

COVID-19 in Children and Adolescents with Endocrine Conditions

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ABSTRACT

The rapid spread of coronavirus disease (COVID-19) worldwide justifies global effort to combat the disease but also the need to review effective preventive strategies and medical management for potentially high-risk populations during the pandemic. Data regarding the COVID-19 manifestations in adults with underlying endocrine conditions, especially diabetes mellitus, are increasingly emerging. Albeit children and adolescents are considered to be affected in a milder manner, paucity of information regarding COVID-19 in children who suffer from endocrinopathies is available. The present review comprehensively collects recommendations issued by various health organizations and endocrine associations for the management of pediatric endocrine conditions during the pandemic. Adhering to the specific “sick day management rules” and undelayed seeking for medical advice are only needed in most of the cases, as the vast majority of children with endocrine disorders do not represent a high-risk population for contamination or severe presentation of COVID-19. Psychological implications in these children and adolescents are also considered.

Introduction

On December 31st 2019, the World Health Organization (WHO) were notified about a cluster of pneumonia cases of unknown cause detected in the city of Wuhan in Hubei province, China [1]. Investigations showed that the causing factor was a previously unknown virus, the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the relative disease was named coronavirus disease 2019 (COVID-19) [1] and was characterized as a pandemic on March 11th 2020 [1]. According to a recent update by WHO on April 19th 2020, laboratory confirmed cases for COVID-19 have risen to 2 245 872 worldwide, including 152 707 deaths [2]. Reasonably, in the case of

such a massive health crisis as the COVID-19 outbreak, questions regarding increased vulnerability in specific population groups arise. One of the potentially high-risk populations is the pediatric population and particularly children with chronic diseases.

It has become evident that the disease can occur amongst all age groups, including the pediatric population [3]. However, early data suggest that the impact of the COVID-19 pandemic in children is modest [4], as it presents less frequently and with milder symptoms and severity [3]. In a population-based study in Iceland, children under 10 years of age and females had a lower incidence of SARS-CoV-2 infection than adolescents or adults and males [5]. The rate of mortality is reported to be much lower in

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children (<0.1%) compared to adults [6]. Suggested possible mechanisms for the milder clinical picture in children include: i) age-related high nasal gene expression of the angiotensin-converting enzyme 2 (ACE2) receptor (the functional receptor of SARS-Cov-2) in children aged > 10 years [7]; ii) a constitutional high lymphocyte count; and iii) trained immunity, an innate immune memory formed by “memory cells” after antigen exposure [8, 9].

Thus far, limited data are available about the possible consequences of COVID-19 on children and adolescents with a chronic illness. The Royal College of Paediatrics and Child Health (RCPCH) in the UK have published “shielding” guidance for children and young people with recent transplantation, immunosuppression, hemato-oncological, cardio-respiratory, renal, and gastrointestinal disorders [10]. Also, the British Society of Gastroenterology has published recommendations for management of inflammatory bowel disease during the COVID-19 pandemic [11]. However, to our knowledge, no reliable data exist associating endocrine disorders and vulnerability to COVID-19, expressed as increased morbidity or mortality and development of endocrine complications related to SARS-Cov-2.

Materials and Methods

The present review summarizes the current knowledge on the possible impact of COVID-19 in children and adolescents with endocrine disorders, considering known and newly developed recommendations from Health and Endocrine societies. Pubmed search for publications was performed in English, Spanish and Greek as of April 18th, 2020. The search terms that were used included “COVID-19”, “children”, “endocrine diseases”, “diabetes”, “thyroid diseases”, “hypopituitarism”, “hypoadrenalism”, “hypoglycemia”, “Cushing syndrome”, “obesity”. The following literature review and recommendations should be read in light of limitations, such as the rapidly evolving knowledge and recently gained experience regarding COVID-19, which also predominantly involves adults.

Discussion

To date, none of the endocrine conditions have been classified as predisposing factors for the Covid-19 infection [12] and hence, children with endocrine diseases have not shown a different disease pattern compared to children without an endocrine disorder. Nonetheless, there are multifaceted endocrine implications of COVID-19.

