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Corpo Editorial

Sobre o jornal

O jornal *Puericultura e Pediatria* é o periódico oficial do Instituto de Puericultura e Pediatria Martagão Gesteira da Universidade Federal do Rio de Janeiro (IPPMG/UFRJ). Trata-se de jornal eletrônico semestral voltado para a divulgação de conhecimentos na área de saúde materno-infantil e na área de medicina do adolescente.

Este periódico também está aberto para a avaliação de trabalhos provenientes de outras unidades de ensino da Pediatria no país e no exterior.

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Sumário

Advance in the diagnosis of pulmonary tuberculosis in children?

Source: Singh M, Sethi GR, Mantan M, Khanna A, Hanif M. *Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children.* IJTLD 2016; 20(6):839-843

The study was conducted in a health reference center in New Delhi, India with 50 children with suspected pulmonary tuberculosis (TB) who underwent: clinical evaluation, chest X-ray, tuberculin test, secretions culture (sputum, induced sputum (IS) and gastric lavage (GL) and GeneXpert-Rif TB test (molecular test based on PCR real-time).

The authors included in the study 2-month to 12-year old patients who had clinical signs or symptoms suggestive of TB: fever or cough for more than 2 weeks, loss or no weight gain and a history of contact with people with TB. Inpatients or outpatients were admitted. On two successive days, spontaneous sputum and then LG were collected from children able to expectorate. LG and then IS were collected from children unable to expectorate. The specimens were taken immediately to the laboratory. In addition, in selected cases, transthoracic-fine needle aspiration and bronchoalveolar lavage were performed. Sputum smear microscopy was performed by Ziehl–Neelsen stain and culture by MGIT method. Xpert was performed according to the manufacturer's instructions and the result was achieved in the laboratory after 1h and 45 min.

Based on clinico-radiological data, smear and tuberculin test patients were classified into TB and non-TB. This analysis, which excluded the result of culture and Xpert, allowed classifying patients with TB into: confirmed (smear positive) or probable TB (cases without smear positive but with clinic-radiological data consistent with pulmonary TB). Statistical analysis included sensitivity, specificity measures, positive predictive value and negative predictive value.

The diagnosis of TB was established in 23 patients (mean age 63.9 months old).

Sputum was positive in 7 (TB confirmed) and negative in 43. After clinico-radiological analysis, 27 patients were considered non-TB and 16 probable TB. In these cases, Xpert was positive in 10/16 and culture in 6 of them. Xpert was not positive (detectable) among the 27 non TB. Among 34 cases of Xpert negative, there was 1 culture positive.

Xpert was positive in 16 (69.5%) patients, and 12 (52.17%) patients were culture positive, out of 23 patients with TB. The other patients were diagnosed in clinico-radiological tests.

The analysis of Xpert showed: sensitivity 91.6% (IC 95% 59.7-99.5) and specificity 86.8% (IC 95% 71.1-95.05). VPP = 68.75% and VPN = 97.05%.

The authors comment on the high sensitivity of Xpert, higher than the values found in the meta-analysis of Detjen1 and reiterate its high specificity. They also emphasize the high sensitivity of Xpert in relation to culture in the group of smear-negative patients, despite the use of MGIT, considered more sensitive than the traditional Loewestein Jensen. In this study, Xpert was superior to culture and the authors consider it a point of care in the diagnosis of TB in children.

Commentary by: Clemax Couto Sant´Anna MD, PhD.
Faculty of Medicine of the Federal University of Rio de Janeiro.

The study has the merit of being one of the few that evaluates Xpert in children along with other conventional diagnostic methods used in hospitals. Xpert test has been used in different researches with children, the results of which were not always consistent, but overall allow us to conclude the following: Xpert is about two times more sensitive than smear microscopy of sputum or gastric lavage in children with bacterial TB. Bacterial TB is a form of the disease in which the presence of acid-fast bacilli (sputum smear or culture) can be identified. This makes sense, as Xpert is a molecular method using real-time PCR and it is capable of detecting fragments of bacillus' DNA. Thus, bacillary fragments would likely to be identified in patients who have advanced TB disease, hence Xpert positive. On the other hand, childhood TB can be divided into two categories: children (<10 years old) and adolescents (≥ 10 years old). The reason for this difference is the fact that the disease in adolescents is often diagnosable by sputum smear microscopy. That is, bacterial TB. Most adolescents are bacilliferous tuberculous patient. However, most children are not. As a factor and confused issue, the articles that evaluated Xpert in childhood consider TB in children the disease among patients under 14 years old. Thus, much of Xpert positive described in these articles is the result of adolescents and children included in the same case. That is, patients with bacterial TB along the microbiologically negative patients.

