

Successful Remote Monitoring During COVID-19 Pandemic of Patients with Inborn Errors of the Amino acid Metabolism not including PKU from a Single Reference center using Filter Paper Samples

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Abstract

Background. Patients with inborn errors of metabolism (IEM) pose specific management challenges, considering their multisystem involvement. Among them, children and adults with organic acidemias (OA) and other disorders of the amino acid metabolism have a high risk for severe metabolic events that need to be recognized and promptly treated, and therefore require frequent clinical and biochemical evaluations. The novel highly pathogenic SARS-CoV2 virus appeared in Europe in the first trimester of 2020. This pandemic has a huge impact on the health care systems all over the world, interrupting the follow-up of many chronic diseases. For metabolic patients, travel to reference units may be reduced due to mobility restrictions but more importantly, attendance to medical facilities can be a risk of infection that can be a danger in itself but also trigger a metabolic decompensation.

Methods. During the first coronavirus disease (COVID-19) outbreak in Spain from March to June 2020, we designed a model of remote monitoring of our patients with amino acid disorders using telephone and/or online clinical assessments and using filter paper samples to continue the biochemical control.

Results. Fourteen patients with inborn errors of amino acid metabolism other than PKU received filter papers and instructions to collect blood and urine samples home and send them to our reference laboratory.

Conclusions. Considering the COVID19 pandemic evolution, new strategies to ensure IEM patients have an evaluation continuity need to be implemented. We believe that blood and urine filter paper biochemical follow-up, together with online or telephone clinical assessments, can help minimize the need for in-hospital visits.

Introduction

During the winter of 2019 a novel highly pathogenic coronavirus strain called SARS-CoV2 emerged in Wuhan, China, and rapidly spread all over the world, causing more than a million deaths so far (WHO Coronavirus Disease (COVID-19) Dashboard, 2020). The consequences of the SARS-CoV2 pandemic is not limited to the people infected by the virus. Fear of SARS-CoV2 infection motivated by hospital clusters made both urgent and chronic patients avoid seeking medical attention (1) (2). Also, mobility restrictions and the collapse of the healthcare systems made live consultations and blood analysis extremely difficult.

People with preexisting medical conditions seem to be at higher risk for severe forms of COVID-19 (3). Among them, patients with inborn errors of metabolism (IEM) pose specific management challenges, considering the multisystem involvement of many of them. This is especially true for patients with pulmonary impairment or alterations of the immune system (splenectomy, primary immunodeficiencies or neutropenia) (4) (5) (6). Even if they are not at risk or do not develop severe forms of COVID-19, any infection can trigger a metabolic decompensation that has its own important morbi-mortality and that needs to be promptly recognized and treated.

Phenylketonuria (PKU) is the most common inborn error of amino acid metabolism. Other diseases frequently followed in metabolic centers include organic acidemias (OA), maple syrup urine disease (MSUD), glutaric aciduria (GA), tyrosinemia or homocystinuria, among others. Inborn errors of amino acid metabolism are genetic conditions with varying clinical presentations, but they share common general features. Many present clinically as a life-threatening episode consisting in severe metabolic acidosis, hyperammonemia, hypoglycemia or hepatic alterations; others might present with acute or chronic neurological involvement and some might have nonspecific clinical manifestations such as failure to thrive or recurrent vomiting, among others. Nowadays, most can be diagnosed by the neonatal screening. Treatment of these disorders is based in most cases in dietary management that includes a protein restrictive diet combined with a special amino acid mixture (SAAM) that contains all amino acids except those prior to the metabolic block. Supplementation might be necessary to avoid the deficiency of the amino acid that has become essential due to the enzymatic defect (7). Treatment might also include specific cofactors such as carnitine, glycine or different vitamins (8) (9) (10) (11). Dietary treatment avoids the accumulation of toxic metabolites and is generally effective in greatly improving the outcome (12), but even well controlled patients tend to develop different physical or neurological long-term complications. All inborn errors of amino acid metabolism share the need for frequent clinical and biochemical monitoring by a multidisciplinary trained team in order to adjust treatment. However, further acute metabolic crisis can be triggered by situations that induce protein catabolism such as intercurrent infections, immunization, surgery, prolonged fasting or certain medications such as the use of high doses of glucocorticoids (13). Depending on the disease, new crisis can be life-threatening, but in all patients frequent bad metabolic controls lead to increased long-term complications. Patients and their families should be trained to early recognize risk situations and implement treatment changes to avoid metabolic decompensations.

