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RESEARCH LETTER

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The dark side of COVID-19: The need of integrated medicine for children with special care needs

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To the Editor:

During the coronavirus disease 2019 (COVID-19) outbreak, the Italian healthcare system dramatically changed in terms of delivery of standard of care. In Italy, about 2 million patients are affected by various rare disorders (70% of these are pediatric patients). A multidisciplinary approach is routinely performed in third-level specialized centers in order to provide an assessment of global disease impact and to prevent and manage disease sequelae and comorbidities. Against this background context, the COVID-19 pandemic completely altered a previously well-organized and carefully planned approach. Medical attention was invariably focused on COVID-19, overshadowing any other potential clinical issue. Families of children affected by rare diseases were often geographically/physical isolated far from their normal treatment centers, and physicians were unable to fulfill their "traditional" role in caring for these patients. In this suddenly and drastically changed system, three main issues have been unmasked; these involve the prevention and management of sequelae and comorbidities in children with rare diseases. We discuss these issues in turn, and describe specific examples we have observed to illustrate these points.

First issue: *lack of expertise*

In this section, we discuss about how lack of knowledge and experience related to congenital disorders may inadvertently lead to severe medical complications. Each genetic condition, especially when the pathogenesis is relatively well known and delineated, is usually characterized by a distinct phenotype and multiple organ involvement; secondary medical complications may frequently impact the everyday life of affected patients. These complications can impact the patient's outcome and the overall family well-being. One crucial role of a physician who is an expert on rare disorders is to recognize the cardinal features related to the syndrome and to be aware of potential complications in order to plan a personalized care plan so as to monitor signs and symptoms, prevent secondary complications, and support interconnections with local healthcare providers.

Clinical report 1

Two girls (15 and 25 years of age) affected by classical Cornelia de Lange syndrome (Kline et al., 2018), with severe intellectual disability, developed gastrointestinal symptoms (vomiting, abdominal pain) associated with irritability. Contact of local professionals via the parents led to suspicion of acute gastroenteritis; a rehydration and "watchful waiting" approach was suggested. Due to persistent vomiting, and worsening of self-aggressive behavior, the parents phoned the referring expert doctors, who recommended urgent clinical evaluation at local hospitals for suspicion of intestinal occlusion (a common medical complication related to the syndrome); this was offered despite advice to wait for the clinical features' evolution because of issues related to the COVID-19 pandemic. Bowel occlusion and malrotation was diagnosed in both girls, and large bowel resection was performed. They were both admitted to Intensive Care Unit; the younger girl was discharged after 21 days of hospitalization, while the older one died after 6 days due to sepsis. Oropharyngeal swabs were negative for Severe Acute Respiratory Syndrome- Coronavirus- 2 (SARS-CoV-2) in both.

Second issue: *lack of experience*

This section refers to how lack of experience about clinical management of specific genetic conditions may affect patient's outcome even

Angelo Selicorni and Giuseppe Zampino contributed equally to this study.

during routine visits. Both physicians and paramedic staff taking care of children with rare disorders must know how to approach the patient during a visit, which kind of movement or posture the patient can tolerate, and which kind of behavior the staff may have in order to decrease patients' anxiety and frustration.

Clinical report 2

A 2-year- old child with osteogenesis imperfecta (Ralston & Gaston, 2020) with left humeral fracture, went to a local hospital to obtain an X-ray. The family went to the local hospital since the referral center was turned into a COVID-19 hospital, according to national healthcare reassessment. Soon after the X-ray procedure, the child showed irritability and pain. Subsequent X-rays showed two new fractures affecting the right humerus and right femur, requiring surgical intervention. The child was then transferred to referral center for treatment. Oropharyngeal swab was negative for SARS-CoV-2.

Third issue: *lack of integrated medicine*

This issue represents a crucial point for chronic conditions. Usually, all medical records of patients followed for genetic disorders are stored in tertiary reference centers; families receive follow-up discharge letters with comprehensive medical recommendations about patient care; the family then delivers the medical documentation to local family doctors. The lack of a facilitated integrated network and direct interconnection between patients' local healthcare services, family doctors, and tertiary reference centers represent a great challenge in the current situation.

Clinical report 3

A 7-year -old girl affected by Kabuki syndrome (Wang, Xu, Wang, & Wang, 2019), with a history of febrile seizures presented with intractable seizures associated with high fever. The child was taken to the local COVID-19 hospital, where oropharyngeal swab for SARS-CoV-2 was negative. The management of acute neurological aspects prolonged the child's admission due to unavailability of her baseline clinical information. This information was stored at the tertiary referral center, which was locked due to the COVID-19 pandemic.

In the era of advanced technologies, including functional genomics, artificial intelligence, and machine learning, the SARS-CoV-2 outbreak shed light on multiple fragile points of medical care. The red line connecting the medical history of our four patients simply summarizes how dangerous the lack of a quick, accessible network between first-care level hospitals, family doctors, and referral centers can be. This pandemic clearly points to the need for a health system reassessment planning to prevent such issues from recurring.

We are beginning the search for a new medical paradigm by examining processes and procedures that could achieve sustainable health system, while guaranteeing adequate access to cures, tailored treatments, and personalized medical care for all patients, especially for those with special care needs. We have been forced to change the classical way we approach the practice medicine, going from bedside to homecare. SARS-CoV-2 may not greatly increase the death risk in our patients, as the prognosis of these infectious diseases in pediatric patients appears less guarded (Cruz & Zeichner, 2020). However, of the effects of the COVID-19 pandemic and the lack of a truly integrated system medicine could ultimately increase morbidity and mortality of these patients if scientific and political community will not field new strategies to improve the "know-how" and relevant patient management in all medical centers (Lazzerini et al., 2020).

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DATA AVAILABILITY STATEMENT

Data available on request from the authors.

AUTHOR CONTRIBUTIONS

Chiara Leoni conceptualized and designed the study, wrote the manuscript, reviewed and revised the final manuscript. Valentina Giorgio acquired clinical data on Case 1 (first patient), reviewed, and revised the manuscript. Roberta Onesimo drafted and reviewed the article. Luigi Tarani acquired clinical data on Case 3, reviewed, and revised the manuscript. Mauro Celli acquired clinical data on Case 2, reviewed, and revised the manuscript. Angelo Selicorni acquired clinical data on Case 1 (second patient), reviewed, and revised the manuscript. Giuseppe Zampino critically reviewed and revised the manuscript for important intellectual content. All authors approved the final version of the manuscript as submitted and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

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