As for the general population, since SARS-Cov-2 is a virus of particularly increased emergence and spread capacity, children and adolescents with endocrine disorders are strongly encouraged to

adhere to preventive and protective measures against viral spread, such as social distancing, home confinement, self-hygiene (hand-washing, avoidance of touching their face, coughing/sneezing into elbow or tissue) and disinfecting frequently-touched surfaces [13]. Furthermore, adherence to local regulations regarding general preventive measures and schooling is of major importance [13]. Remote learning from home, if plausible, is the safest method [12].

In the case of symptoms of infection, such as fever, cough, and dyspnoea in particular, medical advice should be sought and if the symptoms are of increasing severity, visiting the nearest hospital and taking all the necessary measures (e. g., face mask), is imperative. Like with any other pediatric infection, it is important to maintain adequate hydration with frequent fluid intake. If COVID-19 is confirmed, recommended control measures should be promptly implemented together with supportive management of complications [14]. If hospitalization is needed, the health care team should be aware so as to modulate management, particularly in endocrine diseases such as type 1 diabetes mellitus, hypoglycemia disorders and adrenal insufficiency.

Furthermore, it is important that children with endocrine diseases who receive replacement or supplementation therapy maintain a euhormonal status. The necessity of dose adjustment according to the individual needs should be discussed with the treating physician, since no universal recommendation is applicable in all cases. Also, sufficient supply of medications should be ensured at reasonable quantities [12]. Routine hospital visits should be avoided for nonurgent reasons so that exposure to COVID-19 is restricted and those should be replaced by telephone or video consultation to maintain an optimal control of the underlying disease [15, 16]. This requires robust telephone triage and expansion of telehealth visits [16, 17].

► **Table 1** collects pivotal aspects for managing children and adolescents with endocrine disorders during the COVID-19 pandemic.

Endocrine Diseases During COVID-19 – Recommendations

Diabetes Mellitus (DM)

In adults, reports from China [18], Italy [19], and USA [20] indicate that DM is a risk factor for severe COVID-19 disease. Longstanding DM involves low-grade chronic inflammation, which may promote the cytokine storm that seems to be implicated in the severe evolution of COVID-19, as inflammation markers (C-reactive protein, fibrinogen, D-dimer, ferritin, erythrocyte sedimentation rate, IL-6)

► **Table 1** Key principles for managing children and adolescents with endocrine disorders during the COVID-19 pandemic.

- Promote adherence to protective infection control measures (hand hygiene, face mask, social distancing, etc.).
- Provision of reliable information by the health care team so that anxiety related to misinformation is prevented.
- Reassurance of the parents and children/adolescents that the vast majority of children with endocrine disorders do not represent a high-risk population for contamination or severe presentation of COVID-19.
- In case of COVID-19 infection, following the specific “sick day management rules” and seeking for medical advice without delay are adequate in most cases for an optimal outcome.
- Parents should also be reinforced by clinicians to be involved in entertaining children’s anxiety, ensuring good nutritional/fluid intake, active monitoring, and offering supportive therapy for their children.

have been found higher in patients with DM [21]. Hyperglycemia due to the COVID-19-induced stress, hypoglycemia or sharp glycaemic excursions entail detrimental outcomes for DM patients [21]. The identified data from adult studies do not specifically differentiate type 1 from type 2 DM.

With regard to children and adolescents with DM, it is expected that those with type 1 DM and good metabolic control will follow the same course of illness as their peers [12, 13]. Nonetheless, those with a poor control could have a debilitated immunity that puts them at a greater risk for contamination from SARS-Cov-2 [12], and a more severe presentation [22].

The European Society for Paediatric Endocrinology (ESPE) recommends maintaining the usual amount of back-up insulin supplies, for at least a week in advance, without stockpiling copious quantities, as this could jeopardize the supply chain leading to territorial or worldwide scarcity [12].