The metabolic unit of the Hospital Ramon y Cajal in Madrid, Spain, is a national reference center for both children and adults with inborn errors of metabolism. It is currently involved in the active follow-up of more than 700 patients with all kind metabolic diseases including amino acid, fatty acid or carbohydrate metabolism, lysosomal storage diseases or mitochondrial cytopathies. The hospital is a 3rd level

university facility for both children and adults with over 1500 beds and all recognized medical and surgical specialties. It houses not only ours but several other national reference centers for different pathologies.

Spain was one of the earliest and most affected countries during the first wave of COVID-19 that spread all over the world in the first half of 2020 (14). During this period, Madrid, in particular, had the highest rate of infections and hospitalizations in our country. The activity of our hospital during the months of March to May was completely shifted to attending COVID-19 patients. All but one of the physicians of the metabolic unit were transferred to the attention of COVID-19 patients.

We had to adapt our activity to the new conditions. In order to comply with government indications and to prevent the unnecessary exposure to the virus of our patients, live follow-up evaluations were suspended, and patients' consultations were mainly done by phone or via email. Biochemical follow-up became a challenge. Metabolic control using filter paper samples in phenylketonuria has been established for decades. In recent years, measurements of phenylalanine, tyrosine and succinylacetone in tyrosinemia patients has become a common practice. Based on the good results for diagnosis of the neonatal screening programs, and our previous reported experience in long term follow up of propionic acidemia using filter paper samples instead of the usual liquid plasma or urine samples (15), we designed a model of remote monitoring for all our amino acid disorder patients. We report the results of this program from March to June 2020 for these patients, excluding those with PKU in which this is the usual process.

Materials And Methods

All programmed visits for the patients were maintained with their usual frequency, depending on the age or needs of each patient, but they were done via phone or email. Additional calls were attended if necessary. Live consultations were reduced to a minimum but were maintained in very specific situations such as very young children or pregnancies. Emergency attention for adults was maintained and children consultations that could not be solved telematically were referred to one of the only two children's hospitals that were still operational in the city.

Patients were reminded of their emergency recommendations and received both oral and written instructions in case of coronavirus or other concurrent infections, personalized to their disease and situation, having in mind that many of our patients were from different regions of the country and therefore would have difficulties to reach our hospital if needed. The use of capillary glucose and/or ketone body detection was encouraged in those patients that had these devices available.

Filter papers were sent to the patients together with instructions on how to collect the blood and urine samples. Dried blood spot (DBS) and dried urine spot (DUS) were collected by the patient's family in their homes and sent to the laboratory by regular mail.

All laboratory measurements were completed in our ERNDIM approved, reference laboratory (CEDEM, Centro de Diagnostico de Enfermedades Moleculares, Universidad Autonoma, Madrid). Acylcarnitines and amino acids in DBS were determined as their butyl esters by flow injection analysis-tandem mass spectrometry with stable isotope dilution (16) (17). Simultaneously, acylcarnitines were acquired by precursor ion scan of m/z 85 mode and amino acids by neutral loss of 102 amu, except basic amino acids, glycine, leucine and isoleucine which were acquired by MRM (multiple reaction monitoring). Organic acids and acylglycines in DUS were analyzed by HPLC-tandem mass spectrometry and MRM mode (16). In addition, an ACE C18 HPLC column was included to resolve MRM isomers (18). Succinylacetone in DBS was analysed by tandem mass spectrometry in MRM mode with stable isotope dilution ($^{13}\text{C}_5$ -succinylacetone) after butylation.

