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SMART PEDI UPDATE

Pedi smart News Letter
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Dear Doctor,
Greetings from Micro Labs Limited. We are happy to bring you **"PEDI SMART**"which contain latest and interesting news in the field of Paediatrics.

This issue contains:

1. **Effect of the COVID-19 pandemic on appendicitis management and outcomes in children**
2. **Intra and interobserver reliability in assessing bone marrow signal intensity on whole-body MRI in children.**
3. **The characteristics and risk factors of necrotizing enterocolitis in full-term infants with duct dependent congenital heart disease**
4. **A Case Report on Two siblings with X-linked agammaglobulinemia and bronchiolitis obliterans**

Looking forward to your valuable feedback

Best Regards,

Medical Team, Micro Labs Limited

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1. Effect of the COVID-19 pandemic on appendicitis management and outcomes in children

Introduction:

In children, acute appendicitis is the most prevalent surgical condition. For a variety of reasons, including staff redeployment, operating theatre availability, and concerns about transmission of SARS-CoV-2 from patients to healthcare workers, the SARS-CoV-2 (COVID-19) pandemic caused widespread disruption to the provision of all healthcare, but also surgical care in particular.[1] It was recommended that If non-operative treatment was regarded a viable alternative treatment option, non-operative treatment should be undertaken to prevent surgery for all illnesses, including appendicitis.[2] As the pandemic advanced, new evidence suggested that surgery in individuals infected with Covid-19 was associated to negative outcomes, including an increased risk of death.[3] For children with appendicitis, the potential impact of these substantial changes in healthcare delivery was unknown. The influence of the pandemic on the management of children with appendicitis was surveyed among paediatric and adult surgeons who treat children with appendicitis.[1] This paper summarises the findings from the entire four-month research, and it attempts to evaluate the influence of the pandemic on patient management and crucial outcomes by comparing data to a pre-pandemic group.

The COVID-19 has had a big impact on how children with appendicitis are treated. While the use of imaging and non-operative therapy increased, the rate of negative appendicectomy reduced.

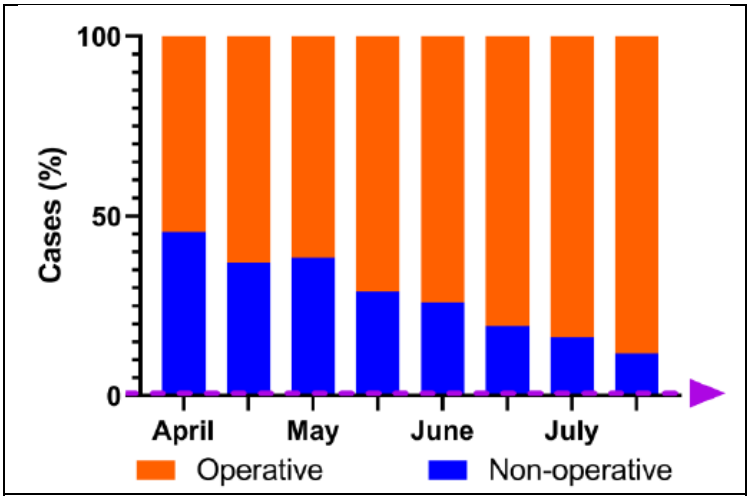
Methods:

A prospective multicentre observational cohort study was conducted on children under the age of 16 at the time of hospital admission who were diagnosed with and treated for acute appendicitis. Children were included in the trial if they were hospitalised and diagnosed with acute appendicitis. Clinical and/or radiological criteria . Children who came with abdominal discomfort but were not suspected of having appendicitis were excluded, but those who were treated for appendicitis but later diagnosed with alternative diagnosis were includedThe primary outcome was the surgical versus non-operative treatment method for acute appendicitis. The number and proportion of open and laparoscopic operating cases, the use of diagnostic imaging, and variation in patient management over time as the epidemic advanced were all secondary outcomes related to patient management. An invasive operation, such as surgical or radiological intervention, such as collection drainage, was defined as re-intervention. The absence of pathology on histological examination of the appendix was defined as negative appendicectomy.