In the instance of symptoms that could be related to COVID-19, such as fever, cough or shortness of breath, it is paramount that medical assistance is sought without delay [13]. As during any other intercurrent illness, glycaemic control may deteriorate, hence following “sick day rules” also apply in the case of COVID-19 [13], as well as contacting the therapeutic team [12, 16]. Recommendations from the International Society for Pediatric and Adolescent Diabetes (ISPAD) include [13]: i) to monitor blood glucose and ketone bodies more frequently; ii) to target blood glucose concentrations between 70–180 mg/dl (4–10 mmol/l) and negative ketones during illness; iii) to never discontinue insulin administration, since increased insulin requirements are expected in case of fever; to watch and support hydration, especially in the presence of fever and/or vomiting/diarrhea; and iv) to treat the underlying sickness and symptoms. Should there be signs of metabolic decompensation (namely dehydration, hyperglycemia with persistent ketosis, hyperventilation, exhaustion), urgent assessment by health care providers is deemed necessary [13]. A pediatric case series from Italy reports delayed access to health care secondary to fear of COVID-19, including two cases of type 1 DM onset with severe ketoacidosis requiring intensive care unit (ICU) admission due to late access to the hospital [23].

Adrenal Insufficiency (congenital and acquired primary adrenal insufficiency, secondary adrenal insufficiency, adrenal suppression after long-term steroid medication)

To date, there is no evidence that patients with adrenal insufficiency are at increased risk of contracting COVID-19. Nonetheless, patients with primary adrenal insufficiency (e. g., congenital adrenal hyperplasia) are slightly more susceptible to infections in general. This may partly be explained by the impaired natural immunity function characterized by a defective action of neutrophils and natural killer cells, which is known to be associated with primary adrenal insufficiency [24]. Furthermore, susceptibility to infections may also be explained by an insufficient increase of the hydrocortisone dosage at the beginning of an infection. Therefore, recommendations suggest that, if asymptomatic, children should remain on regular replacement doses of hydrocortisone and not increased doses. If symptoms suggestive of COVID-19 develop (fever, cough, dyspnoea, vomiting, diarrhoea), the “sick day rules” are recommended,

including immediately increasing the hydrocortisone doses (e. g., > 38 °C: 2-fold increase, > 39 °C: 3-fold increase) until the fever has subsided and adding an extra doubled dose [12]. Adequate hydration is also recommended, particularly in the presence of fever [12]. In the case of more severe symptoms, the health care team should be contacted for further advice and if the medication cannot be orally received due to vomiting, urgent medical care should undoubtedly be sought and parenteral glucocorticoids initiated in the form of intramuscular injection of hydrocortisone, accompanied by glucose, preferably in the form of oral gel [25].

Among patients with COVID-19, it is of major importance to recognize those with a history of possible adrenal suppression secondary to prior exposure to glucocorticoids for more than 3 months, so that parenteral treatment with glucocorticoids is considered [22]. Physiological stress doses of hydrocortisone and not pharmacological doses are recommended in this case.

Of note, it has been proposed that all the patients receiving corticosteroids for other medical reasons and not because of adrenal insufficiency or adrenal suppression, should be considered as high-risk patients for contracting COVID-19 and experiencing more severe symptoms [22]. Supraphysiologic doses of glucocorticoids may further increase susceptibility to COVID-19 due to their immunosuppressive effect.

Hypopituitarism

Children diagnosed with hypopituitarism are not at increased risk for COVID-19. As a significant percentage of these patients have secondary adrenal insufficiency, the same recommendations apply as for children with adrenal insufficiency [12]. Identical advice applies for each of the endocrine deficiencies involved.

Particular attention should be given to children with craniopharyngioma, the most common pediatric tumor in the hypothalamic and pituitary region and an important cause of hypopituitarism in children. In this case, the endocrine deficiencies are attributable to either the tumor itself, due to pressure on the pituitary and hypothalamus, or the operative procedure and/or irradiation following the diagnosis. Tumor location or surgical intervention are also the etiology of the hyperphagia observed in these patients [26], which results in hypothalamic obesity and increased morbidity and mortality rates due to the associated metabolic derangement. Due to the complicated pre- and post-operative course of the disease, the treating health care team should be aware of a possible infection with COVID-19, in order to guide treatment decisions.

Diabetes Insipidus

In addition, in the case of the presence of both secondary adrenal insufficiency and diabetes insipidus, it is important that medications for both conditions are always received. Also, careful monitoring of fluid intake and urinary losses is important, as well as judicious replacement of water, in order to avoid hypo- or hypernatremia, particularly in the presence of fever, tachypnea and the co-existence of impaired ability for fluid intake due to altered level of consciousness [27].

