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Commentary

The impact of COVID-19 pandemic on the diagnosis and management of inborn errors of metabolism: A global perspective

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ABSTRACT

Quantitative estimates for the global impact of COVID-19 on the diagnosis and management of patients with inborn errors of metabolism (IEM) are lacking. We collected relevant data from 16 specialized medical centers treating IEM patients in Europe, Asia and Africa. The median decline of reported IEM related services in March 1st-May 31st 2020 compared to the same period in 2019 were as high as 60–80% with a profound impact on patient management and care for this vulnerable patient group. More representative data along with outcome data and guidelines for managing IEM disorders under such extraordinary circumstances are needed.

SARS-COV-2 virus has impacted health care systems all over the world in an unprecedented manner in recent history. Until August 5th 2020, over 18,300,000 COVID-19 cases have been confirmed with more than 695,000 associated deaths worldwide, and the daily global numbers are still rising [1].

Inborn errors of metabolism (IEM) are a vast group of genetic disorders caused by pathogenic variants in genes controlling enzymes, structural proteins or cofactors affecting various metabolic pathways [2]. Although most IEM are individually rare, more than 1000 well-characterized IEM disorders have been recently classified [3], with an estimated overall incidence of 1:800–2500 live births [2]. Despite the great diversity in the clinical presentations and management strategies of different IEM, they mostly share in common their need for challenging diagnostic procedures requiring specialized labs and for

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multidisciplinary collaborative medical teams for acute and long-term treatment and patient monitoring. Children and adults with an IEM are particularly at higher risk of morbidity and mortality when infected with SARS-CoV-2 due to their chronic preexisting conditions and potentially vulnerable immune system [4,5]. Furthermore, due to the pandemic itself or due to the forced reorganization of health care system activities needed to face the pandemic in many countries [6], medical services dedicated to IEM patients have also been impacted.

Current available data about the impact of COVID-19 on patients suffering from inborn errors of metabolism are very scarce. Published data concerning the pandemic are mainly reports describing expert opinions about management challenges and guidelines for IEM disorders [7–10], and few patient surveys investigating management problems and satisfaction [11–13]. Case reports of IEM patients with confirmed viral infection have also been published recently [13,14].

In an attempt to provide quantitative estimates for the effects of COVID-19 pandemic on different aspects of services provided to IEM patients, we created a survey dedicated to physicians and scientists involved as service providers in managing and monitoring IEM patients during the period extending from March 1st to May 31st of 2020. We further compared the statistics of patients managed at these centers during the three months period with those during the same period in 2019, in order to draw a more accurate picture for the impact of the pandemic over IEM patients globally. An email invitation was sent out to 60 centers for IEM. Twenty-one expressed interest to participate and 15 collaborated actively.

Relevant data were collected from 16 dedicated care centers for the diagnosis and management of IEM disorders from 11 countries in Europe, Asia and Africa. The participating centers collectively cared for approximately 8500 IEM patients (median 450, quartiles 215–1075 patients). Thirteen centers (81%) provided diagnostic work-up and clinical care to metabolic patients; these patients suffered from inborn metabolic disorders from the full spectrum of IEM. Two centers were specialized centers for lysosomal storage disorders and one was a specialized center for ketone body metabolism and organic acid disorders. Regarding the age distribution of patients, all 16 centers (100%) provided clinical services to neonatal and pediatric age groups, while 12 centers (75%) provided their services to adults. Nine of the participating centers (56%) also performed newborn screening for various IEM, particularly those detected by tandem mass spectrometry, such as aminoacidopathies, organic acid disorders and fatty acid oxidation defects.

Among the participating centers only two showed comparable or increased patients statistics in the target period in 2020 compared to 2019. The remainder showed considerable quantitative declines in almost all aspects of the services provided to IEM patients. Table 1 describes the summary statistics of the quantitative data obtained in the survey.

The majority of IEM centers showed considerable disruptions in the numbers of working days affected by the pandemic (median 55%, quartiles 8–79%), leading to the closure of activities in many outpatient clinics during a considerable part of the target period up to 90% in one center. However, three centers reported no disruptions at all and another two centers reported disrupted working days below 10%. On the other hand, the percentages of affected personnel at IEM centers either infected and/or in quarantine or those who requested a leave of absence to take care of children or other family members during the pandemic were relatively limited (median 15%, quartiles 5–24%). Only two centers reported absent personnel percentages above 50%. This is indicative of the widely varying effects of the pandemic on different countries, regions and cities, and also of the different national and local policies followed by different centers. Furthermore, the chosen period to collect data in 2020 (March 1st- May 31st) represented the peak of the pandemic as of yet in most participant countries, but not all of them.