Results:

This analysis comprises 605 children from a similar data set from pre-pandemic and 2002 children treated for acute appendicitis at a median age of 10 (range 1-15) years. 560/2002 (28%) of the pandemic cohort were treated non-operatively at first, with 125/560 (22%) undergoing appendicectomy during their first hospital stay. In the prepandemic group, no non-operative treatment was used. Diagnostic imaging was used more frequently during the pandemic than during the pre-pandemic period (54 % vs. 31 %), although total laparoscopy use was

comparable during both times (62.4 % vs 66.6 %). During the pandemic, hospital readmission rates were lower (8.7% vs 13.9%) than before the pandemic, and re-intervention rates were similar (2.9 vs2.6 %). Negative appendicectomy rates were lower during the pandemic than pre-pandemic (4.4vs15.4 %), and were among the lowest ever documented throughout the pandemic.



Initial management strategy of appendicitis biweekly, operative *vs* non-operative. The red bars represent operative treatment and the blue bars represent non-operative treatment. The purple line represents practice prior to COVID19 pandemic from RIFT study data. During the first two weeks of April the proportion of cases initially treated non-operatively was 46% which reduced to 12% in the last two weeks of July.

Discussion:

When compared to a pre-COVID19 group, this data shows a notable rise in the use of non-operative therapy and open appendicectomy for appendicitis in children during the first four months of the SARS-CoV-2 pandemic . This abrupt shift in practise corresponded with the publication of guidance recommending non-operative treatment whenever possible and cautioning against laparoscopy.[2] As the epidemic progressed, guidelines changed, and clinical practise began to resemble that of the pre-COVID dataset. Based on histological findings, the rate of negative appendicectomy in this dataset is exceedingly low, and it is one of the lowest rates ever documented.[1] As the epidemic progressed, laparoscopy became more common, with a return to normal practise as professional guidelines were updated and the epidemiology of COVID-19 in children became more understood.[4] At the end of the trial, 88 % had undergone laparoscopic appendicectomy, one of the highest rates ever reported in children. Maintaining this high rate of laparoscopy will ensure that children receive the best possible evidence based care.

Conclusion:

In Conclusion, The COVID-19 has had a significant impact on the treatment of appendicitis in children. the use of imaging and non-operative therapy increased, the rate of negative appendicectomy decreased. Overall, the pandemic's treatment changes have had no negative influence on patient outcomes.

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2.Intra and interobserver reliability in assessing bone marrow signal intensity on whole-body MRI in children.

Introduction:

Whole-body magnetic resonance imaging (MRI) is now employed in children for a variety of purposes, including assessing multifocality in inflammatory or malignant disease, as well as detecting preclinical or "silent" lesions. However, no consensus on a standardised imaging protocol or scoring system has emerged to date, and research examining the clinical validity of MRI findings are rare.[1] Previous research has found that up to half of healthy children aged 6–16 years had edema-like changes in their hands and feet that could be misinterpreted as pathology .[2]Several scoring systems for whole-body MRI in children have been proposed, but none of them take into account the whole set of possibilities, from growth and maturation-related findings to actual disease-related signal intensity alterations.[1,3] However, there is currently no definition of what constitutes real pathological bone marrow signal intensity on MRI [1]. The purpose of the study was to look at intra- and interobserver reliability in assessing bone marrow signal intensity on whole-body MRI in children, and to propose a new scoring system based on the most reliable aspects.

The MRI grading of the intensity and extent of high signal intensity areas inside the bone marrow of the pelvis and lower limb is accurate and may be used interchangeably by various observers.

Methods:

This research is part of a multicentre, longitudinal study involving 196 healthy volunteers and 40 patients with nonbacterial osteomyelitis, with the goal of developing a new, MRI-based scoring system for whole-body MRI to describe signal intensity variations in healthy children and distinguish between normal variation and true disease. Researchers used a subset of whole-body MRI examinations from 78 healthy volunteers and 18 patients diagnosed with chronic nonbacterial osteomyelitis between the ages of 6 and 18 to test the variables in our MR-based scoring system. The 96 MR examinations included in this study reflected the entire spectrum of findings, allowing researchers to reliably test the variables within our MR-based scoring system. Two pair of radiologists scored the left lower extremity/pelvis in a blinded fashion using Coronal water-only Dixon T2-weighted images for high signal intensity areas, intensity (0–2 scale), extension (0–4 scale), and shape and contour.