Since hydrocortisone is essential for the clearance of excess water through the kidneys, it should be administered at adequate doses to avoid accumulation of fluid, particularly if the child also receives des-

mopressin. Therefore, the dose of hydrocortisone should be immediately doubled in the presence of a symptomatic COVID-19. In such patients, urination should be monitored closely. If urination is reduced or stopped, desmopressin should be discontinued. If the child has an intact thirst mechanism, fluid intake will be adequate. If the thirst mechanism is not intact, maintenance fluids should be administered, with additional fluids to replace urinary losses [27]. The therapeutic team should be aware of the patient's condition in this scenario.

Thyroid Disorders (Hypothyroidism/Hyperthyroidism)

Children with thyroid disease, even if poorly controlled, are not at increased risk of COVID-19 and no extra measures are needed than those that apply to the general population [28]. However, patients with poorly controlled thyroid disease (e. g., thyrotoxicosis) may be at higher risk of complications from an infection [28]. Furthermore, it is well established that autoimmune thyroid disease does not cause immunosuppression [28]. Medications used for the treatment of thyroid disease, including thyroxine, carbimazole, methimazole, and propylthiouracil do not affect the immune function and do not pose the patients at a heightened risk for COVID-19 [28].

Recommendations from the British Thyroid Association about adults with thyroid eye disease who are on high-dose steroid or mycophenolate or rituximab and are considered as immunocompromized and susceptible to infections, include following the confinement and health protection measures very strictly [28]. Depending on the severity of the eye problem, high-dose steroids or immunosuppressives might need to be suspended [28]. No different recommendations exist for the pediatric population.

Furthermore, for patients who had radioiodine therapy or thyroid surgery for benign thyroid disease, no evidence is available to suggest that these patients are at increased risk of a viral infection [28].

With regard to the treatment when COVID-19 is confirmed in an adult or a pediatric patient, the normal dose of thyroxine should be continued. If gastrointestinal disturbances are severe, the dose may need to be repeated when feasible [28]. In the case of symptoms that may be related to COVID-19, patients with hyperthyroidism who are on anti-thyroid drugs should immediately suspend the medication and be tested for possible agranulocytosis by performing a full blood count, as the symptoms of agranulocytosis (sore throat, mouth ulceration, fever, flu-like illness) may overlap with those from COVID-19 [28].

Hypoglycemia (hyperinsulinemic hypoglycemia and ketotic hypoglycemia)

Receiving the proper medications and regular glucose monitoring should be ensured in children who are prone to have hypoglycemia during illness, especially those with ketotic hypoglycemia or hyperinsulinemic hypoglycemia. These children are not considered vulnerable, with the exception of a minority that receive Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor with immunosuppressive action. For the latter, strict hygiene and confinement measures should be taken during the COVID-19 pandemic. Adequate hydration (small volumes of fluid at frequent intervals) is also highly recommended [29]. In addition, side effects of the medications used to treat hyperinsulinemic hypoglycemia (e. g., diazoxide: water retention and pulmonary hypertension; somatostatin

analogues: cardiac arrhythmias and cardiac conduction disorders) should be taken into consideration in the case of COVID-19.

During this pandemic, children should follow the “sick-day rules” for hypoglycemia, which include close monitoring of glucose levels, adequate hydration, ensuring availability of medications and emergency regime, preferably in the form of a glucose gel/juice or glucose powder solution, and contacting the medical team in the instance of hypoglycemia of unusual frequency and severity.

Cushing Syndrome

Cushing syndrome represents an immunocompromized state, which can increase susceptibility to infections, hence COVID-19 also [30]. Susceptibility to opportunistic infections is caused by prolonged exposure to elevated cortisol concentrations. Glucocorticoids have a potent anti-inflammatory and immunosuppressive action, resulting in the suppression of cellular and humoral immune functions. Hyperglycemia in patients with Cushing syndrome resulting from increased insulin resistance, further contributes to immunosuppression. The higher the concentrations of circulating cortisol, the more severe the infections. Therefore, adherence to preventive self-protective measures, complying with the regular treatment and seeking medical advice in the case of even minor symptoms, is crucial.

Hypoparathyroidism

Children with hypoparathyroidism have no susceptibility to infections, unless hypoparathyroidism exists in the context of 22q11.2 deletion syndrome, which in the majority (64–77%) of the patients, encompasses immunodeficiency of variable severity. In the case of 22q11.2 deletion syndrome, the predominant cause of immunodeficiency is compromised T cell production due to thymic hypoplasia or aplasia, and recurrent infections of the respiratory tract, albeit usually not severe, they represent a common clinical manifestation. Therefore, susceptibility to COVID-19 is increased and special attention should be paid during COVID-19 infection.

