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Impact of COVID19 pandemic on patients with rare diseases in Spain, with a special focus on inherited metabolic diseases

M. Mar Rovira-Remisa [a], Mónica Moreira [b,n], Paula Sol Ventura [c,d], Pablo Gonzalez-Alvarez [d], Núria Mestres [a], Fredzzia Graterol Torres [e], Clara Joaquín [f], Agustí Rodríguez-Palmero Seuma [a], Maria del Mar Martínez-Colls [g], Ana Roche [h], Salvador Ibáñez-Micó [i], Eduardo López-Laso [j], María Jesús Méndez-Hernández [k], Marta Murillo [l], Laura Monlleó-Neila [a], Elena Maqueda-Castellote [a], Mireia del Toro Riera [m], Ana Felipe-Rucián [m], Maria Giralt-López [b,n,1], Elisenda Cortès-Saladelafont [a,n,*,1]

[a] Unit of Inherited Metabolic Disorders and Pediatric Neurology, Department of Pediatrics, Hospital Universitari Germans Trias i Pujol, Badalona., Spain
[b] Department of Psychiatry, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[c] Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol (IGTP), Spain
[d] Department of Pediatrics, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[e] Department of Nephrology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[f] Unit of Adults Inherited Metabolic Disorders, Department of Endocrinology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[g] Unit of Pediatric Pneumology, Department of Pediatrics, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[h] Unit of Pediatric Neurology, Department of Pediatrics, Hospital Universitari Parc Taulí, Sabadell, Spain
[i] Unit of Pediatric Neurology, Department of Pediatrics, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain
[j] Pediatric Neurology Unit, Department of Pediatrics, University Hospital Reina Sofía, IMIBIC, CIBERER, Córdoba, Spain.
[k] Unit of Pediatric Infectious Diseases and Immunological Disorders, Department of Pediatrics, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[l] Unit of Pediatric Endocrinology, Department of Pediatrics, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[m] Pediatric Neurology Department, Hospital Vall d'Hebron, Barcelona, Barcelona, Spain
[n] Universitat Autònoma de Barcelona, Campus Can Ruti, Badalona, Spain

A R T I C L E I N F O

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A B S T R A C T

Introduction: The Covid-19 pandemic soon became an international health emergency raising concern about its impact not only on physical health but also on quality of life and mental health. Rare diseases are chronically debilitating conditions with challenging patient care needs. We aimed to assess the quality of life and mental health of patients with rare diseases in Spain, with a special focus on inherited metabolic disorders (IMD).
Methods: A prospective case-control study was designed, comparing 459 patients suffering from a rare disease (including 53 patients with IMD) and 446 healthy controls. Quality of life (QoL) and mental health were assessed using validated scales according to age: KINDL-R and the Pediatric Symptom Checklist (PSC) for children and the WhoQoL-Bref questionnaire, GAD and PHQ-9 in adults.
Results: First, children and adults (but not adolescents) with IMD showed greater psychological effects than controls ($p = 0.022$, $p = 0.026$ respectively). Second, when comparing QoL, only adult patients with IMD showed worse score than controls (66/100 vs 74,6/100 respectively, $p = 0.017$). Finally, IMD had better quality of life than other rare neurological and genetic diseases ($p = 0.008$) or other rare diseases ($p < 0.001$ respectively) but similar alteration of the mental status.
Conclusions: Our data show that the pandemic had a negative impact on mental health that is more evident in the group of patients with IMD. Young age would behave as a protective factor on the perception of QoL. Furthermore, patients with IMD show a better QoL than other rare diseases.

* Corresponding author at: Department of Pediatrics, (7th floor, Maternity Building), Carretera de Canyet s/n, 08916 Badalona, Catalonia, Spain.
E-mail address: ecortes.germanstrias@gencat.cat (E. Cortès-Saladelafont).
[1] Maria Giralt-López and Elisenda Cortès-Saladelafont should be considered joint senior author.

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1. Introduction

In early December 2019, the first pneumonia cases of unknown origin were identified in Wuhan (China) [1]. The pathogen has been named severe acute respiratory syndrome coronavirus (SARS-CoV-2), causing the coronavirus disease 2019 (Covid-19). In mid-January 2020, Covid-19 was declared by the World Health Organization (WHO) a public health emergency of international concern, and early in 2020 the first scientific publications raised concern about the potential impact of the quarantine [2] on different at-risk populations (children [3,4] or general population alike) [5–7].

To date, >613,000,000 confirmed cases and above 6,500,000 confirmed deaths have been reported by the WHO (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). Focusing in Spain, SARS-CoV-2 has hit it savagely, with a total of >3,500,000 confirmed cases and almost 80,000 cumulative deaths (https://covid19.who.int/table). The impact on mental health and self-perception of quality of life might be specially worrying, and some publications that confront the topic confirm this [3,8].

A study by Orgiles et al. [9] indicates that 85.7% of parents identified changes in the emotional state and behaviour of their children during quarantine. A nationwide study in Germany reports worse scores in quality of life and an increase in mental health problems (especially anxiety) during the COVID pandemic [10]. These results are consistent with Duan et al [11] who find levels of anxiety in children and adolescents much higher than before the pandemic or other studies among university students that show an increase in anxiety, fear, worry, suicidal thoughts, depression and stress [12,13].

More specifically, Ozamiz-Etxebarria et al [14] identified people with chronic diseases as a vulnerable population, particularly exposed to the psychological impact of a health crisis.