In this study, the authors partly found themselves in this ambiguous situation. The age range of the patients goes up to 12 years old. It is not known, however, if the successful outcome was due to Xpert positive among adolescents. In any case, the positive result of the test was superior to culture, different than other authors have reported[2,3,4] Shing et al, in their article, even consider Xpert as a point-of-care testing (that is, state-of-the-art test) for the diagnosis of TB in childhood, in view of its high sensitivity and specificity. One cannot, however, fail to mention that the authors were engaged in processing the collected specimens of their patients as soon as possible so that the method was developed in full. These details are also not clear in other articles and allow reflection on the optimal research conditions obtained in this study, in a reference center, and almost never achieved in routine health care of endemic TB areas. Moreover, one should take into account that the sample of TB patients was small. Small numbers can bring some difficulties in interpretation.

Bringing the reflections on this study to Brazil, we noted that the country makes available Xpert (called in Brazil the rapid molecular MTB test) in the Public Health System since 2014 in various cities of Brazil. Private laboratories also have the method, although its cost is high. Following the guidance of the World Health Organization (WHO), TRM-TB in Brazil is the test of choice for initial diagnostic investigation of adults and adolescents with suspected TB. The test, being automated, allows the result - at the laboratory level - in about two hours and, moreover, offers the possibility to identify patients with rifampicin-resistant TB. This resistance is a multidrug-resistant TB marker (MDR-TB). Therefore, it offers great advantage on the prognosis of some patients who require special treatment schemes.

The Ministry of Health does not recommend MDR-TB in children under the age of 10, because most of them are not bacilliferous TB patients. The diagnosis is done then by indirect methods (clinical and radiological finds, tuberculin test, epidemiological data) (5). However, adolescents with suspected TB can benefit from TRM-TB because most of the cases come along with bacterial TB. Based on the encouraging results of this study, despite the caveats discussed, one should consider developing an investigation under routine conditions and in reference centers of TRM-TB in children in our setting. The rapid arrival of specimens to the laboratory and the prompt release of the test results seem challenges we still have to overcome. The future may show that maybe this is indeed a point of care in TP in childhood.

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Interventions to prevent violence against children: The importance of house calls

Source: Levey EJ, Gelaye B, Bain P, Rondon MB, Borba CPC, Henderson DC, Williams MA. *A systematic review of randomized controlled trials of interventions designed to decrease child abuse in high-risk families.* Child Abuse Negl 2017 Mar;65:48-57

Violence against children is a global problem that brings about serious consequences for the victim, both immediate and in the long run. One is that children from people who have been abused in childhood are at greater risk of living through the same experience. For this reason, to prevent abuse in future generations, high-risk families require interventions to curtail violence against children.

The authors made a systematic review of the literature, including randomized controlled trials, that evaluated the effectiveness of interventions to prevent violence against children born from mothers considered to be at high risk.

Eight studies were included, of which 7 were carried out in the United States and one in the United Kingdom. Although it was not an inclusion criterion, the home visiting (HV) was the intervention performed in the 8 studies. They all involved low-income women. Other risk factors included: young age, maternal depression, family stress, lack of social support and violence between the couple. The intervention duration (weekly or biweekly house calls in the postpartum period, gradually decreasing to monthly or bimonthly) ranged from 3 months to 3 years, and the follow-up lasted from six months to 15 years. The two studies with the longest follow-ups were also those that reported significant differences in the reporting of violence against the child.

The objectives of the interventions included: access to prenatal care, pediatric health care, and social resources and services; improvements in the mothers' knowledge about child development; parents and children bonding encouragement; development of parenting skills; detection of mental illness and abusive use of drugs by mothers; and discussing some problems being faced by the parents.

The studies showed that the HV had an impact on the violence against children, as well as on the mother-child interaction, maternal depression, pregnancy repetition, maternal employment, and it also impacted the children's cognitive development and externalizing behaviors. The factors associated with greater efficacy were: intervention beginning during the gestation and continuing for at least 2 years thereafter; weekly visits in the immediate postpartum; longer follow-up after the intervention; and the specificity of the intervention content.

The literature indicates promising possibilities for reducing violence against children in high-risk families. So far, scientific evidence shows that only the house calls are significant in reducing the problem.

Commentary by: Ana Lúcia Ferreira MD, PhD.
Department of Pediatrics, School of Medicine,
The Federal University of Rio de Janeiro.

The HV relevance to prevent children maltreatment, shown in this study, reinforces this initiative as a priority in the healthcare of children. It should be noted, however, that despite its proven success in causing changes in families, the way these HV programs are deployed plays a crucial role in their success. Factors such as the type of training the healthcare professionals receive, reflective supervision that explores thoughts, experiences and feelings associated with the services of these professionals, as well as the program quality, have a statistically significant association with their effectiveness[1].

