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First case reported of COVID-19 infection in an adult patient with Ellis-van Creveld Syndrome

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ABSTRACT

Ellis-van Creveld syndrome (EVC) is a rare autosomal recessive disorder, the features of the syndrome are: chondral and ectodermal dysplasia characterized by short ribs, polydactyly, growth retardation resulting in dwarfism, teeth and craniofacial abnormalities and heart defects (mostly endocardial cushions and atrial septal defects).

We describe the first case reported of COVID-19 infection in a 24-years-old girl, diagnosed with EVC syndrome. The patient suffered only from a mild illness, she remained stable with normal saturation without need of neither respiratory support nor specific therapy and she was rapidly discharged.

This case appraises the pathophysiological interplay between different specific prognostic variable in a syndromic patient with congenital heart disease and COVID-19. In patients with congenital heart disease, comorbidities related to syndromic picture may affect the clinical course of COVID-19 infection regardless of the anatomic complexity.

1. Background

Ellis-van Creveld syndrome (EVC) is a rare autosomal recessive disorder, firstly described in 1940 by Richard W.B. Ellis and Simon Van Creveld [1]. It is caused by mutations in the EVC or EVC2 genes located on the chromosome 4, coding for components of the primary cilia, and is associated to parental consanguinity in about 30% of cases [2–4].

EVC syndrome, like Jeune asphyxiating thoracic dysplasia (JATD), is part of the skeletal ciliopathies, sharing common clinical and radiological features. There is a large spectrum of severity in skeletal involvement, however, differently from JATD, extreme thoracic hypoplasia is rare in EVC [5].

The EVC syndrome features include chondral and ectodermal dysplasia characterized by short ribs, polydactyly, growth retardation resulting in dwarfism, teeth and craniofacial abnormalities and heart defects [6–8]. The prevalence of cardiac anomalies in patients with EVC syndrome has been estimated to affect 60% of individuals [9]. The cardiac phenotype in patients with EVC syndrome reveals a characteristic pattern of atrioventricular septal defects (AVSD) with systemic and pulmonary venous connection abnormalities and common atrium [10]. We report the first case of COVID-19 in a patient with EVC syndrome emphasizing the possible pathophysiological link between the typical features of this syndrome and the clinical course of the disease.

2. Case description

We describe the first case of COVID-19 infection in a 24-years-old girl, diagnosed with EVC syndrome. She had undergone ostium primum atrial septal defect repair at age of five, genu valgum deformity correction and tibial lengthening at the age of eleven [11]. At age of ten, she was prescribed growth hormone, that she stopped due to headache [12]. The patient displayed all the somatic syndromic signs, including teeth agenesis, short lingual frenulum and obesity. In addition she was on chronic cortisone acetate because of lichen planus.

The patient presented to the emergency department with fever and dry cough lasting for the last two days. She was eupnoic at rest with normal respiratory rate and chest findings on physical examination. BMI was 28. Oxygen saturation in room air was 98%. Laboratory findings were: Hemoglobin 125 g/L, WBC 5.65 10^9/L, Na 141 mmol/L, K 4.1 mmol/L, CRP 0.2 mg/dl, creatinine 0.60 mg/dl, GOT 21 U/L, GPT 27 U/L, LDH 202 U/L. The chest-X-ray beside showing reduced thoracic diameters was unremarkable, in particular, lung transparency was

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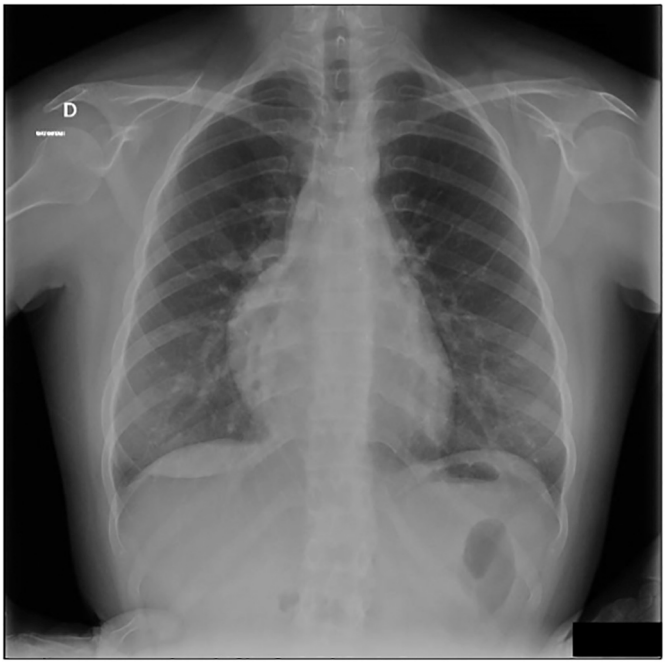

Fig. 1. Chest X ray at admission.

normal (Fig. 1).

The ECG showed sinus rhythm, first degree AV block, left anterior fascicular block, and occasional ventricular ectopics consistent with the underlying congenital anatomy (Fig. 2).