Focusing on rare diseases, Eurordis (https://www.eurordis.org/about-eurordis), a non-governmental patient-driven association that represents 962 rare disease patient organizations in different European countries, conducted a survey during the first wave of the COVID-19 aiming to address the impact of the pandemic on the treatment, care and living conditions of people living with a rare disease and their carers across Europe. The results can be accessed on-line [15] (https://www.eurordis.org/publication/how-has-covid-19-impacted-people-rare-diseases-0) and mainly state that 84% of the people who had answered the survey experienced some sort of disruption of their care due to the COVID-19 crisis. Chung et al [16], described the rare diseases situation in Hong Kong and reported an important impact on mental health and patients' status during the pandemic. Many other groups have since explored the consequences of the pandemic on different populations suffering from various diseases, such as cancer [17], developmental and epileptic encephalopathies [18], ST-segment-elevation myocardial infarction [19], narcolepsy [20], painful polyneuropathy [21], or complex connective tissue diseases [22], among others. All of them report negative consequences for their patients because of the COVID-19 pandemic, stressing the importance of such an event in populations suffering from chronic conditions.

Rare diseases tend to be chronically debilitating conditions, and patient care needs are often complex and challenging.

The aim of this study is to assess the quality of life and to characterize the psychopathological status of patients with rare diseases in Spain, with a special focus on inherited metabolic disorders (IMD).

2. Methods

2.1. Period of study

Participants were recruited and filled the questionnaires from July 2020 to September 2021.

2.2. Patients

The inclusion criteria were fulfilled for all patients suffering from a definite rare disease, diagnosed either with a genetic test, a confirmatory biochemical profile (enzyme activity or definite biomarkers) or clinical criteria (for those diseases that are diagnosed through clinical scores). Children above 4 years of age and adults were included in the study. As for the consideration of rare disease, this study uses the definition of the European Commission, which grants the rare disease status to all conditions with an incidence of up to 1/2000.

All patients from our unit that met these criteria were contacted through telephone, email or personally in the outpatient clinic.

In an attempt to include more patients, other hospitals across the country were invited to participate in the study spreading the information among their patients. Further distribution of the survey was made possible thanks to the contribution of different Catalan and Spanish patients' associations, whose contact data were published on the Spanish Ministry of Health webpage (https://www.mscbs.gob.es/), as well as the Catalan Association for Rare Diseases (FECAMM: https://www.fecamm.org/portal1/M_index.asp) and the Spanish one (FEDER: https://enfermedades-raras.org/). This methodology fits the snowball sampling method, that has been used in qualitative research where a qualified subject is contacted by the researcher or by other similar subject that shares the same diagnostic o qualities, and that is particularly useful in hard-to-reach populations (i.e., rare disorders). [23]

2.3. Healthy controls

Children aged above 4 and adults, without any chronic or rare disease were eligible to participate. The link with the on-line survey was randomly distributed through social networks and contacting the parents' associations of schools and high-schools. When accessing the survey, one of the first questions aimed at clarify if the individual suffered from a rare or chronic disease or not. All children and adults answering a "no" to that question, were eligible to participate as control population.

2.4. Questionnaires and demographic survey

2.4.1. Demographic and health measures

Self-reported or parent-reported information was obtained on demographics (age, gender), diagnosis, disease evolution during COVID-19 (decompensation, hospital admissions), the academic impact of COVID-19 and social network contact maintenance. We also obtained information on the impact of SARS-CoV-2 on relatives' health (infections or death).

2.4.2. Quality of life assessment

- KINDL-R: Children and adolescents' QoL was rated by patients and/or their parent or guardian using the revised Kinder Lebensqualitatsfragebogen- überarbeitet or KINDL questionnaire (KINDL-R) [24,25], a 31-item questionnaire revised by Ravens-Sieberer and Bullinger [26]. It consists of 24 Likert-scaled items grouped into 6 subscales measuring specific aspects of QoL (physical well-being, emotional well-being, self-esteem, family, friends, and school) consisting of 4 items each, followed by an additional module entitled "Disease" with 7 extra items. The Disease module assesses perceptions of how the illness itself impacts the patient (e.g., the patient's feelings regarding the disease, ability to cope with the disease, and sense of being treated differently by others because of the disease) and applies only to patients who are either hospitalized or those suffering from a long long-term illness. Subscale scores are produced by combining the item ratings for each of the 6 subscales and converting each subscale score to a scale of 0–100, with higher scores representing better QoL. Similarly, a total score is produced by combining the item ratings across all 6 subscales (not including the Disease module) and converting this score to a scale of 0–100.

The KINDL-R is a validated scale used as a health outcome measure

across a range of health and mental health issues and has been translated into numerous languages including Spanish. The determination of the reliability and validity of the KINDL-R questionnaire can be located in the manual [26].

- WhoQoL: The World Health Organization's WHOQOL-BREF has been validated in dozens of countries and languages, and among healthy and clinical adult populations [27]. The WHOQOL-BREF explore four domains through 24 items: a 3-item "social relationships" domain of QoL, 7-item "physical health" domain, 6-item "psychological health" domain, and 8-item "environment domain". Two additional items measure overall QoL and overall health. The WHOQOL-BREF uses a five-point Likert scale with answers ranging from "very dissatisfied" to "very satisfied", "not at all" to "an extreme amount", and "never" to "always". Transformed domain scores result in a 0–100 scale in which higher scores indicate higher QoL [28].

2.4.3. Mental health assessment

- Pediatric Symptom Checklist (PSC): It is a 35-item parent-report questionnaire that helps to identify and assess changes in emotional and behavioural problems in children. Each item can be rated as: "Never" (scored 0), "Sometimes" (scored 1), "Often" (scored 2). The total score is calculated by adding the 35 individual scores, so the total score will be 0 to 70.

