

RESEARCH: CARE DELIVERY

The SARS-CoV-2 pandemic is associated with increased severity of presentation of childhood onset type 1 diabetes mellitus: A multi-centre study of the first COVID-19 wave

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Abstract

Objective: Children are usually mildly affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19). However, the pandemic has caused collateral damage to those with non-COVID-19 diseases. We aimed to determine the impact of the COVID-19 pandemic on the presentation of newly diagnosed childhood onset type 1 diabetes.

Methods: This was a cross-sectional study conducted over a 1-year period. We compared the severity of presentation of new-onset type 1 diabetes in children under the age of 18 presenting to the multi-centre North Central London diabetes network before (1 July 2019 to 22 March 2020) and during (23 March 2020 to 30 June 2020) the first wave of the COVID-19 pandemic in the United Kingdom.

Results: Over the 1-year study period, a total of 30 children presented with new-onset type 1 diabetes during the pre-pandemic period and 17 presented during the first COVID-19 wave. Children presented more frequently in diabetic ketoacidosis (DKA) during the first COVID-19 wave compared with pre-pandemic (pre-pandemic: mild 13%, moderate 6.7%, severe 10%; first COVID-19 wave: mild 5.9%, moderate 24%, severe 47%; $p = 0.002$). During the first COVID-19 wave, DKA presentations in children with a family history of type 1 diabetes were fewer compared to those without a family history (33.3% vs. 100.0%; $p = 0.006$). Children presenting in severe DKA pre-pandemic were younger than those not in severe DKA (3.9 years vs. 12.2 years, $p < 0.001$) but this difference was not significant during the first COVID-19 wave (10.1 years vs. 11.2 years, $p = 0.568$). Presenting HbA_{1c} measurement was higher in those presenting during the first COVID-19 wave (13.0 ± 1.7 vs. $10.4 \pm 3.2\%$; 119 ± 19 vs. 90 ± 35 mmol/mol; $p = 0.008$).

Conclusion: The COVID-19 pandemic is associated with increased severity of presentation of childhood onset type 1 diabetes. Whatever the context, young people with suspected new-onset type 1 diabetes should be referred for urgent clinical review.

KEYWORDS

endocrinology, paediatrics, type 1 diabetes

1 | INTRODUCTION

As health systems respond to the 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) pandemic, there is increasing recognition of the unintended, collateral damage to those with non-COVID-19 diseases. For example, since the start of the pandemic, there has been a sharp decrease in the number of adult admissions for cardiovascular diseases and delays in the diagnosis and treatment of cancer.^{1,2} Excess deaths not associated with the virus have been documented since the onset of the pandemic, compared with previous years.^{3,4} The causes of these poorer outcomes are likely to be complex and may in part be due to reduced access to medical care and delayed presentation to healthcare professionals.^{5,6} Fewer data are available for children and young people.

The diagnostic accuracy and availability of defined clinical and biochemical end points permits detailed investigation of the effect of the pandemic on childhood onset type 1 diabetes. Reports show an unusually high proportion of children and young people presenting in diabetic ketoacidosis (DKA) during the pandemic.⁷⁻¹⁰ In a nationwide survey of paediatric diabetes centres in the United Kingdom, delayed presentation was noted in 20% of children with newly diagnosed type 1 diabetes.⁸ These reports also suggest a potential increase in the incidence of newly diagnosed childhood onset type 1 diabetes during the pandemic.^{7,11} However, some reports only collected data during the pandemic, precluding direct comparison with months pre-pandemic. In others, studies were single centre, had relatively small sample sizes, or contained fewer biochemical data. To expand on previous findings and to address some of these limitations, we studied presentations of newly diagnosed type 1 diabetes across North Central London over a 1-year period and compared the severity of presentations occurring before the COVID-19 pandemic to those occurring during the first COVID-19 wave.

