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ORIGINAL ARTICLE

THE IMPACT OF THE COVID-19 PANDEMIC ON INDIVIDUALS WITH DOWN SYNDROME: A CROATIAN SURVEY

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ABSTRACT

Background: Severe acute respiratory syndrome coronavirus-2 infection has spread uncontrollably worldwide. Among the most vulnerable groups in society are populations with multiple comorbidities, including individuals with Down syndrome (DS).

Aim: Our aim was to conduct an online survey to assess the impact of COVID-19 on DS individuals in Croatia. We also explored the views of their parents and caregivers about the challenges they faced during COVID-19.

Methods: The anonymous online survey was launched in March 2022 and remained open until October 2022. Participants were conducted online through closed group on Facebook. The survey included questions about participant characteristics, medical information, clinical presentation of COVID-19, and challenges faced by the parents during COVID-19.

Results: A total of 268 surveys were collected and analysed. We found that age and body mass index of DS individuals were significantly and positively correlated with the clinical presentation of COVID-19. Lack of social activities, cancelled therapies, and psychological problems were the most frequently cited challenges during the pandemic.

Conclusion: Clinicians and caregivers should primarily be alert to the same COVID-19 signs and symptoms that occur in the general population (fever, cough, shortness of breath). Ongoing therapies, social activities, and psychological support should be cited as indispensable for maintaining physical health and emotional well-being in DS individuals.

Keywords: COVID-19; Croatia, Down syndrome; health; pandemic

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has spread uncontrollably worldwide. Among the most vulnerable groups in society are populations with multiple comorbidities, including individuals with Down syndrome (DS) [1]. Down syndrome, an expression of chromosome 21 trisomy (Chr21), is the most common genetic disorder known to date. It is observed in 1 in 400-1500 newborns worldwide [2]. Individuals with DS suffer varying degrees of cognitive disability, morphogenetic abnormalities, and a number of specific comorbidities. In addition, DS is often characterized by upper respiratory tract anatomical differences, immune dysfunction, and cardiovascular disease, which may promote coinfection and increase the risk for more severe clinical outcomes of COVID-19 [3,4]. In addition, Chr21 contains genes directly involved in the cell entry of SARS-CoV-2 (e.g. *TMPRSS2, APP, SYNJ1, ITSN1*) [5], and multiple genes involved in orchestrating immune response (e.g. four interferon receptors, which serve as receptor subunits for the interleukins [6].

To gain insight into the susceptibility, manifestation, and impact of COVID-19 and DS, the Trisomy 21 Research Society (T21RS) conducted the largest survey of individuals with DS who had COVID-19. The survey was designed to describe the epidemiologic and clinical characteristics of COVID-19 and Down syndrome, including risk factors for severe disease progression, compared to those in

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the general population. Preliminary results that are based on >1000 individuals with Down syndrome suggest a more severe manifestation of SARS-CoV-2 infection, with more severe medical complications and a higher mortality rate in individuals with DS compared with individuals without [7]. Since 2021 several studies have examined the impact of the COVID-19 pandemic on health in people with DS from diverse countries [8,9,10,11,12,13,14,15,16,17].

Considering this, we conducted an online survey between March and October of 2022 to assess the impact of COVID-19 on DS individuals in Croatia. In addition, we explored the views of their parents and caregivers about the challenges they faced during COVID-19 and their experience with medical support.

MATERIALS AND METHODS

Study design

This anonymous online survey was launched on March 22, 2022, and remained open until October 10, 2022. It was approved by the Institutional Review Board of the Biomedical Research Ethics Committee of the Faculty of Medicine, University of Rijeka (Ref. No 2170-24-04-3/1-22-13). The survey targeted parents and caregivers of DS individuals in Croatia.

Participants

Participants were recruited online through a closed Facebook support group DS – the strength of chromosome 21 (576 members). The group offered education and support for parents and caregivers of DS individuals. Potential participants received a link to the survey website. Inclusion criteria were a willingness to participate in the study and a completed questionnaire. An information sheet for participants was provided at the beginning of the survey.

