oedema and was underweight even while oedematous, indicating that he was probably nutritionally compromised even before the onset of generalised oedema. Serum albumin and blood proteins were borderline low and it is likely the child had recently had COVID-19. Although ascites is not generally associated with kwashiorkor, he did have a moderately enlarged liver.

From the little information available in these case studies, it does look like the child in Case 3 probably had kwashiorkor with rapid onset due to the COVID-19 infection on top of a poor initial nutritional status. But what of the other two cases? Even in rapid onset kwashiorkor, when many signs do not have time to manifest, we still see low serum albumin. In slower onset cases, low serum albumin is observed even before the development of oedema and may linger for a while after the child clears the oedema.

As the author notes, there are multiple conditions that can lead to generalised oedema which resolves with high quality nutrients and appropriate medical care. Sepsis, whether caused by viral, bacterial or fungal pathogens, can cause oedema, fluid maldistribution and fluid overload by disruption of endothelial barriers and capillary leakage (Kelm et al, 2015). A similar mechanism can occur during intense inflammation such as is experienced when endotoxin (the outer coat of Gram-negative bac-

teria comprising lipopolysaccharide) leaks across a damaged intestinal mucosal surface (translocation). Endotoxaemia is known to occur in severe COVID-19 disease, also potentially arising from capillary leakage (Khan et al. 2021). Endotoxin and increased intestinal permeability have been identified in patients with kwashiorkor (Brewster et al. 1997). It has also been argued that the intestinal microbiota may be associated with kwashiorkor secondary to translocation of bacterial products and metabolites, including endotoxin (Pham et al. 2021). However, one challenge in interpreting human studies has been that children commonly have infections or sepsis concurrently with kwashiorkor, limiting our ability to distinguish effects between the two. Although animal models of malnutrition have not generally been able to replicate the human phenomenon of pitting oedema, evidence from an animal model (pig) has suggested that a combination of nutritional restriction and endotoxin infusion results in greater oedema around the kidneys and oxidative stress compared to nutritional restriction alone (Baek et al. 2020).

Overall, these cases demonstrate several interesting issues. Several types of severe acute disease or physiological insults may result in oedema, and pre-existing nutritional compromise, susceptibility to intestinal translocation of bacterial products and acute metabolic or inflammatory insults, along with their effects on oxidant status and metabolism, are likely to be common underlying mechanisms. Thus, oedema in kwashiorkor and in other conditions is not simply due to a low albumin level alone. A ‘double hit’ explanation may potentially underlie the common form of kwashiorkor that we see in impoverished low and middle-income populations. As the search for an understanding of kwashiorkor to enable preventive and therapeutic interventions goes on, it is helpful to observe that mechanisms in kwashiorkor have much in common with phenomena of oedema associated with other conditions.

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For more information on kwashiorkor, please see a recent views article co-authored by Merry Fitzpatrick in *Field Exchange* issue 65, available at: <https://www.ennonline.net/fex/65/kwashiorkorworkinggroup>

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