An overall score above the cut-off point indicates a potential psychosocial impairment and needs further assessment. The cut-off score for children older than 6 years old is 28 points [29]. For children younger than 6 years old, four items that pertain to school are excluded. As a result, the range of scores is lower and the cut-off score is lowered to 24. Subscale scores for internalizing, externalizing and attention problems can be calculated from specific items. Some studies have used the PSC to explore the prevalence of psychosocial problems among children with specific pediatric problems, including neurological problems [30].

- Patient Health Questionnaire 9 (PHQ-9) [31,32]: It is a 9-item instrument exploring each of the 9 specific symptoms of the Major Depressive Disorder in adults, based on DSM-IV criteria. The items are rated on four-point Likert scales, ranging from 0 (never) to 3 (almost every day), with higher scores indicating higher severity of depressive symptoms (range 0–27). The cut-off point over which the patients is considered to be at risk for a major depressive disorder is 10 [32–35]. The PHQ-9 has been validated in Spanish samples both in primary care and hospital setting alike [36,37].

- GAD: Generalized Anxiety Disorder — 7 item scale (GAD-7) is a one-dimensional scale designed to assess the presence in adults of the symptoms of generalized anxiety disorder (GAD) referred to in the DSM-IV. It is self-administered and the total score is calculated by simple addition of the answers for each item. As in the original English [38], the Spanish version of the GAD- 7 validated by García-Campayo et al. (2010) includes a 4-point response scale ranging from 0 ("never") to 1 ("several days"), 2 ("more than half the days") and 3 ("nearly every day") over the last two weeks, providing a total score that ranges from 0 to 21. According to the original authors [38] the optimum cut-off value for GAD is 10 points.

Given the lack of a universal screening tool to assess the psychopathological status across different ages and in order to allow for comparisons to be made among the different groups, a surrogate variable was created in this study. Thus, children and adults with a positive screening in each of their age-specific tests are grouped under the "altered mental status (AMS)" category.

2.5. Data collection and data analysis

2.5.1. Data collection

Both the demographic questions and the specific questionnaires were transformed in an on-line survey, easily accessible through an internet link or a QR code that were provided to all participants (controls and patients). All their responses were directly collected in an Excel file that was password protected and used afterward for statistical analysis.

2.5.2. Statistical analysis

Data were expressed as means (SD) for continuous variables or as numbers/percentages for categorical variables. The normality of distribution and equality of variances were evaluated through the Kolmogorov-Smirnov test and Levene's test respectively. The Student *t*-test or U Mann-Whitney, according to size and characteristic of the variables, were used to compare independent continuous variables. To compare 3 independent continuous variables, the Kruskal-Wallis nonparametric test was used. A Pearson chi-square test was used to compare categorical variables between groups. The Statistical Package for Social Science SPSS version 23.0 was used to perform all the statistical analyses, establishing the significance at $p < 0.05$.

2.6. Ethics

All patients, caregivers and healthy participants were informed of the study's objectives and data confidentiality standards, and informed consent needed to be obtained from all participants before initiating the survey. The study was approved by our Ethics Committee and follows the standards of the Helsinki declaration and the current Spanish regulations (law 14/2007 from the 3rd July about biomedical research).

3. Results

3.1. Sample characteristics

3.1.1. Sociodemographic description of the sample

A total of 1068 responses to the questionnaire were received, of which 163 had to be excluded for the following reasons: 3 failed to complete the consent form, 73 answered twice the questionnaire, 41 suffered from non-rare diseases, and another 46 tests could not be included because of technical errors committed when answered (wrong age group, etc). The remaining 905 tests were considered valid and entered the study.

Two groups were established among the 905 participants, with a case group adding up to 459 individuals suffering from rare diseases and a control group formed by 445 participants.

The mean age of the 905 individuals included in the study was 33 years (SD 20). This remains the same when performing an analysis by groups, with no significant differences found between cases and controls. Further descriptive data of the sample is shown in Table 1. A slight predominance of female subjects was observed both for cases and controls. There is no specific bias that could explain such distribution, since in the case of patients, very few rare diseases are X-linked (a clear bias that could have explained the female predominance).

Table 1
Sociodemographic description of the sample.

	Cases ($n = 459$)	Controls ($n = 446$)
Gender		
Female	254 (55.3%)	297 (66.6%)
Male	205 (44.7%)	149 (33.4%)
Education		
None	0 (0%)	149 (33.4%)
Primary	28 (6.1%)	12 (2.6%)
Intermediate	98 (21.3%)	65 (14.5%)
University degree	146 (31.8%)	211 (47.3%)
Civil status*		
Single	75/256 (29.3%)	44/270 (16.3%)
Divorced	5/256 (2%)	9/270 (3.3%)
Married	122/256 (47.7%)	135/270 (50%)
Partnered	46/256 (18%)	77/270 (28.5%)
Widowed	8/256 (3.1%)	5/270 (1.9%)

* only answered by those over 18 years. Some participants left the question blank.

No differences were found in the questions aimed at inquire the general impact of the pandemic (neither in the controls nor in the rare disease patients). These questions focused on assessing the impact of the pandemic on social interactions and on the health situation of relatives.

As discussed before, different questionnaires according to the age of the participants were used for the study. Table 2 presents the distribution of cases and controls by age groups, with no statistically significant differences found between them.

3.1.2. Clinical description: Rare diseases categories and inherited metabolic disorders

The total of 459 patients with rare diseases were distributed in different categories. The different groups are represented in Fig. 1 in an attempt to be concise, while supplementary table 1 names the most prevalent diseases among all patients (19 entities adding up to 62% of the rare diseases sample).

For practical reasons and since we are dealing with rare diseases with expected low incidence, some categories were grouped to favour a better analysis. These categories account for: 1) inherited metabolic disorders ($n = 53$); 2) a group consisting of neurological/psychiatric syndromes, as well as ataxia and neuroectodermic diseases (total of patients = 299, 65% of the cases' sample); and 3) others: including autoimmune, pulmonary, digestive, endocrinologic and hematologic diseases ($n = 107$). Detailed information about the diseases included in each category and the number of patients represented in each of them can be found on supplementary table 1 and 2.