During admission, the patient remained stable with normal saturation without need of neither respiratory support nor specific therapy apart from Paracetamol. She was discharged after five days and the nasopharyngeal swab became negative after fifteen days. Follow up at one month was uneventful and the patient at that time had resumed her normal daily activities

3. Discussion

AVSDs and common atria are usually associated with EVC, suggesting a developmental defect in endocardial cushions [6]. Although primary pulmonary involvement has not been reported in association with Ellis-van Creveld syndrome, respiratory function may be affected by skeletal abnormalities of the thoracic cage. Both cardiac and extra cardiac involvement may affect clinical presentation and severity of COVID-19.

This case offers several pathophysiological issues to discuss. The patient had undergone partial atrioventricular septal defect repair at the age of five, therefore we can speculate that exposure to pulmonary overcirculation in the presence of genetic syndromic background might have altered vascular reactivity. Although pulmonary vascular disease in patients with pre-tricuspid shunt is rare, the association of EVC syndrome with pulmonary vascular disease has been reported [10]. Evidence collected so far indicates that in patients with congenital heart disease, prognosis of COVID -19 infection is dictated by the physiologic stage and comorbidities rather than the anatomic complexity [13,14]. Among comorbidities obesity, cyanosis and pulmonary hypertension have been identified as independent risk factors [15]. The presence of genetic syndromes further complicates the picture depending on specific phenotype. Indeed, scheletric chest abnormalities, reduced vital capacity, and increased BMI in EVC syndrome are relevant comorbidities which might potentially affect in many different ways clinical course of COVID-19 [16]. In particular, normal respiratory function relies on a series of complex interactions between the diaphragm contraction and rotation of the costovertebral joints. In order to ensure this mechanism the thoracospinal unit should grow harmonically with the rest of the body, while any loss of symmetry compromises the respiratory reserve [17]. This might be particularly relevant for COVID 19 lung involvement which is characterized by a significant ventilation perfusion mismatch in the early stages of the disease [18].

Kidneys and liver are other uncommon end organs involved in EVC characterized by glomerular and tubular degeneration and periportal fibrosis, respectively [19]. Although we do not have evidence of renal or

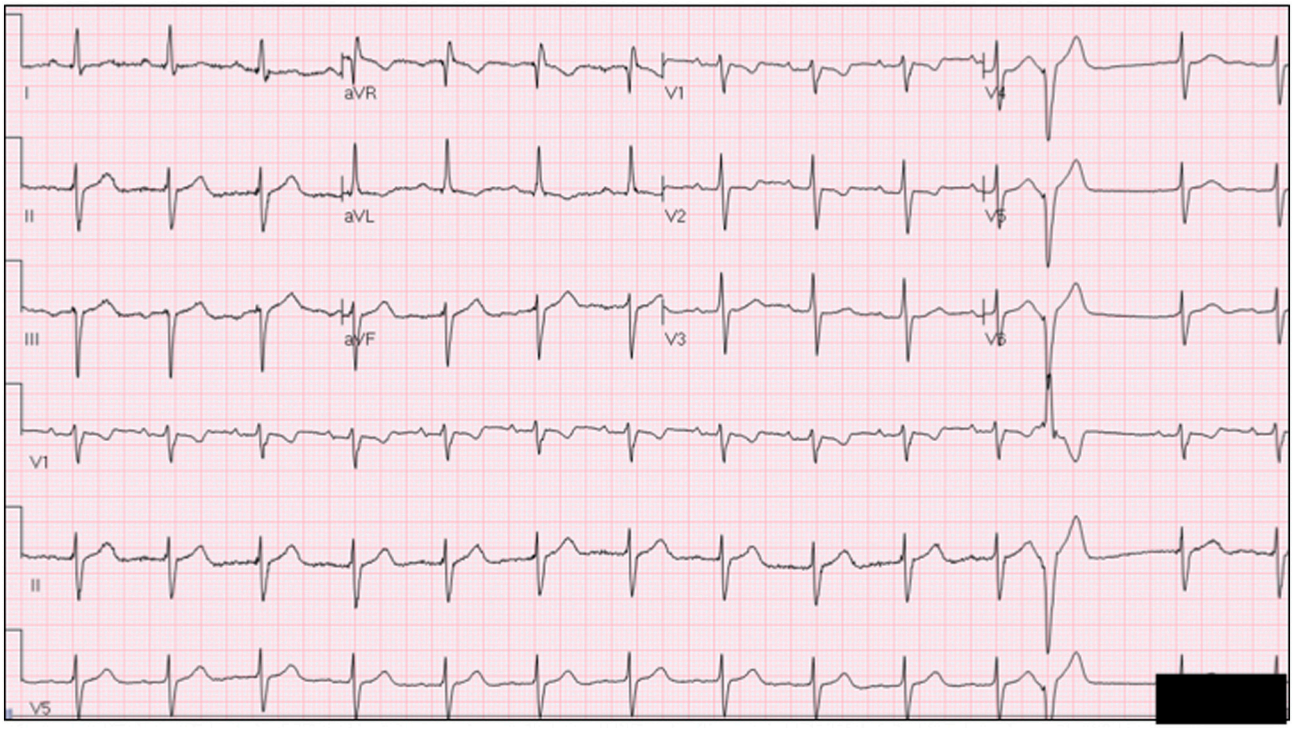

Fig. 2. ECG tracing at admission.

