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RESEARCH ARTICLE

ISONIAZID-INDUCED ACUTE PSYCHOTIC EPISODE IN A CHILD WITH LYMPH NODES TUBERCULOSIS: CASE REPORT AND LITERATURE REVIEW

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Abstract

Tuberculosis (TB) is a bacterial infection caused by Mycobacterium tuberculosis which is an important public health problem in Morocco. The conventional approaches employed to fight TB are good nutrition, Bacillus Calmette-Guerin (BCG) vaccination, anti-TB therapy. The World Health Organization (WHO) recommends a combination treatment of four drugs for two months (isoniazid (INH), rifampicin, pyrazinamide, and ethambutol), followed by two drugs (INH and rifampicin) for 4 months as first line therapy for newly diagnosed pulmonary TB in both pediatric and adult patients. This regimen is generally considered efficacious, safe, and cost-effective. However, adverse effects and drug interactions often complicates the treatment of tuberculosis. INH is associated with 32% of adverse events, of which 1.9% are psychiatric. Isoniazid-induced psychosis, although infrequent, has been reported in patients with and without a psychiatric history, both in isoniazid monotherapy or in combination with other antituberculostatic drugs. We report a case of a 12-year-old, HIV-seronegative boy whopresented with delusions and hallucinations after starting TBtherapy and review the literature on INH-induced psychosis.

Introduction:-

Tuberculosis (TB) is a bacterial infection caused by Mycobacterium tuberculosis. It has both pulmonary and extrapulmonary manifestations. Tuberculosis continues to be a challenge and an important public health problem [1]. By being one of the leading causes of mortality, estimated to infect one in every three individuals worldwide [2]. This preventable condition is responsible for 95% of deaths in developing countries. Worldwide, 10 million people contracted TB in 2019: 5.6 million men, 3.2 million women, and 1.2 million children. The distribution of TB cases around the world is unequal. The region with the largest number of new cases in 2019 was Southeast Asia (44% of all new cases), followed by the African region (25%) and the Pacific region (18%) [3]. In Morocco, although the treatment of patients is free of charge and vaccination coverage with the Calmette-Guérin vaccine (BCG) has been generalized, tuberculosis remains a health problem. In 2020, the number of registered cases was 29,018, all forms combined, corresponding to reported incidence of 80/100.000 residents. Although the incidence estimated by the WHO has decreased between 1990 and 2020 by 34%, this decrease remains slow and below national expectations, as the determinants of the disease are multiple and are related, essentially to socio-economic conditions [4,5].

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The conventional approaches employed to fight TB are good nutrition, Bacillus Calmette-Guerin (BCG) vaccination, anti-TB therapy. The World Health Organization (WHO) recommends a combination treatment of four drugs for two months (isoniazid (INH), rifampicin, pyrazinamide, and ethambutol), followed by two drugs (INH and rifampicin) for 4 months as first line therapy for newly diagnosed pulmonary TB in both pediatric and adult patients [6]. This regimen is generally considered efficacious, safe, and cost-effective. However, adverse effects and drug interactions often complicates the treatment of tuberculosis.

Isonicotinicacid hydrazide or isoniazid (INH) was first discovered in 1912 and was later introduced by Robitzek more than half a century ago in 1952 for the treatment of tuberculosis [7]. INH is a prodrug that must be activated inside M. tuberculosis by the catalase peroxidase enzyme. Activation is associated with a reduction of the mycobacterial ferric KatG catalase-peroxidase by hydrazine and reaction with oxygen to form an oxy ferrous enzyme complex. Once activated, INH inhibits the synthesis of mycolic acids, an essential component of the bacterial cell wall [8]. The daily recommended INH dosage by World Health Organization (WHO) for children is 7 – 15 mg/kg/day or 20 mg/kg twice or thrice doses per week or daily, and 5 mg/kg/day for prophylaxis [9].

INH is associated with 32% of adverse events, of which 1.9% are psychiatric [4]. INH has common side effects that should be explained to patients and assessed during clinical follow-up. These include elevated liver transaminases or hepatitis, nausea, vomiting, peripheral neuropathy related to vitamin B6 deficiency and dermatitis [6,10,11].