2 | RESEARCH DESIGN AND METHODS

We collected data on the new presentation of type 1 diabetes in children and young people in four regional inpatients units (the North Central London Paediatric Diabetes Network) over a 1-year period (1 July 2019–30 June 2020). The time period of 1 July 2019 to 22 March 2020 preceded the COVID-19 pandemic in the United Kingdom ('pre-pandemic'). The time period of 23 March 2020 to 30 June 2020 approximated the first wave of the COVID-19 pandemic in the United Kingdom and the first national lockdown period ('first COVID-19 wave'). The North Central London diabetes network is composed of Barnet and Chase Farm Hospital, the

What is already known

The acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) pandemic has caused collateral damage to children with non-COVID-19 diseases. An increased incidence of newly diagnosed childhood onset type 1 diabetes during the pandemic has been reported.

What has this study found

This multi-centre study conducted over a 1-year period compared the severity of presentation of newly diagnosed childhood onset type 1 diabetes before (1 July 2019 to 22 March 2020) and during (23 March 2020 to 30 June 2020) the first wave of the COVID-19 pandemic. Children presenting during the pandemic were more likely to have a low pH, a high HbA_{1c} and diabetic ketoacidosis.

What are the implications of the study

Paediatricians and primary care providers must be aware of the increased severity of paediatric type 1 diabetes presentations during the COVID-19 pandemic and, whatever the context, refer young people with suspected new-onset type 1 diabetes for urgent clinical review.

Royal Free Hospital, University College London Hospital and the Royal Whittington Hospital. Cases were identified using the hospital records and the electronic patient record system (Epic). Only children 18 years or younger were included and all clinical and biochemical data were extracted from Epic. All newly diagnosed type 1 diabetes diagnoses were antibody positive. The study was registered with the hospital audit department.

We evaluated the severity of presentation with newly diagnosed type 1 diabetes pre-pandemic compared with during the first wave of COVID-19 in the United Kingdom. In these two groups, we compared demographic data and the severity of DKA as measured by the degree of acidosis (pH), DKA admissions requiring paediatric intensive care unit admission, electrolyte imbalance and glycated haemoglobin (HbA_{1c}). HbA_{1c} was measured using the point of care Siemens/Bayer DCA 2000+ analyser. DKA was defined as a pH level less than 7.3 and severe DKA as a pH level less than 7.1.

Ethnicity was self-reported according to the Office of National Statistics definitions of Black, Asian, White, Mixed and Other.¹² Fisher's exact tests (two sided) and independent sample *t* tests were used for statistical analysis and were

conducted using SPSS (IBM v27.0.1). A value of $p < 0.05$ was considered statistically significant.

3 | RESULTS

Over the 1-year study period, a total of 30 children presented with new-onset type 1 diabetes during the pre-pandemic period and 17 presented during the first COVID-19 wave. Presenting mean pH was lower (7.09 ± 0.21 vs. 7.30 ± 0.13 ; $p = 0.001$) and first HbA_{1c} measurement was higher (13.0 ± 1.7 vs. $10.4 \pm 3.2\%$; 119 ± 19 vs. 90 ± 35 mmol/mol; $p = 0.008$) in those presenting during the first COVID-19 wave (Table 1). There was no significant increase in paediatric intensive care unit admissions for DKA during the first COVID-19 wave compared to pre-pandemic (23.5% vs. 6.7%; $p = 0.170$) (Table 1). There were 3.5 presentations per month pre-pandemic and 4.9 presentations per month during the first COVID-19 wave. The sample size precluded any conclusions from being drawn about the statistical significance of this difference.

Children presented more frequently in DKA during the first COVID-19 wave compared with pre-pandemic (pre-pandemic: mild 13%, moderate 6.7%, severe 10%; first COVID-19 wave: mild 5.9%, moderate 24%, severe 47%;

$p = 0.002$; Figure 1). Ethnicity and sex of children presenting with newly diagnosed type 1 diabetes did not significantly differ between the first COVID-19 wave and the pre-pandemic months. During the first COVID-19 wave, DKA presentations in children with a family history of type 1 diabetes were less frequent compared to those without a family history (33.3% vs. 100.0%; $p = 0.006$). Pre-pandemic, children presenting in severe DKA had a lower mean age at presentation compared to those not in severe DKA (3.9 years vs. 12.2 years; $p < 0.001$). However, during the first COVID-19 wave, this difference was no longer significant (10.1 years vs. 11.2 years; $p = 0.568$).