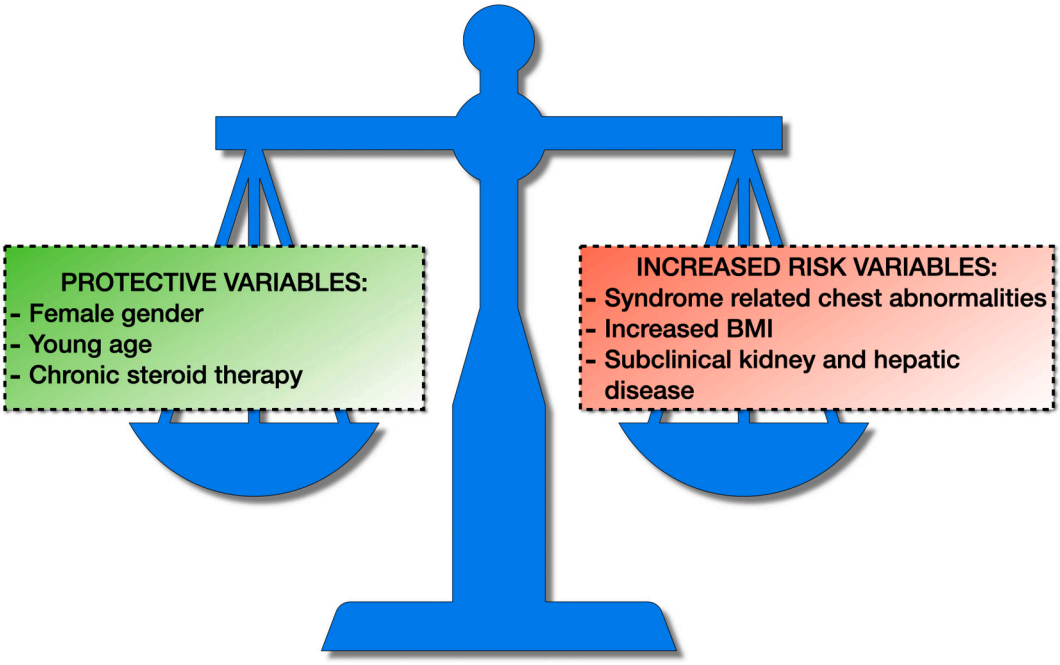

Fig. 3. Diagram summarizing specific variable potentially modulating the risk in EVC syndrome.

hepatic failure in our patient, the aforementioned histologic abnormalities may be subclinical and can be responsible for reduced functional reserve that might be unmasked by COVID-19 infection.

Challenges in the management of COVID-19 infection in patients with genetic syndrome have been widely recognized. Since the initial report of COVID-19 cases, patients with congenital heart disease were globally considered at highest risk [20]. This general concept has been recently challenged by the absence of a documented increased mortality risk in this group of patients as a whole. However has been observed that among patients with congenital defects the coexistence of genetic syndromes, a more advanced physiologic stage, and immunologic disorders [21–24] Most of the literature statements concern the immunodeficiencies and muscular myopathies [25]. The main message is that this particular subset of patients is at higher risk of prolonged hospital stay and mortality, furthermore, the care of these patients should be tailored and lifesaving medications such as steroids should not be withheld but modulated according to the clinical setting [26].

On the other hand, the patient displayed some clinical characteristics that might be considered protective. In particular female gender and young age are recognized as a specific favorable demographic variables [27]. Furthermore chronic steroid therapy with Cortisone acetate might have blunted the inflammatory storm which is deemed to be a crucial pathophysiological mechanism sustaining lung injury (Fig. 3) [28].

4. Conclusion

In conclusion, we present the first case of COVID-19 in a patient with EVC syndrome to be reported. Data on the impact of CHD and syndromes on COVID-19 clinical course are still very scant. This report support the concept arising from preliminary data suggesting that, among CHD patients, the outcome of SARS CoV-2 infection is shaped by the complex interaction of patient specific variables, rather than by the preexisting cardiac condition [13].

Abbreviations

EVC	Ellis van Creveld
JATD	Jeune asphyxiating thoracic dysplasia
WBC	White blood cells
CRP	C-reactive protein
AVSD	Atrioventricular septal defect
ASD	Atrial septal defect
CHD	Congenital heart disease

Ethics approval and consent to participate

Obtained.

Consent for publication

Obtained.

Availability of data and materials

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Dr Isabelle Piazza collects the data and writes the paper.
Dr Paolo Ferrero reviewed and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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