If COVID-19 is confirmed and the child is unable to receive oral tablets, parenteral treatment should be initiated with intravenous calcium. Of note, hypocalcaemia may worsen breathing capacity due to weakening of the chest muscles [31].

Obesity

It is well established in the literature that excess weight promotes immune dysregulation and chronic inflammation, which result in the cytokine storm associated with the Acute Respiratory Distress Syndrome seen in influenza and other viral infections [32]. Limited data is available regarding the impact of COVID-19 in patients with obesity. It has been reported that severe obesity may be a risk factor for respiratory complications during the course of COVID-19 [12]. It has also been reported that young people suffering from severe obesity may develop destructive alveolitis resulting in respiratory failure and death (author's personal experience) [16]. In addition, it is well known that obesity is associated with sleep apnoea syndrome and surfactant dysfunction, which may worsen the clinical course of COVID-19 infection. Therefore, it is important that children with obesity, and those with severe obesity in particular, strictly follow self-protective strategies to avoid COVID-19.

For these patients, COVID-19 may have an additional negative impact on obesity itself. Due to the confinement measures that include school closure and prohibition of outdoor exercise or exercise in a gymnasium, regular exercise may be restricted. Furthermore, home restriction can lead to increased caloric intake and especially of calorie-dense comfort foods. Additionally, sedentary activities and screen time are expected to expand [33]. For these reasons, it is estimated that the COVID-19 pandemic may result in exacerbation of childhood obesity [33]. It is important that these patients continue exercise through home-based exercise programs and that they follow a well-balanced diet.

COVID-19 and Psychological Consequences in Children and Adolescents with Endocrine Disorders

It becomes evident that as the COVID-19 pandemic peaks, it is causing widespread concern, fear and stress. This is understandable due to the high morbidity and mortality rates of the disease in adults, the restrictive preventive measures that result in a drastic change of everyday life, affecting work, education, social life, entertainment, and the long period sustained fear of the unknown outcome of this outbreak [34–40].

The impact of the COVID-19 pandemic to the pediatric population may be worsened by the co-existence of a chronic disease. It is well established that a chronic illness may impair the immunologic reaction of an individual to infections. Specifically, chronic stress from a permanent disease may erode immunologic mediators, increase risk of infections and cytokine production and decrease antibodies and defensive mechanisms [41–43].

On the other hand, children suffering from a chronic disease are already experiencing higher stress and additional pressure compared to healthy children due to the need for compliance to chronic medication and regular doctor visits, but also because of school disruption and fear of death [44–46]. Children's stress due to a chronic endocrine disease can be magnified by a pandemic, as children are likely to experience anxiety and fear of death or of their relatives dying and they may also see the supportive family structure previously provided, to fall apart. Of note, parental anxiety about children exposure to COVID-19, potentially further complicating their chronic endocrine disease, should not be ignored. This may lead to retaining children out of school, thereby adding to social marginalization of the patients as well as aggravating their feeling of distress and impacting their wellbeing.

Hence, therapeutic teams should be aware of the possible psychological consequences of the current pandemic and monitor psychological responses, even screen for psychological distress using psychometric tools, such as validated questionnaires. This could promote the implementation of stress management strategies and interventions in order to avoid potential future psychological distress that may affect the feeling of wellbeing and adherence to treatment, allowing an optimal control and outcome of the endocrine disease.

Conclusions

The COVID-19 pandemic represents the greatest global public health care crisis since the influenza outbreak in 1918. Thus far, the available data on the impact of COVID-19 on patients with endocrine disorders is reassuring for the majority of the cases. In case of COVID-19 infec-

tion, “sick day” rules apply. However, lack of sufficient and reliable data, particularly for the pediatric population, should prompt health care providers to be more vigilant in the assessment of children with endocrine disorders and concerning symptoms, such as fever and dyspnea.

Author Contributions

PS contributed to the conception of the manuscript. EK and MG designed and drafted the article. EK, MG, and PS revised the content and gave final approval of the version.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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