Survey

The questionnaire was originally developed in Croatian by the authors for the current survey. It included 18 questions on participant characteristics (six questions), medical information (three questions), clinical presentation of COVID-19, treatment, and vaccination (six questions), as well as challenges parents faced during COVID-19, the impact on the child, and medical support for them (three questions). To preserve the anonymity of the survey, no internet log addresses were collected. The full questionnaire can be found in the Supplementary material. Additionally, participant characteristics were compared with data of T21RS.

Data analysis

Statistical analysis was performed using SPSS version 13.3 (StatSoft, Inc., Tulsa, OK, USA), for Windows. Descriptive statistics were used to summarize the data. Categorical data were described as frequencies (percentages), and quantitative variables were expressed as means (SD). A chi-square test examined the differences between categorical variables to determine if they were related. Post hoc tests were applied to detect specific differences between groups when results were statistically significant. One-way ANOVA was used to compare independent and dependent variables, whereas Pearson correlation measured the statistical relationship between the variables.

Results

We collected 268 surveys from parents or caregivers of individuals with DS from March to October 2022. Results stratified by category are shown below.

Participant characteristics

Participant characteristics are listed in Table 1. The most common age category was 5-12 years (38.4%), with a mean age 8.7± 8.1 (mean±SD) years. The proportion of male children was slightly higher (54.1%). Our study showed that 60.8% of DS individuals had body mass index (BMI) <18.5 kg/m^2. There was a statistically significant association between BMI and age (r=0.811). The majority of cases (74.7%) had full trisomy 21 and a moderate level of intellectual disability (34.7%). Most of the cases lived at home with their family (95.5%). In comparison with high-income countries (HICs), all analysed participant characteristics (except gender) were significantly different (p<0.05).

Medical information

We catalogued 18 different comorbidities that are common in individuals with DS. Congenital heart defect (CHD) was the most common comorbidity (41.4%), followed by thyroid disorder (19.5%) and allergies (8.6%). Among CHDs, the most common type was atrioventricular septal defect (AVSD) (32.4%). Overall, 69.8% of cases reported not taking any supplements, whereas the others who reported their daily intake, mainly used probiotics (34.0%), multivitamins (29.8%), and vitamin D (25.6%) (Table 2). There was no statistically significant correlation between CHDs/supplementation with symptom severity (r= -0.190; r=0.001).

Clinical presentation of COVID-19, treatment and vaccination

About half of the cases reported being SARS-CoV-2 positive (50.7%). The main signs and symptoms associated with COVID-19 in individuals with DS were fever, cough, and shortness of breath - alone or in combination (Table 3). The chi-square test for a relationship between

Table 1. Participant characteristics (N=268) in comparison with high income countries (T21RS data)

	Count (N)	Percent (%)	Count (N)	Percent (%)	
	CROATIA		HIC		P – value*
AGE, mean (SD)	8.7 (8.1)		33.5 (19.1)		<0.001
0-1	49	18.3			
2-4	55	20.5			
5-12	103	38.4			
13-19	32	11.9			
>20	29	10.9			
GENDER					0.773
Female	123	45.9	355	44.7	
Male	145	54.1	436	54.9	
Other	0	0.0	3	0.4	
BMI, mean (SD)	19.1 (6.2)		not reported		
<18.5	163	60.8			
18.5-25	56	20.9			
25-30	27	10.1			
>30	14	5.3			
Missing	8	2.9			
TYPE OF TRISOMY 21					<0.001
Full/standard	201	74.7	274	88.4	
Mosaic	11	4.1	29	9.4	
Translocation	17	6.3	5	1.6	
Don't know	39	14.9	2	0.6	
LEVEL OF INTELLECTUAL DISABILITY					<0.001
Borderline/mild	91	34.0	126	18.3	
Moderate	93	34.7	404	58.7	
Severe/profound	19	7.0	158	23.0	
Don't know	65	24.3	0	0.0	
LIVING SITUATION					<0.001
Living at home with family	256	95.5	425	55.5	
Living at home with caregivers	2	0.8	10	1.3	
Residential care facility	6	2.2	181	23.6	
Other	4	1.5	149	19.5	