Acute INH toxicity frequently manifests itself as severe but less frequent neurological effects such as optic neuritis, optic atrophy, toxic encephalopathy, cerebellar ataxia and death. INH toxicity can result in CNS stimulation or depression. These changes can range from transient memory loss to acute psychosis. CNS stimulation due to isoniazid may manifest as agitation, euphoria, insomnia, and headache. Nervous system effects due to isoniazid toxicity or overdose are primarily due to such causes as depletion of pyridoxine (vitamin B6) levels and decreased gamma amino butyric acid (GABA) production. Cerebellar symptoms, psychosis and seizures have been reported with the conventional dose of this drug. Memory impairment and even death after isoniazid administration have also been reported. [7]

Shortly after INH was introduced as an antitubercular agent in 1952, reports of cases exhibiting psychotic symptoms as adverse effects were published [12,13]. Since then, multiple publications have addressed INH-induced psychosis and explored the associated risk factors [12,14,15]. Though several case reports on isoniazid related psychiatric disorders are reported, its frequency of incidence is not well defined.INH induced psychotic disease are rarely encountered, and the most common ones are psychosis, obsessive compulsive disorder, and mania. Symptoms of INH induced psychosis includes disturbed sleep, restlessness, agitation, euphoria, withdrawn, complex delusions, emotional instability and suicide [16]. The exact mechanism of INH induced psychosis is unknown, but it has been suggested that asINH interacts with various metabolites which are necessary for normal functions of neurons, it may lead to psychosis depending problems caused by these mechanisms.

Only recently has the international literature identified cases of INH-induced psychosis within the pediatric population [17]. Pediatriciansassessing children on antitubercular therapy in an emergencyroom or in a clinic setting need to be aware of this adverseeffect.

We report a case of a 12-year-old, HIV-seronegative boy whopresented with delusions and hallucinations after starting TBtherapy and review the literature on INH-induced psychosis.

Methodology:-

The case and caretakers were interviewed for obtaining information after their consent.

The data in the patient profile forms and laboratory investigation reports were assessed. The causality assessment was done by the WHO Scale, and Naranjo's scale. Oral informed consent was obtained from Patient and his parents.

Cases report:

A previously healthy 12-year-old Moroccan boy was diagnosed with lymph node tuberculosis on the basis of an incidental finding of a painful submandibular adenopathy with no evidence of fever, cough or weight loss. a cervical ultrasound showed the existence of two bilateral sub-Angulo mandibular adenopathies measuring 1.5 centimeters in

diameter associated with infracentimetric jugulo-carotid nodes. the biopsy and anatomopathological examination confirmed the tubercular etiology.

The started an antitubercular treatment based on rifampicin, INH, pyrazinamide and ethambutol. A pyridoxine (vitamin B6) supplement was not prescribed. He was on INH 10mg/kg/day, rifampicin 15mg/kg/day, ethambutol 20mg/kg/day, and pyrazinamide 30mg/kg/day.

Two weeks after the start of his antituberculosis treatment, he presented with isolation and behavioral changes that had intensified within a week. He manifested emotional lability, soliloquy with verbalization of delusions, visual, tactile and auditive hallucinations, and sleep disturbances.

He had no history of fever, headaches, abnormal movements, recent travel, previous medical or psychiatric illnesses, or family history of psychiatric disorders. He did not use any other medicinal agents, and the mother reported that he was compliant with his TB medications.

On physical examination, the child weighed 41 kg and his body mass index (BMI) was 18.5 kg/m^2. the physical examination did not reveal any significant abnormalities.

His laboratory results, including CBC, renal, liver, lipid, thyroid, and blood glucose were within normal range. Toxicology screening was negative. Serologies (syphilis-HIV) were negative.

Sputum examination did not reveal the presence of Koch's bacillus. The culture was negative and the standard radiography of the lung did not show any lesion in favor of pulmonary tuberculosis.

Because of the acute onset of symptoms and behavioral changes, brain imaging and cerebrospinal fluid (CSF) studies were ordered to evaluate the possibility of extrapulmonary tuberculosis involving the central nervous system (CNS). CSF analysis, including cell count, protein, and glucose levels, was normal, with negative bacterial culture, mycobacterial culture, and TB CRP. Brain MRI was normal.

Neurologic and psychiatric evaluations were performed and drug-induced side effects, including INH-related psychosis, were considered.