This figure represents the different subgroups of rare diseases included in this study, which are defined as conditions with an incidence of up to 1/2000. They are distributed in different categories, the most prevalent being genetic syndromes (34%), followed by neuromuscular (13%), inherited metabolic disorders (12%), neurologic/psychiatric syndromes (12%) and autoimmune diseases (12%).

Special focus was devoted to inherited metabolic disorders, including a total of 53 patients suffering from a range of different diseases, from intermediary metabolism to small and complex molecules, which are listed on Table 3. Table 4 shows the distribution of the inherited metabolic disorders sample by age groups.

3.1.3. Description of the QoL and psychopathological status

Data referring to the quality of life and the mental status in terms of anxiety and affective symptoms (altered mental status or AMS) is shown in Table 5. QoL is described by a score in a 0–100 scale in which higher scores indicate higher QoL.

3.2. Group comparison between inherited metabolic disorders and controls

3.2.1. Quality of life analysis

Data don't show significant statistical differences when comparing QoL between cases and controls in children nor in adolescents.

However, adult data show that quality of life of cases ($Mdn = 66$) was worse than that in controls ($Mdn = 75$). A Mann-Whitney test indicated that this difference was statistically significant, U ($N_{cases} = 26$, $N_{controls} = 291$) = 2713.5; $z = -2.39$, $p = 0.017$.

Table 2
Distribution of the sample by age groups.

Age	Cases (n = 459)	Controls (n = 446)
4-6yo	35 (7.6%)	47 (10.5%)
7-13yo	77 (16.8%)	60 (13.5%)
14-17yo	40 (8.7%)	48 (10.8%)
≥ 18yo not self-filling the questionnaire	35 (7.6%)	2 (0.4%)
≥ 18yo self-filling the questionnaire	272 (59.3%)	289 (64.8%)

3.2.2. Mental status analysis

In the group of children, a chi-square test found that patients with IMD showed more alteration of the mental status than controls (20% vs 3.8% respectively), χ^2 (1) = 7.450, $p = 0.022$.

While in the adolescent group, the differences observed are not significant, adult patients showed more altered mental status than controls (42.3% vs 21.3% respectively), χ^2 (1) =5.94, $p = 0.026$.

When analysing differences by age in each group (patients and controls) data show that in both group, children show a better mental status preservation in comparison with adolescents and adults, however, only in the control group these differences were statistically significant ($p < 0.01$).

3.3. Group comparison between inherited metabolic disorders and other rare diseases

A subgroup analysis, comparing IMD with other rare diseases is shown in Table 6, while Fig. 2 shows the distribution of QoL by subgroup of rare disease.

A Kruskal-Wallis test showed that the type of rare disease significantly affects the quality of life, H(2) = 14.91, $p < 0.001$. Post-hoc Mann-Whitney tests using a Bonferroni-adjusted alpha level of 0.017 (0.05/3) were used to compare all pairs of groups finding that IMD had better quality of life than neurological and genetic diseases: U ($N_{IMD} = 53$, $N_{neurogen} = 299$) = 6101 $z = -2.67$, $p = 0.008$ and other rare diseases: U ($N_{IMD} = 53$,$N_{other} = 107$) = 1843.5 $z = -3.60$, $p < 0.001$.

Data did not show any differences in the alteration of the mental status between the three groups of rare diseases.

In order to compare inherited metabolic disorders with other rare conditions, some categories were grouped: 1) inherited metabolic disorders, 2) neurological/psychiatric syndromes; and 3) others. Patients with inherited metabolic diseases (IMD) had better quality of life than neurological and genetic diseases: U ($N_{IMD} = 53$, $N_{neurogen} = 299$) = 6101 $z = -2.67$, $p = 0.008$ and other rare diseases: U ($N_{IMD} = 53$,$N_{other} = 107$) = 1843.5 $z = -3.60$, $p < 0.001$.

4. Discussion

COVID-19 has had an impact on the global population, but this study attempts to focus on its effects on patients suffering from rare diseases and particularly on IMD, for whom changes in medical care could translate into life-threatening decompensation episodes due to their condition.

IMDs are a heterogeneous group of genetic diseases that affect metabolic pathways. >1400 disorders are described (with >600 new disorders described in the last 6 years), 85% presenting with predominantly neurologic manifestations [39], but may present with many symptoms and affect any organs at any age. The phenotypes range from mild to severe. To date, mostly lack effective therapies, although targeted metabolic treatments (with small molecules), gene therapy, treatment with chaperones, and other individualized approaches are in constant development and improvement. Some of them receive specific nutritional supplements to minimize the risk of decompensation, and/or require a restricted lifelong diet as part of their treatment. All these restrictions and lifestyle modifications in this group of IMD affect patients and their families, with an undeniable effect on their disease acceptance and QoL perception [40]. Consequently, the evaluation of health-related QoL might be of particular relevance in this population, with very few studies published in the literature on this topic. Fabre et al. [41] reported that the QoL of children and their parents in those children with IMD that require protein restricted diet was lower than the average QoL in other pediatric chronic diseases. AbdoulayeOuattara et al. [42] concluded that psychosocial factors appear to be major determinants of QoL impairment in children with IMD receiving a restricted diet. A multicenter study showed that children and adolescents with intoxication-type IMD have significantly impaired health-