Results

During this period, 14 patients aged 1 to 24 years with different amino acid inborn errors of metabolism other than PKU required monitoring by our metabolic unit: 4 patients with propionic acidemia (PA), 2 patients with *cbfC* type methylmalonic acidemia (*cbfC* type MMA+Hcty), 2 patients with isovaleric acidemia (IVA), 2 patients with maple syrup urine disease (MSUD), 1 patient with glutaric aciduria type I, 1 patient with glutaric aciduria type III, 1 patient with hereditary tyrosinemia type I (HT type 1) and 1 patient with classic homocystinuria. Other patients had had recent live consultations and/or biochemical analysis was not deemed necessary during this period. The demographic and clinical characteristics of these patients are presented in Table 1.

Table 1
Clinical and demographic characteristics of the patients.

March-June 2020 (COVID-19 lockdown)							
Diagnosis	Age	Age at diagnosis	Chronic complications	Current treatment	Follow up samples	Complications	Treatment changes
1. Propionic acidemia	14y	Neonatal (hyperammonemia)	Recurrent pancreatitis	NP: 0.5 g/kg/day SAAM: 1.7 g/kg/day Carnitine Ile supplements	Regular control 1 sample DBS (acylcarnitines, amino acids) DUS (organic acids)	None	None
2. Propionic acidemia	8y	Neonatal (screening)	Autism	NP: 1 g/kg/day SAAM: 2 g/kg/day Carnitine Ile supplements	Regular control 1 sample DBS (acylcarnitines, amino acids) DUS (organic acids)	None	None
3. Propionic acidemia	12y	3 months (hyperammonemia)	Severe neuromotor delay	NP: 0.6 g/kg/day SAAM: 2 g/kg/day Carnitine Ile supplements	Regular control 1 sample DBS (acylcarnitines, amino acids) DUS (organic acids)	None	None
4. Propionic acidemia	10y	Neonatal (hyperammonemia)	Severe neuromotor delay Anemia Neutropenia	NP: 0.6 g/kg/day SAAM: 2 g/kg/day Carnitine Ile supplements	Regular control 1 sample DBS (acylcarnitines, amino acids) DUS (organic acids)	Acrodermatitis (diaper rash)	Initiation of Val supplements
5. Isovaleric acidemia	15y	Prenatal (affected sibling)	None	NP: 1 g/kg/day Carnitine Glycine	Regular control 1 sample DBS (acylcarnitines, amino acids) DUS (organic acids)	None	None
6. Isovaleric acidemia	24y	2 years (recurrent vomiting)	None	NP: 1.5 g/kg/day Carnitine Glycine	Regular control 1 sample DBS (acylcarnitines, amino acids) DUS (organic acids)	None	None
7. Glutaric aciduria type I	18y	1 years (dystonia)	Severe neuromotor delay Dystonia	NP: 1.5 g/kg/day Carnitine	Regular control 1 sample DBS (acylcarnitines,	None	None