*tested with $\chi 2$ test (categorical variables) or t-test (continuous variables); BMI=body mass index, HIC=high income countries

age and symptoms of COVID-19, showed a statistically significant positive association ($\chi 2$=23.35; P=0.025). A post hoc test revealed that this difference originated from age group 3 (5-12 years), which was found to have the lowest number of symptoms, compared with all other groups ($\chi 2$=12.28; P=0.006). BMI was significantly and positively correlated with clinical presentation of COVID-19 (F(1.13)=5.44; P=0.021). The most common medications were paracetamol, azithromycin, and natural remedies - alone or in combination. 4.4% of cases reported medical complications due to COVID-19 and were hospitalised. Vaccination against SARS-CoV-2 was reported in 11.2% of DS individuals (Table 3).

Challenges for parents during COVID-19, impact on the child and medical support for parents

Overall, 144 (53.7%) of parents reported one or more challenges during COVID-19. The lack of social activities, cancelled therapies, and psychological problems were most frequently mentioned (Table 4). Significant impairment of the child's physical health and/or emotional well-being was reported in 19.7% of cases. Parents' level of satisfaction with medical support ranged from 'not satisfied' (12.7%) to 'very satisfied' (17.9%), with the highest proportion in the 'moderately satisfied' group (21.7%) (Figure 1, Table 4).

Table 2. Medical information (N=268)

	Count (N)	Percent (%)
COMORBIDITIES		
Allergy	23	8.6
Blood cancer	2	0.8
Celiac disease	8	2.9
Chronic lung disease	3	1.2
Congenital heart defect	111	41.4
Epilepsy/seizures	7	2.6
Gastroesophageal reflux	6	2.2
Immune-compromised	10	3.7
Obesity	11	4.1
Obstructive sleep apnoea	5	1.9
Thyroid disorder	52	19.5
Other	8	2.9
No comorbidities	22	8.2
Congenital heart defect type		
Aortic stenosis	2	1.8
Atrial septal defect	24	21.6
Atrioventricular septal defect	36	32.4
Combined heart defect	10	9.0
Ductus arteriosus persistens	6	5.4
Tetralogy Fallot	2	1.8
Ventricular septal defect	22	19.8
Don’t know	9	8.2
SUPPLEMENTATION		
No	187	69.8
Yes, one	47	17.5
Yes, two or more	34	12.7
Supplements		
Multivitamins	28	29.8
Omega 3	10	10.6
Probiotics	32	34.0
Vitamin D	24	25.6

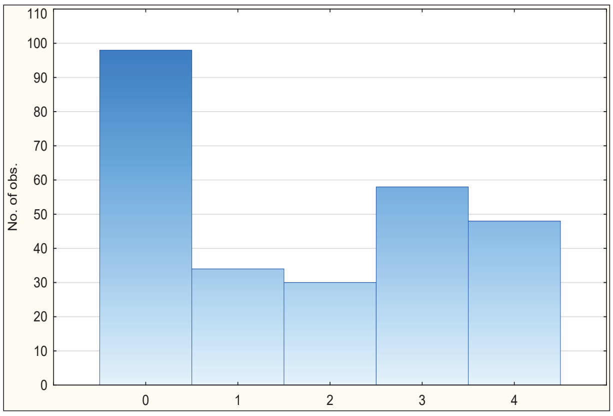

Figure 1. Parents’ level of satisfaction with medical support (0=N/A 1=Not satisfied, 2= Slightly satisfied, 3- moderately satisfied, 4= Very satisfied)

Table 3. Clinical presentation of COVID-19, treatment and vaccination (N=268)

