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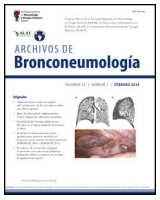

Editorial

Childhood Interstitial Lung Diseases (chILD) Recognition: When Epidemiology Increases a Rare Disease Incidence

Reconocimiento de la enfermedad pulmonar intersticial en niños (chILD): cuando la epidemiología aumenta la incidencia de una enfermedad rara

Rare diseases have always been a challenge for clinicians and researchers: how could it be possible to study and understand a disease when each center sees so few patients? During the last decade, rare diseases networks have importantly increased the connections between the centers, at a national but also at an international level, allowing to collect the cases and to initiate large epidemiologic studies as the one provided by Torrent-Vernetta et al. in the previous issue of this journal.[1]

Childhood interstitial lung diseases (chILD) is even more a challenge than other rare lung diseases, as it is an umbrella term for a multiplicity of exceptional disorders. Even if they share a common designation of their radiologic patterns under the name "interstitial signs", the etiologies of chILD and consequently their clinical presentation, management and prognosis are highly variable, from newborns to teenagers, from pauci-symptomatic to fatal diseases and from supportive care to lung transplantation.

This heterogeneity is illustrated by the complexity of chILDs classification. A couple years ago, chILD were classified according to their histologic aspect, as in adult ILD. However, it became quickly obvious that the pathologic pattern of a congenital alveolar dysplasia, or even of a surfactant disorder did not fit inside the items used in adults such as usual interstitial pneumonia/non-specific interstitial pneumonia/desquamative interstitial pneumonia classification. Thus, pediatric classifications have been proposed over time to include specific pediatric ILD conditions. Almost all of them distinguished two age groups: chILD of infancy (or <2 years-old) and chILD of children older than 2 years-old. To date, many classifications have been proposed by pathologists or clinicians, but the most used classifications are still those provided in the US and in Europe by Kurland et al. in 2013 and Griese et al. in 2015.[2,3]

These efforts in classifying the diseases constituted the first necessary step of a chILD recognition and of a better understanding of each entity's pathophysiology. Progressively, this led to the descriptions of the first national chILD epidemiological studies (Table 1).

In Europe, networks for chILD have been set up since 2013, allowing close collaborations between expert clinicians and researchers of the involved countries, and promoting joints efforts to "put the orphanage out of business".[4] More than 25 countries including non-European countries are currently participating in this chILD-EU network, within various programs that were funded between 2013 and 2021 by the European Union. Today, the "Clinical Research Collaboration for chILDEU" funded by the ERS since 2016 and the European Rare diseases Network (ERN)-lung represent important organizations for the chILD networks.

Between 2013 and 2019 the "chILD better together – European management Plateform for Childhood Interstitial Lung Disease" funded by the FP7 program has allowed to create the kids lung register, first multi-country register for chILD that included in 2021 more than 750 patients with reviewed chILD conditions from 179 centers all over Europe.[5] However, collecting all the incidental cases of chILD is very difficult and chILD's incidence and prevalence remain highly underestimated, due to the lack of systematized reporting process and the high neonatal mortality.

The article provided by Torrent-Vernetta et al. constitutes a new major stone to the chILD building.[1] Since the beginning of the chILD networks, Spain has been an active European member and Spanish authors has largely contributed to describing and better understanding rare chILD. With an elegant prospective methodology on a 2-years period, the major strength of this study is its national recruitment that is very close to a complete population screening. A number of chILD diagnoses is reported herein in 381 patients aged 0–18 years. Interestingly, this very exhaustive study evaluates the chILD's incidence as 8.18 cases/million of children per year, which is much higher than previously suggested (1.32/million in Germany). The prevalence follows the same trend with a prevalence of 46.53 cases/million of children that is also much higher than previously reported (3.6/million in UK and Ireland, 1.5 cases/million in Australasia).[5–7] This increased prevalence may be due to a better collection of the cases, but also to an improvement in chILD management over time. The authors also confirm an infant predominance at disease onset (60% of the cases) despite the absence of recorded case of diffuse developmental disorder during the study period.

Importantly, this study also highlights that at least 12% of chILD are related to a genetic disease with identified mutations in surfactant related genes, multisystemic and auto-inflammatory disorders genes, storage diseases genes and congenital immunodeficiency genes. This large panel of molecular etiologies of chILD points out the importance of a genetic screening as part of the initial diagnosis work-up.[8] Molecular panels using next generation sequencing

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Table 1
Main reported chILD cohorts.

Country/areas	Number of patients	Period of time	Comments	Reference
UK and Ireland	46	3 years		Dinwiddie et al. Ped Pulm 2002.[6]
	46	1 year	BPOLD registry	Laverty et al. Ped Pulm 2008[11]
Denmark	884	10 years	Children <15 years	Kornum et al. BMC Pulm Med 2008[12]
Germany	56	1 year		Griese et al. Orphanet J Rare Dis 2009[13]
France	205	4 years	RespiRare registry	Nathan et al. Orphanet J Rare Dis 2012[14]
Australia and New Zealand	71	5 years	ARNOLD registry	Casamento et al. Orphanet J Rare Dis 2016[15]
	115	10 years		Saddi et al. Orphanet J Rare Dis 2017[7]
USA	93	18 years	Monocentric	Soaers et al. Pediatrics 2013[16]
	256	1 year	ChILDRN network	Young et al. Eur Respir J suppl 62 2018[17]
China	133	5 years	Children >2 years	Tang et al. Ped Pulm 2020[18]
Europe and above	575		Kids Lung Register (179 centers)	Griese et al. Thorax 2017[5]
Spain	381	2 years		Torrent-Vernetta et al. Archivos de Bronconeumologia[1]

technics or whole exome sequencing are now available in many countries and it is possible that in the coming years, it could replace lung biopsy as gold standard for the diagnosis of chILD.

Epidemiologic studies on chILD are reported – and mostly red - by pediatricians. However, with the improvement of chILD management, most of these children will reach adulthood and will be followed in adult pulmonology departments. Adult pulmonologists are not yet prepared to receive these new patients with unknown diseases evolving since a very young age, with specific cares and potential long-term side effects of the treatments.[9] A better collaboration between pediatricians and adult pulmonologists is a crucial step for ensuring a smooth transition of care between the teams, for the patients, but also for the parents and the caregivers.[10] The recently launched ERS statement on Transition of pediatric patients with ILD to the adult care (Task Force number TF-2021-14) includes pediatricians and adults to better prepare the patients to their adult ILD care.

Finally yet importantly, our next goal is providing personalized medicine to children with rare lung diseases. This usually needs to be able to identify the patients in their respective centers. With this challenging aim, the article provided by Torrent-Vernetta et al. should encourage all countries to collect chILD cases and to report them, eventually with longitudinal data, in order to create easily accessible data for each etiology of chILD.

Conflict of interest

None declared.

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