					amino acids)		
8. Glutaric aciduria type III	16y	Neonatal (hyperammonemia)	None	NP: 1 g/kg/day SAAM 1 g/kg/day Carnitine	Regular control 1 sample DBS (acylcarnitines, amino acids) DUS (organic acids)	None	None
9. Cobalamin deficiency type <i>cb/C</i> (MMA + Hcty)	7y	Neonatal (hyperammonemia)	Severe neuromotor delay Epilepsy Cardiomyopathy	NP: 2 g/kg/day Vitamine B12 Carnitine Betaine	Febrile episode and control 2 samples DBS (acylcarnitines, amino acids) DUS (organic acids)	Lactic aciduria No clinical changes	Stop of protein intake and rise of caloric intake during 48 hours
10. Cobalamin deficiency type <i>cb/C</i> (MMA + Hcty)	9y	Neonatal (encephalopathy, rash and cardiomyopathy)	Maculopathy Cardiomyopathy ADHD	NP: 1 g/kg/day SAAM: 1 g/kg/day Vitamine B12 Carnitine Betaine	Regular control 1 sample DBS (acylcarnitines, amino acids) DUS (organic acids)	None	None
11. Maple syrup urine disease	1y	Neonatal (screening)	None	NP: 1 g/kg/day SAAM: 1 g/kg/day Thiamine	Regular control 1 sample DBS (acylcarnitines, amino acids)	None	None
12. Maple syrup urine disease	8y	Neonatal (screening)	None	NP: 0.7 g/kg/day SAAM: 1.7 g/kg/day Thiamine	Regular control 1 sample DBS (acylcarnitines, amino acids)	None	None
13. Tyrosinemia type I	8y	Neonatal (screening)	ADHD Speech delay	NP: 0.8-1 g/kg/day SAAM: 1-1.5 g/kg/day	Regular control 1 sample DBS (succinilacetone, amino acids)	None	None
14. Homocystinuria	3y	Neonatal (screening)	None	NP: 1 g/kg/day SAAM: 1.5 g/kg/day Vitamine B12 Folinic acid Betaine	Regular control 1 sample DBS (amino acids)	None	None
DBS: dried blood spots; DUS: dried urine spot; SAAM: special amino acid mixture; NP: natural protein; ADHD: attention deficit/hyperactivity disorder; Ile: isoleucine; Val: Valine; MMA+Hcty: methylmalonic acidemia with homocystinuria							

During the follow up we continually assessed patients by phone or email so the patients received the same number of virtual visits as usual (1 medical visit each 3-6 months if no emergency situations arise). No patient needed hospital admission for severe metabolic crises. One of

the patients with cobalamin metabolism type C deficiency had a concurrent mild non-SARS-CoV2 respiratory infection and her parents began the emergency regimen at home with full control of symptoms in 48 hours. The DBS/DUS sample taken at the time detected a mild metabolic decompensation (lactic aciduria of 543 mmol/mol creat (VN: 61±41)) but no further measures were necessary and the biochemical control a few days later was normal. Another male PA patient called and sent pictures because of diaper rash. He already was on isoleucine supplements, so, based on the very low DBS valine levels (26 µmol/L (VN: 102±23)), we decided to supplement with this amino acid. There was an important clinical improvement in a few days and the metabolic control done a few months later was adequate. None of the other patient had any significant change in their clinical or metabolic status, so they did not require any treatment modifications during this period other than small adjustments done due to weight gain.

Discussion

Many aspects interfere with IEM care during the COVID-19 pandemic. Newborn screening programs (NBS) had to be adapted in many countries. In some cases, early discharge from maternity wards required sending nurses to the homes of newborn children to collect the samples; in other countries such as China, consensus recommends that neonates whose mothers are suspected or diagnosed of COVID-19 would not be performed routine NBS, and testing should be delayed until their mothers were released from a 14-day quarantine and had two negative results of 2019-nCoV's RNA testing (19).

Regarding the long-term follow-up of IEM patients, a global survey study of the health service provided to these patients between March 1st and May 31st 2020 concluded that the specific IEM units activity decreased between 60-80% comparing with the same period of 2019 (20). In some cases, this reduction is derived from the patients, due to fear of infection if going to medical facilities and/or the difficulty to reach the metabolic center due to mobility restrictions or fear of using collective means of transportation. Also, live attention was suspended in many hospitals and even some centers, such as ours, had severe staff reductions as many of their members were asked to attend other COVID-19 related activities.

Metabolic units around the globe have tried to adapt the patients' follow up to the new conditions. Most have amplified or implemented phone, email or other platforms of communication in order to maintain the contact with the patients and their families (21). In patients with lysosomal storage diseases, home infusion or higher doses were suggested in order to adapt the treatment (22). However, biochemical control of patients requires in many cases blood extractions and urine samples that need to be collected in a medical facility, and this kind of attention could not be performed in many centers during the worst weeks of the coronavirus pandemic.