Considering that this problematic parenting behaviors occur in more families than those served by the child protection services, Prinz[2] advocates that public policies should be implemented to prevent violence against children. Given that stigma may alienate families from programs specifically aimed at preventing maltreatment, routine and affordable interventions to support parents become essential, with HV being one of them.

In Brazil, the Family Health Strategy (FHS) uses HVs as a means for interaction in basic health care to gather information on the living and health conditions of the families under its responsibility. It is one of the most outreach actions carried out in the communities served by the clinics. Regular training, team reflections and supervision of the professionals, are part of the strategy and have been carried out in the country, even though still unevenly in different cities[3].

The conditions for HVs to be used to develop actions to prevent violence against children seem to have been in place in Brazil: the home visiting represent an important action of the FHS, which in turn is considered a priority of the public health policies in the country; among the HV objectives in the FHS are the inspection of family structure and dynamics and the identification of individual and family risk factors[4]; the use of HVs by the professionals in basic healthcare is ample. Considering also its proven effectiveness, it is recommended that contents be included in the home visiting, to help reduce this violence against children phenomenon in our country.

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Celiac disease - the monitoring challenge

Source: Leonard MM, Weir DC, DeGroote M, Mitchell PD, Singh P, Silvester JA, Leichtner AM, Fasano A. *Value of IgA tTG in Predicting Mucosal Recovery in Children With Celiac Disease on a Gluten-Free Diet.* J Pediatr Gastroenterol Nutr. 2017 Feb;64(2):286-291.

Celiac disease (CD) is an autoimmune inflammatory disease of the small bowel precipitated by the consumption of gluten. It was believed to be a childhood illness, but we now know that it can occur at any stage in life. Clinical manifestations vary greatly, from silent disease to systemic manifestations. It is also strongly associated with autoimmune conditions and genetic syndromes. Diagnostic criteria rely on serologic antibody tests while consuming gluten containing food, especially IgA anti- tissue transglutaminase (tTG) and autoantibodies against endomysium (EMA). The total IgA level should be measured before the test, because more than 2% of patients with celiac disease have a selective IgA deficiency.

The histologic evaluation according to the Marsh classification (which considers inflammatory infiltrate, crypt hyperplasia, and villous atrophy) is the gold standard for the diagnosis. Treatment consists of a strict gluten-free diet (GFD) for life[1]. The clinical response and the serological are both methods for monitoring adherence to the GFD. It is expected that a child who follows a GFD will have a serologic normalization within 12 months[2].

Commentary by: José Cesar da Fonseca Junqueira MD, PhD;
Silvio da Rocha Carvalho MD, MSc;
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This was a retrospective study conducted at two quaternary care centers, involving 103 patients under 21 years, with histological-proven CD according to Marsh criteria (Marsh 3 lesions). Those patients have undergone a second endoscopy with duodenal biopsy at least 12 months on a GFD (median of 2.4 years, ranging from 1 to 12 years). In 70% of them, the biopsy was repeated because of persistent or new gastrointestinal symptoms. 34% of the patients had persistently elevated serology when the biopsy was repeated. Only seven asymptomatic patients underwent biopsy to confirm mucosal healing. Eleven asymptomatic patients with persistently elevated tTG had a repeat biopsy. Four asymptomatic, seronegative children underwent a repeat biopsy to assess for mucosal recovery and confirm the CD diagnosis. The adherence to a GFD was based on a physicians' or dieticians' subjective assessment at the time of the clinic visit[3].

The authors found that 19% of CD children exhibited persistent villous atrophy (VA) consistent with a Marsh 3 lesion at the time of the repeat endoscopy[3].

They also found that at the time of the repeat biopsy, tTG was elevated in 43% of children with persistent VA and 32% of children with mucosal recovery. They suggest that IgA tTG was not an accurate measure of mucosal healing in

this pediatric population. It is important to note that the authors themselves mentioned that the IgA tTG assay was run in multiple laboratories, performed within 4 months of the repeat biopsy. One important finding is that only 55% of patients with persistent VA at the time of the repeat biopsy were symptomatic[3].

The authors emphasize that neither the absence of symptoms nor a negative tTG could be surrogate markers of mucosal recovery in patients with CD on a GFD[3].

In CD adults the studies demonstrate that over 50% have persistent enteropathy on repeat biopsies despite being on a GFD for 2 or more years[4].

Among adults, the VA persistency is correlated to iron-deficiency anemia, low blood ferritin level and additional risk factors for lymphoproliferative disease[5].

Commenting on the study, Doctor Ivor D. Hill highlights the urgent need for more studies to prospectively consider a repeat endoscopy to confirm remission. He argues that now very few CD children on a GFD undergo repeat biopsies, so it is possible that the amount of children with persistent enteropathy is much higher than is currently believed[6].