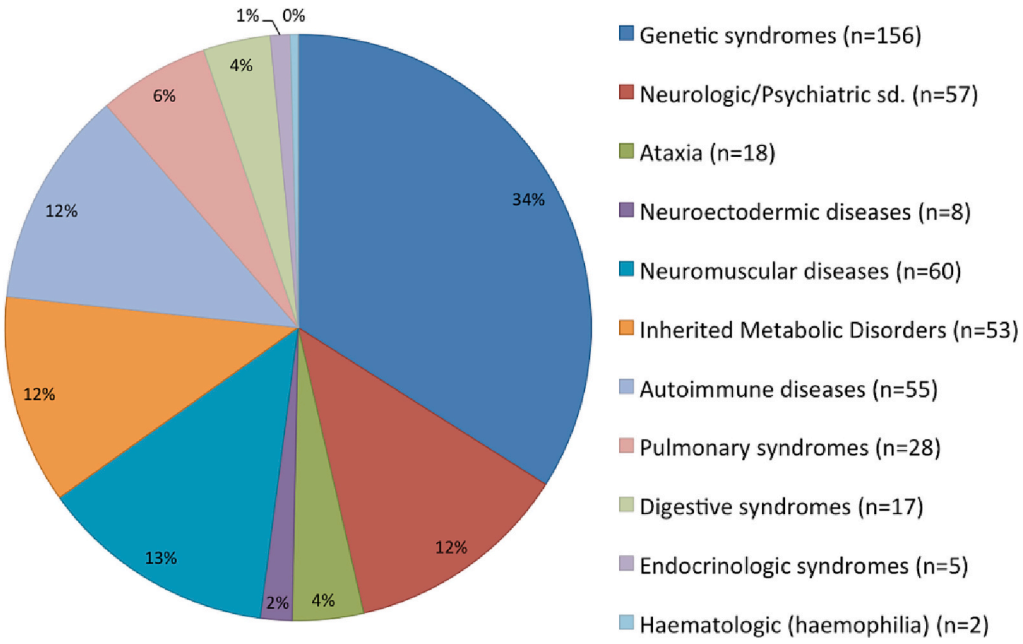

Fig. 1. Subgroups of rare diseases (N = 459).

Table 3
Patients with inherited metabolic disorders.

Inherited metabolic disorders (n = 53)	n
Mitochondrial syndrome	12
Succinic semialdehyde dehydrogenase (SSADH) deficiency	7
Wilson disease	7
Lysosomal acid lipase deficiency	4
Fabry disease	4
Very long-chain acyl-coa dehydrogenase deficiency (VLCAD)	3
Mucopolysaccharidosis type 2	2
Glutaric aciduria type 1	2
X-linked adrenoleukodystrophy	2
Dopamine transporter deficiency	1
Smith-Lemli-Opitz syndrome	1
Trimethylaminuria	1
2-hydroxyglutaric aciduria	1
Ornithine transcarbamylase deficiency (OTC) deficiency	1
Carnitine palmitoyltransferase II (CPT II) deficiency	1
Congenital hypertriglyceridemia	1
Citrullinemia	1
Mucopolysaccharidosis type 1	1
Classic galactosemia	1

Table 4
Distribution of the inherited metabolic disorders sample by age groups.

Age	Cases (n = 53)	Controls (n = 445)
Children (4-13yo)	20 (37.7%)	106 (23.8%)
Adolescents (14-17yo)	7 (13.2%)	48 (10.8%)
Adults ($\geq$ 18yo)	26 (49.1%)	291 (65.4%)

related QoL compared to healthy controls and concluded that dietary treatment is considered a major burden, since it affects the daily routine of patients and their families [43].

The results of our study stress the vulnerability of the IMD population, whose psychopathological status seems to be worsened during the pandemic. While this is true for children and adults, differences between cases and controls in the teenager group do not reach statistical significance. This might be partially explained by the size of the sample, too small to highlight the potential differences, but could also be caused by the special vulnerability to stressful events that can trigger the onset of mental illness in this age group.

Although most of the articles that investigated the early stages of the pandemic already demonstrated high levels of anxiety and depression in the general population during the quarantine period [6,7,9], our results were obtained in a stage in which the restrictions began to be gradually withdrawn. A recent report by Save the Children [44] highlights an increase from 1.1% to 4% in mental disorders in children and adolescents compared to official data from 2017 before the pandemic.

When our study began, quarantine was being lifted, but the restrictions on social interactions were maintained, school attendance in bubble groups was necessary, online classes were required intermittently, and participation in activities of leisure and spaces for relationships with their peers were limited. These aspects have been a challenge that this age group has had to face and impacted both adolescence with and without IMD. Adolescence is a crucial period of maturity and growth, a phase of learning to regulate oneself and, precisely, of building oneself and incorporating tools that help manage the different episodes of stress, anxiety and fear (fear of not seeing colleagues again, not to return to presential learning, not being able to do practicums, not being able to start working…). Both, adolescent with and without IMD had to learn to do it in the midst of a major crisis. Furthermore, they had to do it in isolation, when they are used to doing it while being physically interconnected with others. For all aforementioned, non-IMD related challenges may have precipitated the onset of symptoms that affect mental well-being of all adolescent population.

There are a number of factors that could account for the changes in mental status observed in adults and children. On one hand, uncertainty, the possible impact of restriction measures and changes in routines (such as adaptation to bubble groups, the use of a mask, online schooling, the reduction of leisure activities) can be decisive for the appearance of anxiety or behavioural changes in these children [9,10]. For children with chronic diseases, the maintenance of normal routines and the certainty of returning to normal activities for their age are usually factors that allow a good mental state. However, the measures imposed by the pandemic situation may have affected these routines, facilitating the appearance of mental illness [4,45]. On the other hand, for adults the vulnerability to alterations in their mental status seems to be related with a poorer QoL perception. The implications of teleworking and the possible economic impact may be relevant factors for the results in their quality of life and their mental state. Another aspect to consider is the

Table 5
Mental status and QoL descriptive data by age.