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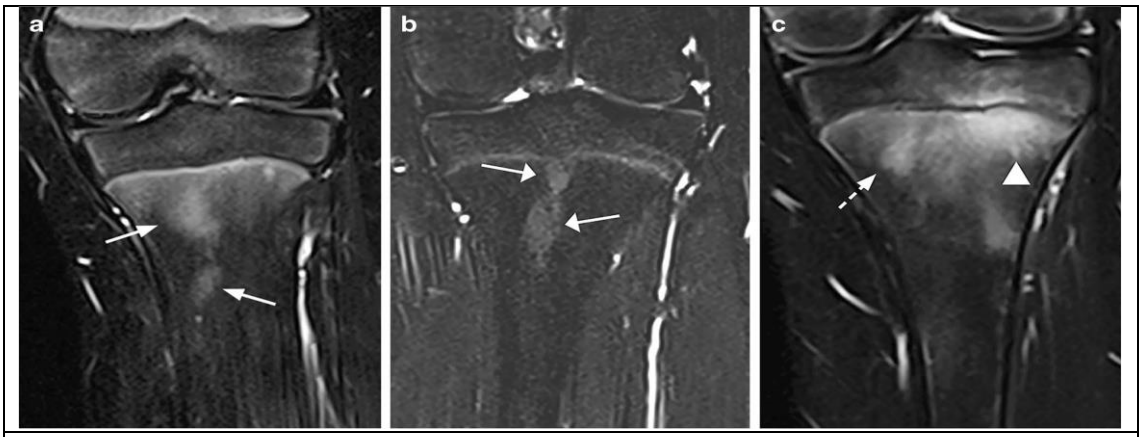

Coronal water-only Dixon T2-weighted magnetic resonance images in **(a)** a 10-year-old boy with an area of increased signal intensity in the metaphysis of the tibia with a diffuse contour (*arrows*), **(b)** a 16-year-old girl with an area of increased signal intensity in the metaphysis of the tibia with a sharp contour (*arrows*) and **(c)** a 14-year-old boy with an area of increased signal intensity in the metaphysis of the tibia with both a sharp and a diffuse contour (*dotted arrow* and *arrowhead*, respectively)

Results:

With kappa values of 0.51–0.94 and 0.41–0.87, respectively, the grading of bone marrow signal in the pelvis demonstrated moderate to good intra- and interobserver agreement. The corresponding numbers for the femur were 0.61–0.68 within and 0.32–0.61 between observers, and 0.60–0.72 and 0.51–0.73 for the tibia, respectively. Except for the femur metaphysis/diaphysis, which had interobserver kappa values of 0.29–0.30, agreement for assessing extension was moderate to good both within and between observers for the pelvis (k = 0.52–0.85 and 0.35–0.80), femur (0.52–0.67 and 0.51–0.60), and tibia (k = 0.59–0.69 and 0.47–0.63). With kappa values of 0.40–0.73 and 0.18–0.69, respectively, form scoring was moderate to good within observers but inferior between observers. The equivalent results for contour were 0.35–0.62 and 0.09–0.54, respectively.

Discussion:

Researchers have identified a set of markers that may be used to explain a wide variety of bone marrow alterations in children and adolescents as measured by whole-body MRI. Researchers believe that grading bone marrow signal strength could help distinguish normal variation from actual pathology, as well as evaluate the severity of pathology and treatment response in a clinical context. For the same observer, grading intensity on a 0–2 scale worked well in general, especially in the lateral sacrum and periacetabular region. The ischiopubic area, the femoral diaphysis, and the distal femoral metaphysis had moderate to fair agreement amongst observers, likely due to the inherit high amount of red bone marrow and high background signal, underlining the significance of rigorous calibration before scoring.[2] Zhao et al.[3]found a mean kappa value of 0.75 for evaluating signal intensity of the long bones on a 0–2 scale in a study of 45 children with a median age of 11 years. However, because they used a freemarginal version of kappa, their results are not directly comparable to those of this study. Researchers in this study looked at the reliability of identifying and rating bone marrow findings, which is an important step toward developing a scoring system for whole-body MRI. Panwar and

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colleagues explain their first consensus-driven phase of designing a wholebody MRI scoring system for screening juvenile idiopathic arthritis patients in a recent review.[4]

Conclusion:

Grading of intensity and extension of high signal intensity areas inside the bone marrow performs well in virtually all sites and can thus be used interchangeably by various observers, whereas shape and contour assessment is reliable for the same observer but less reliable between observers. When conducting clinical studies, this should be considered.