The use of filter paper samples for the follow-up of phenylketonuria (PKU) patients is well established and therefore not included in this paper. For other amino acid disorders the use of this method for their detection in NBS is already standardized (23), but there was no validation of the long-term use of this kind of samples. Other authors have validated the filter sample method of monitoring patients with hereditary tyrosinemia type I (24). We recently published our experience in long term follow up of propionic acidemia with DBS and DUS (15). Both papers highlight that DUS and DBS correctly reflect the metabolic status in propionic acidemia and type I tyrosinemia respectively, allowing to adjust the treatment and facilitate the metabolic control.

During the first COVID-19 wave in Spain from March to June 2020, we maintained communication with all our metabolic patients via phone or email. Attention of some patients that could only be evaluated through live visits was either done under strict measures or postponed, but for most patients with amino acid disorders the use of filter paper samples and remote clinical evaluation allowed us to maintain their regular schedule and had the same number of visits as in 2019. None of these patients experienced a major metabolic event and the previous education, together with the telephone communication and filter paper samples allowed us to adequately manage the mild decompensation of the patient with cobalamin metabolism type C deficiency. In the patient with propionic acidemia with skin abnormalities in the diaper area, low valine levels could be observed and treated with good clinical and biochemical results. Acrodermatitis enteropathica-like skin lesions have been previously described in maple syrup urine disease patients and less frequently in propionic and methylmalonic acidemia, associated with low levels of isoleucine and valine (9) (25) (26) (27) (28). To avoid them, treatment guidelines for these diseases suggest single amino acid supplementation (7) (8).

It is obvious that remote monitoring in IEM cannot fully ensure the proper continuity and the high-level care that these patients need. Remote clinical assessments in children many times are done with parents but might exclude the patient. Physical examination, a pillar of the medical evaluation, is lacking. Due to staff shortage and because of the nature of this kind of communication patients were not evaluated by the complex multidisciplinary team that is usually standard. Even the biochemical control was incomplete, as filter papers could be used to measure amino acids and acylcarnitines but cannot be used for the full nutritional evaluation that has to be performed regularly.

On the other hand, remote clinical assessments and filter paper samples did provide a good method to maintain communication with patients during the time of the COVID-19 outbreak and allowed us to detect biochemical changes that could be managed by the patients at

home without having to use other medical facilities. Taking into consideration the evolution of this pandemic, it will be necessary to maintain this kind of attention in the future. Even outside of this situation, using remote attention of patients will probably become more common as it reduces time and travel inconveniences for the patient and their families. This kind of extraction is also easier and more convenient, even in an in-clinic setting.

Conclusions

New strategies to ensure IEM patients continuity need to be implemented, considering the COVID-19 pandemic evolution. Remote clinical assessments are now indispensable and probably will become part of the regular schedule in the future, minimizing in-hospital visits and increasing the patients' autonomy. Filter paper samples have been shown to be useful not only in the diagnosis but also the long-term follow-up of many amino acid disorders. The simplicity of extraction and transportation of these samples have considerable advantages.

Declarations

Ethics approval and consent to participate:

This article does not contain any studies with human or animal subjects performed by any of the authors. The patients signed a consent statement previous to the inclusion in the study. The study was approved by the Ethical Committee of our hospital (Hospital Universitario Ramon y Cajal, Madrid, Spain).

Consent for publication:

not applicable.

Availability of data and materials:

The data and materials are available upon request

Potential competing interests

SS has received travel and speaker fees from Nutricia, Mead Johnson, Genzyme, Recordatti Rare Diseases, Vitaflo-Nestlé, BioMarin.

ABQ has received travel and speaker fees from Nutricia, Mead Johnson, Genzyme, Recordatti Rare Diseases, Vitaflo-Nestlé, Takeda, BioMarin; advisory fees from BioMarin and Merk Serono.

FA has received travel and speaker fees from Nutricia, Mead Johnson, Recordatti Rare Diseases, Vitaflo-Nestlé, BioMarin.

PA declares that she has no conflict of interest.

PRS declares that he has no conflict of interest.

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Authors' contributions:

SS and ABQ had a significant contribution to the conception and design of the study. All authors have contributed to the acquisition and the interpretation of the data and gave the final approval for the article.

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