	IMD (n = 53)			Controls (n = 445)		
	Children (20)	Adolescent (7)	Adult (26)	Children (*n* = 106)	Adolescent (*n* = 48)	Adult (*n* = 291)
AMS N (%)	4 (20%)	3 (42.9%)	11 (42.3%)	4 (3.8%)	9 (18.6%)	62 (21.3%)
QoL (Mdn)	81	73	66	83	73	75

AMS: Altered Mental Status.
QoL: Quality of life.

Table 6
Mental status and Quality of Life (QoL) descriptives by type of rare disease.

	IMD (n = 53)	Neuro & Gen (n = 299)	Others (n = 107)
AMS N (%)	18 (34%)	130 (43.5%)	47 (43.9%)
QoL (Mdn)	74.67	66.54	62.67

IMD: Inherited Metabolic Disorder, Neuro & Gen: Neurologic and Genetic Disorder.

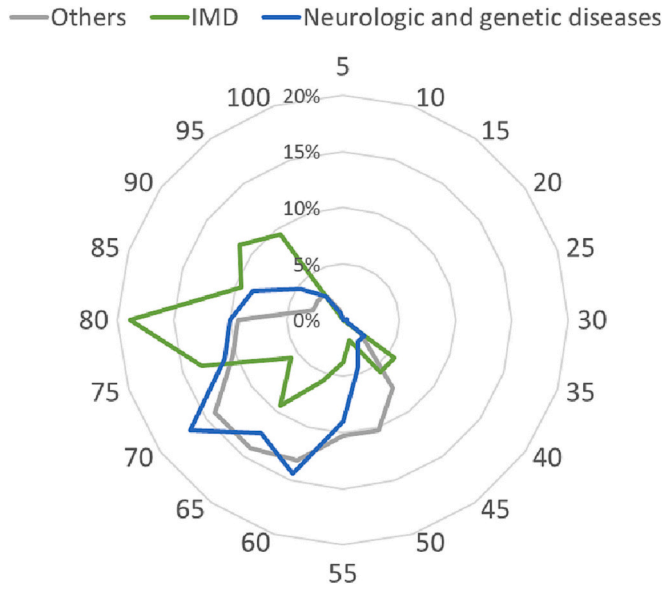

Fig. 2. Quality of life distribution by type of rare disease.

possible impact that the limitations in access to health centres and regular check-ups of their illness, as well as the fear associated with a possible perception of loss of adequate care, can be an important stressor for this [5,7].

Finally, we found that patients with IMDs had better outcomes in quality of life compared to other rare diseases. These differences could be explained by better metabolic control with a lower risk of decompensation, considering that more than half of the sample with IMD (29 out of 53) correspond to patients with intoxication type disorders and energy metabolism (who are really prone to infectious diseases and decompensation). Thanks to the global measures established during the pandemic, there was less exposure to all viral infections (which are a frequent trigger of metabolic decompensation) and these patients probably had better adherence to dietary and medical treatment as they spent more hours at home with their primary caregiver.

In conclusion, our data show that the pandemic had a negative impact on mental health that is more evident in the group of patients with IMD. The results of our study show that adolescents with IMDs didn't behave worse than controls, though maybe children and adults did. While IMDs might provide more stress during a pandemic, it seems that the non-IMD related stresses, especially in adolescent predominate. Nevertheless, further studies and new analyses in larger samples and in other pandemic moments would be needed.

We acknowledge some limitations to our study. First, a potential bias exists for all those patients not able to answer the questionnaires by themselves; in their case, their caregivers answered the tests by representation, and their own psychological/psychiatric status may have influenced their answers. It is well recognized that depression and/or anxiety tend to be worse in patients suffering from chronic illnesses like it is the case with IMD. Another limitation is that the individual perception of quality of life might be influenced by the degree of dependence of the patient, and we did not explore this in our questionnaires. Also, since no data exist on the QoL or psychological status of our population prior to the pandemic, no comparisons can be made, so the results are very difficult to interpret. Consequently, the results found cannot be attributed to Covid-19 itself. Another limitation is that very different diseases are compared, without sufficient clinical data available in order to know the severity of the disease of respondents. Finally, it is not possible to extrapolate these results to the whole Spanish population with rare disorders, since our sample is not representative. Despite the efforts made to reach as many patients as possible (with the snowball sampling method described earlier), the low prevalence of this group of diseases makes reaching representativity difficult.

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Data availability

the data that support the findings of this study are available on request from the corresponding author (MRR, MGL, ECS).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2023.100962.