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3. The characteristics and risk factors of necrotizing enterocolitis in full-term infants with duct dependent congenital heart disease

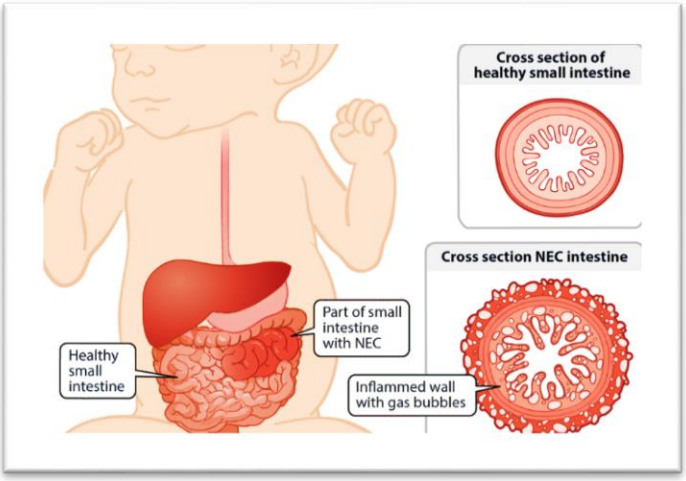
Introduction:

NEC is a medical and/or surgical condition in newborn that is caused by necrosis of the intestinal mucosa or entire gastrointestinal layer. Although NEC is most commonly seen in premature infants, about 10% of cases have been documented in full-term infants. A link between congenital heart disease (CHD) and NEC has been reported in the literature in full-term infants.[1] Primary hypoxia/ischemia, rather than inflammation, has been proposed as a possible mechanism of NEC in full-term infants with CHD, unlike in preterm children. Heart lesions that rely on patent arterial ducts to deliver pulmonary or systemic blood flow are known as duct dependent congenital heart disease (DD-CHD). Administration of prostaglandin E1 (PGE1) to patients with DD-CHD helps to maintain the medical palliative shunt until an interventional surgery can be performed. Although various studies have found that children with DD-CHD have a higher chance of having NEC than infants with other CHDs, information on the clinical features and risk factors for NEC in the former is still lacking.[2]The goal of this research is to look at the clinical characteristics and risk factors of NEC in full-term infants with DD-CHD who have been treated with PGE1.

Necrotizing enterocolitis developed in 3% of full-term newborns with duct dependent congenital heart diseases.

Methods:

A retrospective analysis was carried out at a tertiary newborn critical care unit. The trial comprised fullterm infants with DD-CHD who were given PGE1 within seven days of birth. Infants with DD-CHD were classified into three groups: (i) duct dependent pulmonary circulation, (ii) duct dependent systemic circulation, and (iii) duct dependent with insufficient blood mixing between the two circulations. According to the modified Bell's staging, NEC was defined as stage IIA or higher. The researchers gathered information on demographic and clinical variables such as gestational age, birth weight, sex, and CHD type, as well as age at NEC diagnosis, NEC treatment, feeding status at the time of NEC diagnosis, and whether the patients were mechanically ventilated. Patients were classified as mechanically ventilated if ventilator care was provided between the delivery of PGE1 and hemodynamic intervention. The total PGE1 administration time was recorded. The time from the start of PGE1 infusion to the diagnosis of NEC in patients with NEC was recorded. The route of birth and if the patient's mother had chorioamnionitis or pregnancy-induced hypertension were also gathered for patients with NEC.



Results:

Necrotizing enterocolitis was discovered in ten cases(3.0 %). Their average gestational age was 38.2 weeks, and their birth weight was 2783.5 g. At the time of diagnosis, the median age was 8.0 days (2–70 days). One patient had stage IIA necrotizing enterocolitis, five had stage IIB, two had stage IIIA, and two had stage IIIB; two (20%) of the patients required surgery. Necrotizing enterocolitis was more common in the duct dependent pulmonary circulation group (4.4%) than in the duct dependent systemic circulation (2.0%) or parallel circulation (1.3%) groups. The birth weight (2783.5 g vs 3170.9 g, respectively) and gestational age of the necrotizing enterocolitis and other groups were significantly different (38.2 weeks vs 39.1 weeks, respectively). Significant risk factors were gestational age less than 38 weeks (OR 8.87, p = 0.002), birth weight less than 2500 g (OR 5.1, p = 0.042), mechanical ventilation (OR 4.6, p = 0.021), parenteral feeding (OR 107.7, p 0.001), and functional single ventricle (OR 5.8, p = 0.009).The case-fatality rate in the necrotizing enterocolitis group (40.0%) was greater than in the other group (8.3%, p = 0.009).