The parents decided to consult the child psychiatrist 2 months after the evolution of the symptoms, so he was put on risperidone 0.5 then 1mg then 2 mg per day with progressive improvement of his clinical condition.

The pulmonologist who was called upon decided, based on the stability of the child on risperidone, and the frequency of resistance of tuberculosis to antibiotics, to keep the same therapeutic protocol, especially since the child was on rifampicin and isoniazid at the time of the consultation. this was combined with close monitoring of the child and regular child psychiatric follow-up.

After stabilization of the child on risperidone, the doses were decreased and a dose of 0.5 mg/day was maintained with strict monitoring of the child's condition.

The child continued on isoniazid and rifampicin for 3 months, after completion of the treatment protocol, the child psychiatrist discontinued the risperidone, and follow-up revealed a complete remission of symptoms with return to normal premorbid status and resumption of social and school functioning, and no recurrence of abnormal behavior or hallucination.

Discussion:-

Tuberculosis accounts for millions of active disease cases and deaths in both developed and developing countries and although tuberculosis most commonly affects the lungs, any organ or tissue can be involved. In countries with comprehensive diagnostic and reporting systems, extrapulmonary tuberculosis (EPTB) accounts for 20–25% of reported cases.

Of specific forms of EPTB, lymphatic, pleural, and bone or joint disease are the most common. Pulmonary and extrapulmonary disease should be treated with the same regimens [18].

Psychosis is a rare adverse effect of INH. Older reports place the incidence of psychiatric symptoms at 1.9% from a US surveillance program in the 1970s and 1% in a review of cases of TB in Peru between 1991 and 1999 [12]. No recent surveys have been conducted. Yang et al. did a retrospective study on MDR-TB patients (N = 256) in South Korea and reported the incidence of psychiatric side effects to be 5.5% [16].

Jackson first highlighted the first description of isoniazid causing psychosis in the year 1957 [19]. He published five instances of INH induced psychosis that presented with argumentative behavior, mental depression, euphoria, grandiose ideas, and elaborate delusions; none of these patients had any previous history of mental illness [7]. Since then there has been many case reports showing the association between isoniazid and psychosis [20].

Psychosis in children is rare and it is important to evaluate the differential diagnosis before concluding an iatrogenic dug-induced cause. This includes ruling out infectious or autoimmune encephalitis, seizure disorder, tumors, endocrinopathies, and toxic agents among other differentials [21]. Excluding alternative causes along with the temporal correlation of symptoms and drug ingestion/ cessation strengthens the likelihood of causality.

Side effects of INH:
Isoniazid is one of the primary drugs of ATT regimen because of its low cost, safety, and potency. However, it is known to have common side effects such as peripheral neuropathy, hepatitis, psychosis, hematological disorder, hypersensitivity reaction, metabolic and endocrine reaction, rheumatic syndrome and systematic lupus erythematous like syndrome [7].

The most common adverse effects are those of the liver, manifested most often by an asymptomatic rise in serum concentrations of hepatic transaminases, followed by neuropsychiatric effects. These neuropsychiatric effects include perceived cognitive impairment and lethargy (the most common), headaches, blurred vision, peripheral neuropathy, sleep disturbance, and depression. Other uncommon neuropsychiatric disturbances including optic neuritis, generalized convulsions, and psychosis can develop in susceptible individuals [7].

Isoniazid (first-line) and cycloserine (second-line) are the two most common anti-TB drugs associated with psychiatric ADR. However, ethambutol, ethionamide, and fluoroquinolones have also been reported to be associated with neuropsychiatric ADR [16].

Isoniazid-induced psychosis, although infrequent, has been reported in patients with and without a psychiatric history, both in isoniazid monotherapy or in combination with other antituberculostatic drugs [7].

Neuropsychiatric ADR of antitubercular drugs are not uncommon. Psychiatric ADR pose an important challenge in the management of tuberculosis and significantly lower the quality of life of an individual on ATT.

For our patient, apart from his acute psychotic attack, he did not present any other notable side effects. His paraclinical tests came back without any particularity and on the level of his clinical state he did not present any symptom in favor of an anomaly.

Risk factors for isoniazid-induced psychosis:
According to various case reports the risk factors for isoniazid causing psychosis includes age greater than 50 years, personal and family history of psychological illness, alcohol intake, diabetics, uremia, malnutrition, hepatocellular insufficiency and hyperthyroidism [22].