References

[1] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet. 395 (10223) (2020) 497–506.
[2] S.K. Brooks, R.K. Webster, L.E. Smith, et al., The psychological impact of quarantine and how to reduce it: rapid review of the evidence, Lancet. 395 (10227) (2020) 912–920, https://doi.org/10.1016/S0140-6736(20)30460-8.
[3] L. Vallejo-Slocker, J. Fresneda, M.A. Vallejo, Psychological wellbeing of vulnerable children during the COVID-19 pandemic, Psicothema. 32 (4) (2020) 501–507, https://doi.org/10.7334/psicothema2020.218.
[4] C.A. Wong, D. Ming, G. Maslow, E.J. Gifford, Mitigating the impacts of the COVID-19 pandemic response on at-risk children, Pediatrics. 146 (1) (2020 Jul), e20200973.
[5] L.N. Ferreira, L.N. Pereira, Brás M. da Fé, K. Ilchuk, Quality of life under the COVID-19 quarantine, Qual. Life Res. 30 (5) (2021) 1389–1405, https://doi.org/10.1007/s11136-020-02724-x.
[6] Q. He, B. Fan, B. Xie, et al., Mental health conditions among the general population, healthcare workers and quarantined population during the coronavirus disease 2019 (COVID-19) pandemic, Psychol. Health Med. 27 (1) (2022) 186–198, https://doi.org/10.1080/13548506.2020.1867320.
[7] E. Öztürk Çopur, F. Karasu, The impact of the COVID-19 pandemic on the quality of life and depression, anxiety, and stress levels of individuals above the age of eighteen, Perspect Psychiatr Care. 57 (4) (2021) 1645–1655, https://doi.org/10.1111/ppc.12730.
[8] C. Valiente, A. Contreras, V. Peinado, A. Trucharte, A.P. Martínez, C. Vázquez, Psychological adjustment in Spain during the COVID-19 pandemic: positive and negative mental health outcomes in the general population, Span J Psychol. 24 (2021), e8. . Published 2021 Feb 8, https://doi.org/10.1017/SJP.2021.7.
[9] M. Orgilés, A. Morales, E. Delvecchio, C. Mazzeschi, J.P. Espada, Immediate psychological effects of the COVID-19 quarantine in youth from Italy and Spain, Front. Psychol. 11 (2020 Nov 6), 579038, https://doi.org/10.3389/fpsyg.2020.579038.
[10] U. Ravens-Sieberer, A. Kaman, M. Erhart, J. Devine, R. Schlack, C. Otto, Impact of the COVID-19 pandemic on quality of life and mental health in children and adolescents in Germany [published online ahead of print Jan 25, 2021], Eur. Child Adolesc. Psychiatry (2021) 1–11, https://doi.org/10.1007/s00787-021-01726-5.
[11] Li Duan, Xiaojun Shao, Yuan Wang, et al., An investigation of mental health status of children and adolescents in China during the outbreak of COVID-19, J. Affect. Disord. (275) (2020 Oct 1) 112–118, https://doi.org/10.1016/j.jad.2020.06.029 (Epub 2020 Jul 2).
[12] W. Cao, Z. Fang, G. Hou, et al., The psychological impact of the COVID-19 epidemic on college students in China, Psychiatry Res. 287 (2020), 112934, https://doi.org/10.1016/j.psychres.2020.112934.
[13] M. Wathelet, S. Duhem, G. Vaiva, et al., Factors Associated With Mental Health Disorders Among University Students in France Confined During the COVID-19 Pandemic, JAMA Netw. Open 3 (10) (2020), https://doi.org/10.1001/jamanetworkopen.2020.25591 e2025591. Published 2020 Oct 1.
[14] N. Ozamiz-Etxebarria, M. Dosil-Santamaria, M. Picaza-Gorrochategui, N. Idoiaga-Mondragon, Stress, anxiety, and depression levels in the initial stage of the COVID-19 outbreak in a population sample in the northern Spain, Cad Saude Publica. 36 (4) (2020), e00054020. Published 2020 Apr 30, https://doi.org/10.1590/0102-311X00054020.
[15] Eurordis, Rare Barometer 2020. https://www.eurordis.org/publication/how-has-covid-19-impacted-people-rare-diseases-0. Accessed November 2020.
[16] C.C. Chung, W.H. Wong, J.L. Fung, R.D. Hong Kong, B.H. Chung, Impact of COVID-19 pandemic on patients with rare disease in Hong Kong, Eur J Med Genet. 63 (12) (2020), 104062, https://doi.org/10.1016/j.ejmg.2020.104062.
[17] L. Rosenbaum, The untold toll - the Pandemic's effects on patients without Covid-19, N. Engl. J. Med. 382 (24) (2020) 2368–2371, https://doi.org/10.1056/NEJMms2009984.
[18] Á. Aledo-Serrano, A. Mingorance, A. Jiménez-Huete, et al., Genetic epilepsies and COVID-19 pandemic: lessons from the caregiver perspective, Epilepsia. 61 (6) (2020) 1312–1314, https://doi.org/10.1111/epi.16537.
[19] C.F. Tam, K.S. Cheung, S. Lam, et al., Impact of coronavirus disease 2019 (COVID-19) outbreak on ST-segment-elevation myocardial infarction Care in Hong Kong, China, Circ Cardiovasc Qual Outcomes. 13 (4) (2020), e006631, https://doi.org/10.1161/CIRCOUTCOMES.120.006631.
[20] A.C. Rodrigues Aguilar, C. Frange, L. Huebra, A.C. Dias Gomes, S. Tufik, F. M. Santos Coelho, The effects of the COVID-19 pandemic on patients with narcolepsy, J. Clin. Sleep Med. 17 (4) (2021) 621–627, https://doi.org/10.5664/jcsm.8952.
[21] D. Kersebaum, S.C. Fabig, M. Sendel, et al., The early influence of COVID-19 pandemic-associated restrictions on pain, mood, and everyday life of patients with painful polyneuropathy, Pain Rep 5 (6) (2020), https://doi.org/10.1097/PR9.0000000000000858 e858. Published 2020 Oct 14.
[22] R. Talarico, S. Aguilera, T. Alexander, et al., The impact of COVID-19 on rare and complex connective tissue diseases: the experience of ERN ReCONNET, Nat. Rev. Rheumatol. 17 (3) (2021) 177–184, https://doi.org/10.1038/s41584-020-00565-z.