On the other hand, Koletzko et al commenting on the study stated that the tTGA should be performed within 2 to 4 weeks to the repeat biopsy, because mucosal lesions may be induced by incidental or voluntary ingestion of gluten. This DC group advises against re-biopsies for all CD chidren, reserving this test for selected cases - seronegative or symptom persistent children on a GFD[7].

Considering the findings in adult studies, the fact that anti-tTG do not correlate well with histological findings or symptoms in CD patients on a GFD as well as those findings, it is important to consider a repeat biopsy for monitoring those patients. This study raises the possibility to consider biopsies not only a key component for diagnosis, but also for monitoring disease in some cases.

We also agree that the management criteria of CD in childhood should be revisited as new studies and additional information are available.

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Brain Morphometry in ADHD

Source: Silk TJ, Beare R, Malpas C, Adamson C, Vilgis V, Vance A, Bellgrove MA. *Cortical morphometry in attention deficit/hyperactivity disorder: Contribution of thickness and surface area to volume.* Cortex 2016 Sep;82:1-10

Studies published so far are consistent with the reduction of brain volume observed in Attention Deficit Hyperactivity Disorder (ADHD) patients when compared to healthy controls. Cerebral volume results from the interaction between cortical thickness and cortical surface area.

Researchers from the University of Melbourne (Australia) conducted a cross-sectional study of brain magnetic resonance imaging (MRI) in ADHD children in order to clarify which of these two parameters has a greater influence on the brain volume difference between these patients and healthy controls. Cortical thickness is influenced by the number, size and density of cortical neurons, as well as myelination at the border between white and gray matter. The cortical surface area has its dimensions mediated by the intrinsic properties of neuronal layers in each region. Finally, it should be emphasized that cortical thickness and cortical surface area have independent genetic determinants.

The study was carried out with 35 male children (median age = 13.5 years) and an equal number of controls (median age = 12.9 years). Patients were selected in the University Hospital of Melbourne and met DSM-IV diagnostic criteria. The most common comorbidities were oppositional defiant disorder and dysthymia. Twenty of these patients were drug-naive. Controls were recruited at local schools in Melbourne. Patients and controls necessarily had a quotient of intelligence equal to or greater than 70.

MRI scans were performed on a 3-Tesla Siemens TIM Trio scanner. The FreeSurfer program was used to obtain data on cortical thickness, area and volume (mm3).

The results showed that children with ADHD had lower total cortical volume (7.3%), lower cortical surface area (4.3%) and lower cortical thickness (2.8%), even when controlled for differences in intracranial volume. The greatest differences from control subjects were observed in the volume of the right and left parietal lobes. The right and left frontal cortical regions as well as the left temporal lobe also presented lower cortical thickness and volume in cases when compared to typically developed children. It should be noted that the influence of cortical thickness and cortical surface area on the volume of the cortex showed to be variable according to each region of the brain.

Cortical thickness was a more important determinant of cortical volume in parietal regions, except in the pre-cuneus, where the surface area was more relevant. This region has several connections with other parietal regions and, mainly, with the frontal lobes. Recently published studies highlight the relevant role of pre-cuneus in the neurobiology of ADHD. Finally, cortical surface area proved to be an important determinant of cortical volume also in the left pars opercularis, located in the ventrolateral prefrontal cortex.

The main limitation of this study was the selection of some patients who were using stimulant medication during MRI, what has the potential to influence the results.

The authors conclude that both cortical surface area and cortical thickness have an important role on cortical volume differences between ADHD patients and controls. Considering that these two variables have different genetic determinants, it is important to study both in ADHD patients in order to clarify the neurobiology of this clinical condition.

Commentary by: Giuseppe Pastura MD, PhD.
Department of Pediatrics, School of Medicine,
The Federal University of Rio de Janeiro.

The work of the Melbourne researchers addresses important issues. On the one hand, there are many published works demonstrating a lower brain volume of children with ADHD when compared to healthy controls[1]. On the other, until now, there were no studies exploring the components of brain volume, in this case, cortical thickness and cortical surface area. The results show that there is no standard for the importance of each factor. Within the same region, as the parietal, the thickness and the area behave differently.

It is important to emphasize that regions of lower volume depicted in the present study are the same as those found in other researches, mainly frontal and parietal regions[2,3]. Frontal regions are classically involved in the genesis of ADHD, mainly the dorso lateral prefrontal cortex[4]. The parietal region has received increasing attention and this work demonstrates that ADHD children present smaller volume in this area, especially the pre-cuneus. These findings are important because they suggest a deficient functioning of the antero-posterior attentional network in the brain, which is probably involved in the genesis of ADHD.

Finally, it would be important to add a limiting factor of this study that was not mentioned by the authors. The main comorbidities cited among the patients in the sample were oppositional-defiant disorder and mood disorders. The latter is usually less prevalent than childhood anxiety disorders[5]. Thus, the presence of dysthymia may have influenced the findings of the study.

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