Discussion:

Researchers looked into the prevalence of NEC in DD-CHD patients who were administered with PGE1. Previous research has found that NEC manifests earlier in full-term infants or infants with CHD with a median postnatal age of 4 days.[3] However, research on whether the average age of full-term and preterm infants at the onset of NEC is significantly different is ambiguous (28.2 vs 19.6 days). It is widely known that infants born at a younger gestational

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age have a higher risk of developing NEC [27]. Early-term infants have been linked to more adverse outcomes, such as the requirement for respiratory support, hypoglycemia, feeding intolerance, or neonatal intensive care unit care.

Conclusion:

NEC developed in 3% of full-term newborns with DD-CHD. Low birth weight, gestational age less than 38 weeks, functional single ventricle, and neonates on assisted mechanical ventilation or parenteral nutrition are at greater risk.

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4.A Case Report on Two siblings with X-linked agammaglobulinemia and bronchiolitis obliterans

Introduction:

Panhypogammaglobulinemia and low B lymphocyte counts define X-linked agammaglobulinemia (XLA), an Inborn Errors of Immunity (IEI) caused by mutations in the BTK gene. XLA patients are usually immune to viral respiratory infections and do not develop interstitial lung disease (ILD) like bronchiolitis obliterans (BO) as a result of acute or chronic bacterial infections of the respiratory tract.[1,2] Despite the fact that multiple harmful variants in XLA have been identified, the diverse clinical manifestations of afflicted patients imply a more complicated genetic landscape underlying this condition.[1] Researchers describe two cases of severe B lymphopenia, recurrent infection episodes, and antibody deficiency identified as XLA in two male siblings. Both patients had substantial pulmonary impairment, which tomographic criteria defined as bronchiolitis obliterans, which is unusual in XLA.

This report demonstrates a potential role for whole-exome sequencing in patients with known inborn immunity errors but unusual clinical presentations, providing a personalised understanding of genetic basis

Case Presentation:

Patient 1 (P1) and Patient 2 (P2) are non-consanguineous male siblings. They had a history of recurrent respiratory infections, primarily pneumonia, severe wheezing, and sepsis, with symptoms beginning within the first year of life in P1 and before two years of age in P2. The initial manifestations included severe wheezing and subsequent bacterial pneumonia. During