The likelihood of presenting in DKA was not significantly influenced by weight-for-age nor time from symptom onset to first presentation. Serum electrolyte concentrations (potassium, sodium, calcium, phosphate) did not differ significantly between the groups. However, one patient with a positive COVID-19 PCR result on admission presented in cardiac arrest and was found to be hypokalaemic (1.7 mmol/L) and hypophosphataemic (0.45 mmol/L). This child and one other had detectable COVID-19 antibodies (IgG). COVID-19 PCR status did not significantly influence mean pH nor likelihood of presenting in DKA. However, data on COVID-19 antibody and PCR status were not available for several children (Table 2).

TABLE 1 Characteristics of all patients with newly diagnosed type 1 diabetes between 1 July 2019 and 30 June 2020 (1 July 2019 to 22 March 2020) and during (23 March 2020 to 30 June 2020)

| | Pre-pandemic (1 July 2019–22 March 2020) | First COVID-19 wave (23 March–30 June 2020) | <i>p</i> value |
|---|--|---|----------------|
| Sample size | 30 | 17 | — |
| Presentations per month | 3.5 | 4.9 | — |
| Age (years) | 11.4 (range 2.2–17.6) | 10.6 (range 3.2–16.3) | 0.571 |
| Men sex | 15 (50.0) | 9 (52.9) | 1 |
| Ethnicity | | | |
| Black | 2 (6.7) | 0 (0.0) | 0.79 |
| Asian | 4 (13) | 2 (12) | |
| White | 15 (50) | 10 (59) | |
| Mixed | 2 (6.7) | 0 (0.0) | |
| Other | 7 (23) | 5 (29) | |
| DKA at presentation | | | |
| No DKA | 21 (70) | 4 (24) | 0.002 |
| Mild DKA | 4 (13) | 1 (5.9) | |
| Moderate DKA | 2 (6.7) | 4 (24) | |
| Severe DKA | 3 (10.0) | 8 (47) | |
| Paediatric critical care unit-treated DKA | 2 (6.7) | 4 (24) | 0.17 |
| HbA _{1c} % (mmol/mol) at diagnosis | 10.4 ± 3.2 (90 ± 35) | 13.0 ± 1.7 (119 ± 19) | 0.008 |
| pH at diagnosis | 7.30 ± 0.13 | 7.09 ± 0.21 | 0.001 |

Note: Data are *n* (%) or mean ± SD unless otherwise indicated.

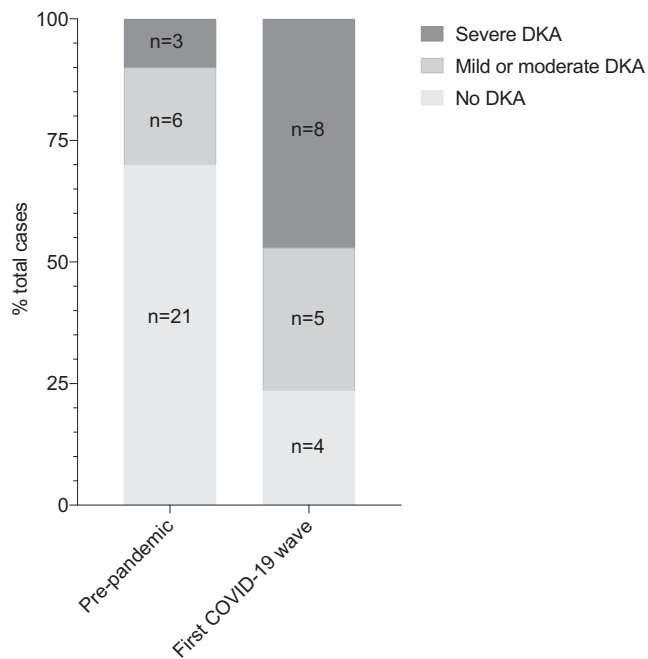


FIGURE 1 Incidence (%) of newly diagnosed type 1 diabetes presenting without diabetic ketoacidosis (DKA), with mild or moderate DKA, and with severe DKA before and during the first wave of the COVID-19 pandemic. Absolute numbers of patients are included