	Count (N)	Percent (%)
SARS-CoV-2		
-	132	49.3
+	136	50.7
NUMBER OF SYMPTOMS		
0	13	9.5
1	60	44.2
2	40	29.4
≥3	23	16.9
Symptoms		
Cough	6	4.8
Runny nose	9	7.3
Fever ≥38°C	45	36.6
Fever ≥38°C + cough	21	17.1
Fever ≥38°C + shortness of breath	4	3.3
Fever ≥38°C + muscle or joint pain	4	3.3
Fever ≥38°C + nasal signs	6	4.9
Fever ≥38°C + cough + shortness of breath	9	7.3
Fever ≥38°C + cough + nasal signs	8	6.5
Other	11	8.9
TREATMENT		
At home	130	95.6
In hospital	6	4.4
MEDICATIONS		
Azithromycin	7	5.1
Natural remedies	17	12.5
Paracetamol	49	36.1
Paracetamol + azithromycin	4	2.9
Paracetamol + natural remedies	7	5.1
Nothing	47	34.6
Other	5	3.7
MEDICAL COMPLICATIONS DUE COVID-19		
-	130	95.6
+	6	4.4
VACCINATION AGAINST SARS-CoV-2		
-	238	88.8
+	30	11.2

DISCUSSION

It is known that individuals with DS have specific comorbidities and immune response dysfunctions that lead to a significantly higher risk of developing severe symptoms of infectious disease, in this specific case, COVID-19 [4]. While the difference in severity of COVID-19 between

Table 4. Challenges for parents during COVID-19, impact on the child and medical support for parents (N=268)

	Count (N)	Percent (%)
NUMBER OF CHALLENGES		
0	124	46.3
1	72	26.9
2	58	21.6
≥3	14	5.2
Challenges		
Cancelled therapy	20	13.9
Cancelled therapy + lack of social activity	22	15.3
Cancelled therapy + lack of social activity + psychological problems	9	6.3
Lack of social activity	32	22.2
Lack of social activity + psychological problems	24	16.7
Psychological problems	16	11.1
Other	21	14.5
IMPACT ON THE CHILD		
No impact	125	46.6
Emotional well-being	32	11.9
Physical health	10	3.7
Physical health + emotional well-being	11	4.2
N/A	90	33.6
MEDICAL SUPPORT FOR PARENTS		
Not satisfied	34	12.7
Slightly satisfied	30	11.2
Moderately satisfied	58	21.7
Very satisfied	48	17.9
N/A	98	36.6

individuals with and without DS is well established, the question is whether we can apply the conclusions from the international T21RS online survey to different cultural and demographic groups [7,18]. To investigate this, we conducted an online survey in Croatia to collect COVID-19 information on the clinical presentation of COVID-19 and disease progression in individuals with DS and the challenges for their parents during the COVID-19 pandemic.

Our group of DS individuals were children with a mean age of 8.7± 8.1 years. This is important to note because previous studies suggest that children do not have the same risk of COVID-19 related mortality as older adults [19]. However, compared with children without intellectual and developmental disabilities, the mortality rate from COVID-19 was reported as increased in individuals with DS [20]. Our results showed a statistically significant positive association between age and the number of symptoms. This may serve as one of the markers for the severity of COVID-19. Interestingly, post-hoc analysis showed that the least affected age group was that of 5-12-year-olds. The reasons for the differences in clinical manifestations between children and adults are likely age-related comorbidities, along with age-related factors that may modulate the antiviral immune response: a more vigorous innate response that promotes more efficient viral clearance, a stronger local innate IFN response in the airways mediated by cells producing IL-17A and IFN-γ, higher baseline innate activity in nasal mucosae, and increased frequency of naïve T cells, depletion of natural killer (NK) cells, and lower frequency of cytotoxic T cells in peripheral blood immune cells [21,22].