[23] S. Berg, Snowball sampling 1- sequential estimation of the mean in finite population to Steiner's most frequent value, Encyclopedia Stat. Sci. (2006), https://doi.org/10.1002/0471667196.ess2478.pub2.
[24] U. Ravens-Sieberer, M. Bullinger, KINDL: Questionnaire for Measuring Health-Related Quality of Life in Children and Adolescents. https://www.kindl.org/english/questionnaires/, 2020.
[25] M. Bullinger, KINDL: a questionnaire for health-related quality of life assessment in children, Zeitschrift für Gesundheitspsychologie. 1 (1994) 64–77.
[26] U. Ravens-Sieberer, M. Bullinger, Assessing health-related quality of life in chronically ill children with the German KINDL: first psychometric and content analytical results, Qual. Life Res. 7 (1998) 399–407, https://doi.org/10.1023/A:1008853819715.
[27] S. Skevington, M. Lotfy, K. O'Connell, The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group, Qual. Life Res. 13 (2) (2004) 11.
[28] The WHOQOL Group: WHOQOL-BREF: Introduction, Administration, Scoring, and Generic Version of the Assessment. In.: World Health Organization, 1996, p. 18.
[29] M.S. Jellinek, J.M. Murphy, B.J. Burns, Brief psychosocial screening in outpatient pediatric practice, J. Pediatr. 109 (2) (1986 Aug 1) 371–378, https://doi.org/10.1016/S0022-3476(86)80408-5.
[30] D.L. Anderson, E.G. Spratt, M.M. Macias, et al., Use of the pediatric symptom checklist in the pediatric neurology population, Pediatr. Neurol. 20 (2) (1999) 116–120, https://doi.org/10.1016/s0887-8994(98)00121-0.
[31] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (9) (2001) 606–613, https://doi.org/10.1046/j.1525-1497.2001.016009606.x.
[32] K. Kroenke, R.L. Spitzer, The PHQ-9: a new depression diagnostic and severity measure, Psychiatr. Ann. 32 (9) (2002) 509–515, https://doi.org/10.3928/0048-5713-20020901-06.
[33] S. Gilbody, D. Richards, S. Brealey, C. Hewitt, Screening for depression in medical settings with the patient health questionnaire (PHQ): a diagnostic meta-analysis, J. Gen. Intern. Med. 22 (11) (2007) 1596–1602, https://doi.org/10.1007/s11606-007-0333-y.
[34] L. Manea, S. Gilbody, D. McMillan, Optimal cut-off score for diagnosing depression with the patient health questionnaire (PHQ-9): a meta-analysis, CMAJ. 184 (3) (2012) E191–E196, https://doi.org/10.1503/cmaj.110829.
[35] L. Manea, S. Gilbody, D. McMillan, A diagnostic meta-analysis of the patient health Questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression, Gen. Hosp. Psychiatry 37 (1) (2015) 67–75, https://doi.org/10.1016/j.genhosppsych.2014.09.009.
[36] C. Diez-Quevedo, T. Rangil, L. Sanchez-Planell, K. Kroenke, R.L. Spitzer, Validation and utility of the patient health questionnaire in diagnosing mental disorders in 1003 general hospital Spanish inpatients, Psychosom. Med. 63 (4) (2001) 679–686, https://doi.org/10.1097/00006842-200107000-00021.
[37] A. Pinto-Meza, A. Serrano-Blanco, M.T. Peñarrubia, E. Blanco, J.M. Haro, Assessing depression in primary care with the PHQ-9: can it be carried out over the telephone? J. Gen. Intern. Med. 20 (8) (2005) 738–742, https://doi.org/10.1111/j.1525-1497.2005.0144.x.
[38] R.L. Spitzer, K. Kroenke, J.B. Williams, B. Löwe, A brief measure for assessing generalized anxiety disorder: the GAD-7, Arch. Intern. Med. 166 (10) (2006) 1092–1097, https://doi.org/10.1001/archinte.166.10.1092.
[39] J.M. Saudubray, À. Garcia-Cazorla, Inborn errors of metabolism overview: pathophysiology, manifestations, evaluation, and management, Pediatr. Clin. N. Am. 65 (2) (2018) 179–208, https://doi.org/10.1016/j.pcl.2017.11.002.
[40] C. Lampe, C. Dionisi-Vici, C.M. Bellettato, et al., The impact of COVID-19 on rare metabolic patients and healthcare providers: results from two MetabERN surveys, Orphanet J Rare Dis 15 (2020) 341, https://doi.org/10.1186/s13023-020-01619-x.
[41] A. Fabre, K. Baumstarck, A. Cano, A. Loundou, J. Berbis, B. Chabrol, et al., Assessment of quality of life of the children and parents affected by inborn errors of metabolism with restricted diet: preliminary results of a cross-sectional study, Health Qual. Life Outcomes 11 (1) (2013) 1.
[42] A. Ouattara, N. Resseguier, A. Cano, et al., Determinants of quality of life in children with inborn errors of metabolism receiving a restricted diet, J. Pediatr. 242 (2022) 192–200.e3, https://doi.org/10.1016/j.jpeds.2021.11.021.
[43] F. Bösch, M.A. Landolt, M.R. Baumgartner, et al., Health-related quality of life in paediatric patients with intoxication-type inborn errors of metabolism: analysis of

an international data set, J. Inherit. Metab. Dis. 44 (1) (2021) 215–225, https://doi.org/10.1002/jimd.12301.

[44] Save the Children, Crecer Saludable(mente). Un analisis sobre la salud mental y el suicidio en la infancia y la adolescencia, Save the Children España, 2021. https://www.savethechildren.es/sites/default/files/2021-12/Informe_Crecer_saludablemente_DIC_2021.pdf?utm_source=NotaPrensa&utm_medium=referral&utm_campaign=SaludMental.

[45] Hasina Samji, Wu Judy, Amilya Ladak, Caralyn Vossen, Evelyn Stewart, Naomi Dove, David Long, Gaelen Snell, Review: mental health impacts of the COVID-19 pandemic on children and youth – a systematic review, Child Adolesc. Mental Health 27 (2) (2022) 173–189, https://doi.org/10.1111/camh.12501.