4 | DISCUSSION

Over a 1-year period, presentations of newly diagnosed childhood onset type 1 diabetes were more severe during the first COVID-19 wave compared with the nine preceding pre-pandemic months. This was evidenced by a lower pH at diagnosis, a higher presenting HbA_{1c}, and a greater risk of developing DKA and severe DKA. These observations are consistent with other reports documenting the higher rates of DKA in both paediatric and adult patient populations during the first months of the pandemic.^{7–10,13,14} Pre-pandemic, younger children presented more severely compared to older children, and this may relate to the known difficulty with recognizing diabetes symptoms in this age group.¹⁵ However, this difference was not seen during the first COVID-19 wave, with a high proportion of children of all ages presenting in DKA. The reasons for these more severe presentations overall are likely to be complex and multifactorial. The pandemic is a time of great uncertainty and rapid change to clinical services and public health messaging. A delay in presentation to paediatric services during the pandemic is now well-documented.^{16,17} This is possibly due to difficulty accessing usual frontline services; fear of contracting COVID-19; limitations of remote consultations; or a lack of appreciation of the urgency of the diagnosis.^{5,6,8,9} During the first COVID-19 wave, our finding that children with a positive family history of type 1 diabetes presented less severely may indicate that these families were more aware of the possibility of a

diabetes diagnosis and its symptoms. This highlights the well-recognized need for heightened awareness of diabetes symptoms. Interventions to increase awareness of type 1 diabetes among schools, families, health care providers and wider communities are associated with reduced DKA at diagnosis.^{18–20} Public health messaging needs to reinforce that the risks of delaying presentation to primary or secondary care with new onset type 1 diabetes—indeed any significant paediatric illness—are greater than the risk of contracting COVID-19 in hospital.

From a pathogenesis perspective, it is unclear to what extent COVID-19 directly precipitates or accelerates the development of diabetes and DKA. A bidirectional relationship between diabetes and COVID-19 infection has been proposed.²¹ Hyperglycaemia and DKA have been reported in up to half of adult patients with known type 1 diabetes presenting with COVID-19 infection.²² There is also an association between hyperglycaemia and severe COVID-19 in the absence of a diabetes diagnosis.^{23–25} A direct effect of SARS-CoV-2 infection on the pancreatic β -cell is also possible. SARS-CoV-2 can bind to ACE2 receptors within the pancreas, potentially leading to entry into and damage of islet β cells and a resultant increased incidence or severity of new-onset type 1 diabetes temporally related to clinical peaks of COVID-19 infection.²⁶ Type 1 diabetes is an antibody-mediated disease and it has long been hypothesized that preceding viral infections may contribute to its development. COVID-19 may be one such viral trigger. Furthermore, the emergence of PIMS-TS (Paediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19) suggests that children may be susceptible to a post-COVID-19 immunological, inflammatory disease.²⁷ Our study was conducted early in the pandemic and may not have captured a later rise of immunologically driven new-onset type 1 diabetes.

It is notable that the one child who was both antibody and PCR positive for COVID-19 presented the most severely—in cardiac arrest, profoundly acidotic and markedly hypokalaemic (1.7 mmol/L). A similar case was described in the London region during the same time period.⁷ Hypokalaemia in the context of non-diabetic patients with severe COVID-19 has been observed.^{7,28,29} The binding of SARS-CoV-2 to ACE2 receptors results in reduced ACE2 expression, decreased angiotensin II degradation, increased aldosterone secretion, and resultant renal potassium loss.^{30,31} This potentially explains COVID-19-associated hypokalaemia. This effect would be potentiated by the total body decrease in potassium concentration associated with the insulin deficient DKA state. Clinically, the heightened risk of renal potassium loss should translate to particularly careful electrolyte monitoring and replacement in this context.