Moreover, our analysis showed a significant and positive correlation between BMI and clinical presentation of COVID-19. Obesity is the other known risk factor for more severe cases of COVID-19, and obesity is common in individuals with DS [23]. The proposed mechanism that leads to COVID-19 is immune system dysregulation leading to chronic meta-inflammation that can blunt the host antiviral response [24]. In addition, obesity is associated with upper airway obstruction, obstructive sleep apnoea, lower lung capacity and reserve, which can make ventilation more difficult, especially with DS, where this is exacerbated by specific anatomical differences. The T21RS survey highlights obesity as a significant risk factor for hospitalisation in paediatric COVID-19 patients with DS [7]. Another statistically significant pattern found in our study is the increase in BMI with age, which is consistent with data from the literature [24, 25]. The unusual distribution is seen in the different types of trisomy 21. Indeed, the full/standard type is represented by only 74.7%, while the other types (mosaic; translocated) have the expected distribution (4.1%; 6.3%). This can be explained by the high percentage of parents (14.9%) who do not know the type of T21, which is probably regular and therefore, consistent with the expected numbers and the reports from HICs. Similar pattern can be observed in the levels of intellectual disabilities [7].

As expected, the most common comorbidity in our group was CHD. Structural heart defects were reported in approximately 40% of DS individuals, with AVSDs, being the most common, which is consistent with the literature [26,27]. In DS individuals, the interplay of complicated cardiovascular and respiratory anatomy and pathophysiology may lead to increased severity and mortality of respiratory infections [28]. Nevertheless, we did not find any statistically significant correlation between CHDs and symptom severity in our group.

Dietary supplementation as the main reason of improved immunity has continued to increase, especially during COVID-19 pandemics [29]. In addition, there is considerable clinical interest in whether children with DS benefit from therapeutic supplementation to improve their development, cognitive decline, and overall health [30]. Accordingly, we analysed this field and found that the most commonly used supplements were probiotics, multivitamins and vitamin D. However, there was no significant association with the milder COVID-19 disease symptoms.

As with the general population, fever, cough and shortness of breath were the most common signs and symptoms associated with COVID-19 in individuals with DS [31]. Interestingly, less than 10% of DS individuals were hospitalized and developed complications due to infection with COVID-19 in our study, while T21RS reported 38.8% hospitalised DS patients [7].

Accordingly, the medications used for treatment were predominantly paracetamol, azithromycin, and natural remedies. Possible explanations for this phenomenon include non-participation of older adults with DS, the most vulnerable group, or underrepresentation of patients from the lowest socioeconomic groups who may have been at increased risk for poor outcomes. It would also be interesting to consider whether intellectual disability and young age are also associated with underdiagnoses of symptoms.

The final part of the survey addressed parents' (caregivers') experiences with health services and support during the pandemic. Overall, the largest proportion of parents reported being moderately satisfied with the medical support they received. This is consistent with the European survey of parents' experiences with health services related to COVID -19 and children with congenital anomalies. Reports for Croatia were in a similar range [32]. In addition, many participants reported disruptions in their child's routine care that appeared to affect the physical health and emotional well-being of some children. Most of the disruptions were related to discontinued therapies, lack of social activities, and psychological problems, similar to the European survey reports [32].

Our study has some limitations. Since we included only DS patients, we could not consider some specific differences compared to DS the rest of the population infected with COVID-19. In addition, our sample was limited to Croatian individuals and was therefore smaller compared to data from some other T21RS countries. Most of the respondents were parents of children with DS, so we lacked data from the DS adult group. This is a possible reason for the small sample of hospitalized patients, which prevented us from inferring any severe complications of COVID-19.

CONCLUSION

Our study examined the effects of COVID-19 on individuals with DS in Croatia. We found that age and BMI of DS individuals significantly and positively correlated with clinical presentation of COVID-19. Given the limited data, the present study also suggests that younger individuals are unlikely to develop severe disease. Clinicians and caregivers should primarily look for the same signs and symptoms that occur in the general population (e.g., fever, cough, shortness of breath). Considering the views of parents and caregivers of DS individuals and the challenges they faced during COVID-19 and their experiences with medical support, ongoing therapies, social activities, and psychological support should be cited as inevitably important for maintaining physical health and emotional well-being in DS individuals.

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