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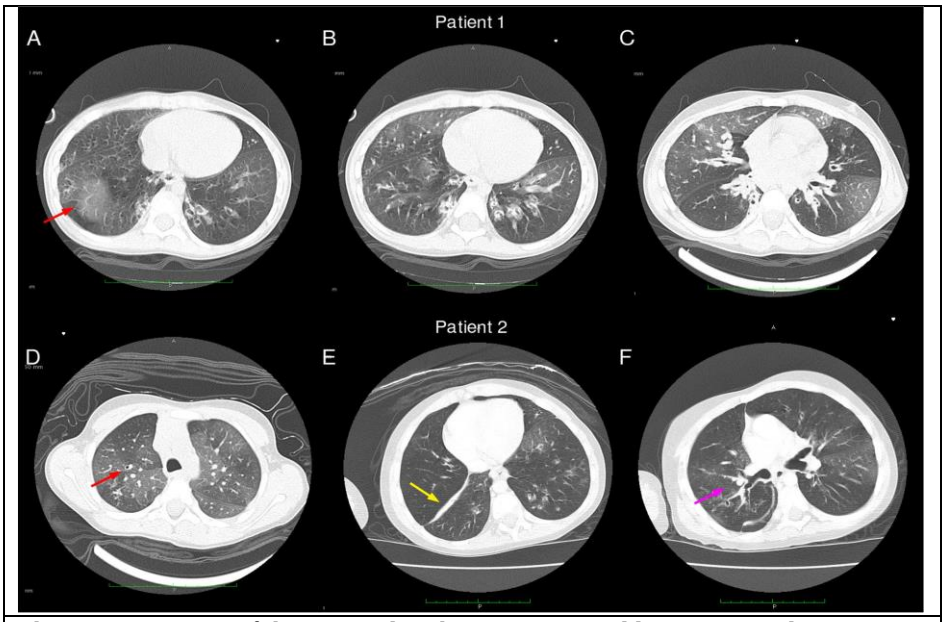
their initial ICU stay, both children were seen for the first time. Each subject was diagnosed with XLA at the ages of 11 months and 2 years and 5 months. At the time this study was conducted, P1 was 3 y.o and P2 was 5 y.o. Immunological findings revealed CD19 and CD20 less than 1% in both patients. P1 showed levels of IgG < 270 mg/dL, IgM = 12 mg/dL and IgA = 20 mg/dL. On the other hand, P2 had IgG = 100 mg/dL, IgM = 24.9 mg/dL, IgA < 5 mg/dL. Both had undetectable levels of IgE isotype. After the diagnosis, patients were kept on a regular infusion of intravenous immunoglobulin replacement and azithromycin prophylaxis. Patients with agammaglobulinemia, low B cells, and chronic wheeze had already been classified as having XLA. Both patients had recurrent and severe wheezing, and thorax computed tomography scans suggested bronchiolitis obliterans. They progressed as a result of recurring respiratory virus infections, severe bronchospasm, many hospitalizations, and deteriorating CT imaging. Since the start of immunoglobulin replacement, neither patient has had a serious bacterial illness. Patient 1 is currently 6 years old and has partial control of bronchospasm despite receiving large doses of inhaled corticosteroids in combination with long-acting beta-agonists (LABA) and long-acting muscarinic antagonists (LAMA). Patient now has symptoms of chronic pulmonary illness, such as an increase in anteroposterior chest width and digital clubbing. Patient 2 had more severe lung illness and was treated with a combination of inhaled corticosteroids, LABA, and LAMA, as well as oral cyclosporine and regular oral corticosteroid brief sessions. However, at the age of six, Patient 2 died of respiratory insufficiency. In 96 % of exonic regions, whole-exome sequencing (WES) mapped 99 % of reads to the human reference genome with a mean depth of coverage more than 100X. There were a total of 73,668 SNVs found among common and unusual variations, with 40,372 of them shared by both patients. The BTK gene of both patients had an unusual hemizygous missense mutation NM 000061.2(BTK):c.1751G>A(p.Gly584Glu) identified by whole-exome sequencing (WES). Researchers also discovered a TGF1 (rs1800471) gain-of-function mutation previously linked to transforming growth factor-beta1 production, fibrotic lung disease, and graft fibrosis following lung transplantation. TGF1 is involved in the regulation of immunological processes and the inflammatory response in pulmonary dysfunction.

Discussion:

The patients in this study were diagnosed with XLA after an initial episode of sepsis and severe bronchospasm, which was most likely caused by a bacterial lung infection. They have not experienced a relevant bacterial illness since starting to replace intravenous immunoglobulin on a regular basis and using preventive antibiotics. However, both patients' clinical outcomes were marked by recurring and severe episodes of wheezing, several of which necessitated hospitalisation, as well as a lack of response to the planned therapy. Both patients' clinical and radiological imaging supported the diagnosis of post-infectious bronchiolitis obliterans. Post-infectious bronchiolitis obliterans(BO) is most usually caused by adenovirus infections of the respiratory system, although it can also be caused by bacterial infections. Overall, people with XLA are not susceptible to viral respiratory tract infections, and they rarely develop BO as a result of acute or chronic bacterial respiratory infections.[2] According to Weinberger et al. 2019, the incidence of BO manifestation in XLA patients from the US Immunodeficiency Network is less than 1%.



Thorax CT imaging of the two study subjects. Upper and lower rows indicate patient 1 (a-c) and patient 2 (d-f) images, respectively. a-c) was obtained in 2016 at 3 y.o of P1. Chest CT scan in d) was obtained in 2015 at 3y7mo, whereas e and f were taken in late 2017 at 6 y.o. Red arrows indicate mosaic attenuation patterns and Bronchiectasis. Yellow arrow shows atelectasis. In pink, we showed a large bronchiectasis and bronchial wall thickening

Conclusion:

Overall, this report demonstrates a potential role for WES in individuals with known IEI and unusual clinical presentations, offering an individualized understanding of genetic underpinnings, with potential implications in identifying viable therapies and prognosis for patients and their families.

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