The median decline of numbers of reported IEM related services by survey participants in March-May 2020 compared to the same period in 2019 were mostly in the range of 60 to 80% (Table 1). Those include the numbers of actual patient visits to the participating centers, which were in total 865 patient visits in March-May 2020 (median 61, quartiles 23–85 visits per center) compared to 2902 patient visits in the same period in 2019 (median 138, quartiles 85–297 visits per center), $P = 0.009$. There was no significant difference between the effects on routine scheduled visits (77% median decline) and first time visits (72% median decline). The numbers of laboratory samples obtained from IEM patients were decreased by a median of 60%, while the numbers of established new metabolic diagnoses were decreased by a median of 80% (total 47 new diagnoses in March-May 2020 compared to 195 in March-May 2019). The latter is one of the most informative statistics of the pandemic's impact on the IEM field.

The least affected services during the target period were understandably the number of patients coming for emergency visits, such as decompensated children (24% median decline) and patients coming to receive specialized treatments, such as enzyme replacement therapy (37% median decline). In contrast, the most affected services were those needing direct physical interaction, such as physiotherapy (100% median decline) or facial contact with the physician, such as psychological support (86% median decline).

Newly diagnosed IEM during March-May 2020 included phenylketonuria being the most common IEM disorder reported in eight participating centers. Other diagnosed disorders included organic acid disorders, such as glutaricaciduria type 1, methylmalonic acidemia and propionic acidemia in seven centers, lysosomal storage disorders, such as Gaucher, Fabry, Krabbe disease and Hurler syndrome in six centers, other aminoacidopathies, such as MSUD and urea cycle disorders in five centers, fatty acid oxidation defects, mainly MCADD, in four centers, mitochondrial disorders, such as COX deficiency, MELAS and Leigh syndrome in three centers, carbohydrate metabolism disorders mainly galactosemia in three centers, and finally vitamin metabolism disorders were reported in two centers. 21/47 (45%) of the newly diagnosed patients were diagnosed on newborn screening, while in 26 patients (55%) diagnosis was clinically/biochemically based. Among those patients, 24 were infants or children and 2 were adults.

Among decompensated patients presenting to the participating centers mitochondrial disorders were the most commonly reported in six centers, followed by urea cycle disorders in five, organic acid disorders in four, lysosomal storage disorders in three and fatty acid oxidation defects in two centers. Only 2 of the 38 decompensated patients (5%) were confirmed with COVID-19 infection. Both patients suffered from Gaucher's disease and one of them succumbed to his illness. A third PKU patient was also confirmed with COVID-19, but did not suffer from any serious complications and was self-isolating at home until recovery.

Other measures that may explain the decline in the flow of IEM patients and the services provided to them were also investigated in the survey. 88% of participating centers (14/16) reported limiting the numbers of routine patients' visits per day by the hospital administration to minimize patient/patient and doctor/patient contact along with potential transmission of infection. This is of course, while taking all the precautionary measures against viral transmission in all centers from an early stage of the pandemic. 20% of participating physicians (3/15) reported that they have arranged the referral of some of their patients to other IEM clinics and centers within the same city or country during the target period. The inflow of patients in 93% of participating centers (14/15) has been affected by travel restrictions enforced by the governments in their countries. In nine reporting centers the rate of missed follow-up visits during the target period has escalated quickly to a median of 3.2-fold (quartiles 1.6 to 9.4-fold) of the normal rate of missed scheduled visits in the year before. Travel restrictions played a role in this rate, including disruption of public transport services; however, the detrimental factor in missing scheduled routine visits was probably the fear of the patient and the family from going to the hospital during a pandemic [11]. 43% of participating physicians (7/16)

Table 1
The impact of COVID-19 pandemic on the diagnosis and management of patients with IEM.