Limitations to this study included its retrospective design, lack of data on social deprivation, and inadequate power to evaluate potential effects of ethnicity. Furthermore, although

TABLE 2 Characteristics of children and young people with newly diagnosed type 1 diabetes presenting during the first COVID-19 wave

| | Not in DKA | Mild/moderate DKA | Severe DKA |
|---|----------------|-------------------|-----------------|
| Sample size | 4 | 5 | 8 |
| Age | 8.6 (6.1–15.6) | 13.2 (10.4–16.3) | 10.1 (3.2–15.1) |
| Family history type 1 diabetes | | | |
| Yes | 4 (100) | 0 (0) | 2 (25) |
| No | 0 (0) | 5 (100) | 6 (75) |
| Days from symptoms to presentation (median (IQR)) | 7 (2.5–17.5) | 14 (10.5–21.0) | 7 (3.5–19.3) |
| Weight for age z-score | −0.90 ± 0.75 | 0.36 ± 1.34 | −0.43 ± 1.76 |
| SARS-CoV-2 PCR | | | |
| Positive | 0 (0) | 0 (0) | 1 (13) |
| Negative | 1 (25) | 4 (80) | 4 (50) |
| Not done | 3 (75) | 1 (20) | 3 (38) |
| SARS-CoV-2 IgG | | | |
| Positive | 0 (0) | 1 (20) | 1 (13) |
| Negative | 0 (0) | 0 (0) | 1 (13) |
| Not done | 4 (100) | 4 (80) | 6 (75) |
| pH | 7.37 ± 0.12 | 7.16 ± 0.03 | 6.91 ± 0.13 |
| Bicarbonate | 24.9 ± 1.1 | 10.9 ± 0.8 | 7.0 ± 2.7 |
| Base excess | −0.1 ± 0.7 | −16.9 ± 1.6 | −22.2 ± 7.5 |
| Potassium (mmol/L) | 3.5 ± 0.5 | 3.6 ± 0.7 | 3.8 ± 1.1 |
| Sodium (mmol/L) | 136.0 ± 1.4 | 140.4 ± 3.4 | 142.6 ± 9.4 |
| Corrected calcium (mmol/L) | 2.3 ± 0.4 | 2.3 ± 0.2 | 2.2 ± 0.48 |
| Phosphate (mmol/L) | 1.3 ± 0.5 | 1.0 ± 0.4 | 0.8 ± 0.6 |
| Pre-existing co-morbidities | None | None | None |

Note: Data are *n* (%) and mean (SD) unless otherwise indicated.

other reports have suggested an increased incidence of newly diagnosed type 1 diabetes during the COVID-19 pandemic,^{7,11} our sample size was not large enough to determine relative incidence between the pre-pandemic months and the first COVID-19 wave. The impact of seasonal variation was also considered, as a winter peak of type 1 diabetes diagnoses has been found for some northern hemisphere centres.³² This would have made differences in type 1 diabetes diagnoses between the pre-pandemic period (encompassing the winter months) and the first COVID-19 wave (spring and summer months) more difficult to elucidate.

The direct comparison of longitudinal data from before and during the first COVID-19 wave in this study clearly demonstrates the increased severity of presentation of newly diagnosed type 1 diabetes in children and young people in the context of high circulating COVID-19 cases in the community. This may be indirectly due to delayed presentation or directly due to the emerging complex relationship between SARS-CoV-2 infection and glucose metabolism or diabetes pathogenesis. It is paramount that paediatricians and primary care providers are aware of this link between COVID-19 and

new-onset diabetes severity. This is particularly true in view of the ongoing disruption to usual clinical care caused by the COVID-19 pandemic; whatever the context, children and young people with suspected new-onset type 1 diabetes require urgent clinical review.

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AUTHOR CONTRIBUTIONS

SMB researched, analysed and verified the data and wrote the manuscript. CP, KT and SD reviewed and edited the

manuscript and contributed to the discussion. RA conceptualized and supervised the study as well as writing/reviewing the manuscript and researching and verifying data.

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