	Percentages of change in the numbers reported by individual IEM centers (March-May 2020 compared to March-May 2019) Median (25th / 75th percentiles)	Total numbers reported (2019)	Total numbers reported (2020)	Percentages of change in total numbers reported (March-May 2020 compared to March-May 2019) (%)	Number of feedbacks
Numbers of patients' total visits	−67% (−79% / −39%)	2902	856	−70%	15
Numbers of patients who visited the center for first time	−72% (−86% / −48%)	543	171	−68%	15
Numbers of patients who visited the center for follow up	−77% (−84% / −37%)	2359	685	−71%	15
Numbers of emergency visits*	−24% (−81% / +19%)	53	38	−28%	13
Numbers of patients whose samples were sent for laboratory analysis	−60% (−83% / −40%)	1641	461	−72%	12
Numbers of patients with established new diagnoses	−80% (−87% / −39%)	195	47	−76%	12
Numbers of patients who received specialized treatments**	−37% (−67% / −19%)	665	398	−40%	13
Numbers of patients who received blood transfusion or similar procedures***	−50% (−75% / −42%)	14	10	−29%	5
Numbers of patients who received physiotherapy	−100% (−100% / −95%)	318	20	−94%	8
Numbers of patients who received nutritional support	−82% (−92% / −30%)	663	269	−59%	11
Numbers of patients who received psychological support	−86% (−97% / −38%)	488	161	−67%	9
Numbers of patients referred for other clinical consultations within the same institute****	−71% (−81% / −56%)	215	65	−70%	7
	March 1st to May 31st 2020				
Numbers of working days disrupted due to the COVID-19 pandemic	55% (8% / 79%)				14
Numbers of medical staff/employees at IEM centers affected by COVID-19 infection or had a leave of absence due to a pandemic related issue	15% (5% / 24%)				13

* e.g. referrals to the ICU for a decompensated IEM condition or another life threatening condition.
** e.g. enzyme replacement therapy, substrate reduction therapy, dietary formula or a specialized drug.
*** e.g. transfusion of plasma or platelets, IV immunoglobulins or plasmapheresis.
**** e.g. ophthalmology, nephrology, cardiology, gastroenterology, endocrinology, dermatology.

reported that patients or family members contacted them or their colleagues at the clinics asking for advice for being diagnosed or suspected of COVID-19. The actual numbers of IEM patients confirmed with COVID-19 in participating centers were not investigated in this study.

50% of participating centers (8/16) reported delayed scheduling or receiving the results of investigational services, such as laboratory and radiological investigations. A considerable delay was defined as more than 25% increased time compared to the normal situation. Similarly, 50% of participating centers (8/16) reported that the external technical support for instruments was delayed or interrupted due to a pandemic related issue. Moreover, 31% of centers (5/16) reported that the manufacturer supply of specialized chemicals, kits or consumables needed for the laboratory or radiological services was interrupted during the target period. On the other hand, only 20% of centers (3/15) reported that the manufacturer supply of one or more specialized drugs or dietary formulas was interrupted.

Measures that may help in closing the gap of the defective services were also reported. Phone calls and online communication platforms were used to schedule regular meetings to care and give advice to IEM patients in 69% of reporting centers (11/16), among those 3 centers were already applying some sort of online service to the routine care for patients before the pandemic. Dietary formulas and drugs that do not need in-patient care during administration were home delivered to many IEM patients during the pandemic in as many as 80% of reporting centers (12/15). For laboratory analysis, some patients were asked to send dried blood spots from home to minimize patient travel and potential exposure. This was particularly feasible for certain analytes/IEM with valid methodology in dried blood spots, such as those already applied in newborn screening.

Recent evidence suggests that susceptibility to severe respiratory distress and life threatening complications of SARS-COV-2 could have a genetic background [15,16]. A new hypothesis backed by genome-wide association studies even suggested that the susceptibility of severe SARS-COV-2 infection may be caused, at least in part, by a monogenic inborn error of metabolism. It proposed that low activity of the proline transporter SIT1, caused by pathogenic variants in *SLC6A20,* altering proline concentration at sites of protein folding, may lead to an exaggerated unfolded protein response in helper T-lymphocytes and macrophages, thus contributing to the characteristic cytokine storm accompanying severe COVID-19 infections [17].

It is clear by now that the impact of SARS-COV-2 virus is truly global. It dominated the health care scene in most countries in an abrupt and unprecedented way. Although its impact on the services provided for IEM patients was significant as documented in our report, including the potential risk of missed or delayed diagnoses, compensatory measures were developed to combat its harmful effects and many health care systems are currently in the recovery phase. However, in order to minimize such harmful effects in future similar outbreaks, a well orchestrated response between medical IEM communities and health care policy makers should be planned ahead. Furthermore, law and medical policy experts should collaborate to issue new directives in order to legalize telemedicine consultation as a recognized medical activity in countries where it is not. Finally, clear guidelines for patient management in each IEM disorder or group of disorders should be prepared to consider such circumstances.

Declaration of Competing Interest

The authors declare no conflict of interest regarding the current study.

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