In their case series, Menon et al. Highlighted the influence of malnutrition when they presented a 35-year-old woman, a 55-year-old man, and a 60-year-old man who all developed INH-induced psychosis with documented body-mass indices of 13, 18, and 16.8 kg/m2 respectively [14]. In these cases, the standard dose of 300mg was equivalent to > 5mg/kg/day. Oninla et al. also present pediatric cases with severe undernutrition [17].

The adverse effects are more common among patients in whom pyridoxine is not supplemented; however, they are also known to affect 5% of patients on adequate pyridoxine supplementation (10-50 mg/ day).8 However non-administration of pyridoxine was the only identifiable risk factor among these patients [23].

Another possible reason may be due to the pharmacokinetic properties of isoniazid. In general, the drug is rapidly absorbed from the gastrointestinal tract within one to two hours of ingestion. However, it is estimated that 40% of the Indian population are slow acetylators, which leads to accumulation of the drug and more side effects [1].

Thus, the rate of acetylation may affect the metabolism of INH and may also be a factor influencing the risk of psychosis [14,17]. Acetylation is genetically determined and occurs with racial differences but cannot be tested systematically on an individual basis. Slow acetylation can lead to drug accumulation and may be a pharmacokinetic risk factor.

Our patient was 12 years old, he had no signs of undernutrition (BMI = 18.5), no personal or family psychiatric history, and no metabolic disorder or dysthyroidism. Furthermore, the child did not receive pyridoxine supplementation, which could be a risk factor for this case.

Mechanism of Psychosis:

The mechanism of INH-induced psychosis is not fully understood. Common theories suggest a relation to interference with neurotransmitters. INH is a monoamine oxidase inhibitor and thus can result in elevated levels of catecholamines and serotonin [24]. Also, through oxidative stress, it can reduce N-methyl Daspartate receptors (NMDAR), affecting memory and learning and contributing to psychosis [15]. Through the excretion and the depletion of pyridoxine, INH can also affect the levels of tryptophan and serotonin [14]. And through the inhibition of pyridoxine activation, it decreases the levels of gamma-aminobutyric acid (GABA), an important inhibitory neurotransmitter [15].

Pallone et al. suggested these two hypotheses regarding the mechanism of isoniazid-associated psychosis. The first is that isoniazid acts as monoamine oxidase (MAO) inhibitor, preventing the degradation of catecholamines and serotonin with a resultant increase in the concentrations of these neurotransmitters within the Central Nervous System (CNS). The other mechanism proposed by Pallone et al. entails pyridoxine deficiency induced by isoniazid. Isoniazid may lead to pyridoxine deficiency since it combines with pyridoxal and this complex inhibits the activity of pyridoxal kinase. The result is a disturbance in the normal tryptophan metabolism. Since pyridoxine deficiency may be secondary to the prescription of isoniazid, pyridoxine supplementation has been thought to prevent this situation. Nevertheless, the role of pyridoxine supplementation in prevention or treatment of isoniazid-associated psychiatric symptoms is unclear since the systematic use of pyridoxine does not seem to prevent the emerging of psychosis, suggesting that pyridoxine deficiency could only have a partial implication. It was proposed that higher doses of pyridoxine (e.g., 50 mg/day) would be probably required to prevent the occurrence of isoniazid induced psychosis [25].

INH causes vitamin B6 deficiency by increasing its excretion. INH metabolites inhibit the activation of pyridoxine to pyridoxal 5-phosphate, which is a cofactor of the enzyme glutamic acid decarboxylase that catalyzes the conversion of glutamic acid to gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. The resulting GABA depletion leads to central nervous system dis-inhibition and clinically, isoniazid-induced psychosis or seizures may follow INH overdose [8].

Additionally, it is also claimed that isoniazid may cause oxidative stress, which can cause decreased levels of N-methyl-D-aspartate (NMDA) 2A receptors in the hippocampus. Changes in NMDA receptor density may be one of the mechanisms of isoniazid-induced neuropsychiatric disorders [18].

Reports suggest N-methyl-D-aspartate (NMDA) receptor antagonism, partial agonism at the NMDA receptor-associated glycine site, and gamma-aminobutyric acid receptor antagonism as possible mechanisms of ATT-induced psychosis.

Another possible reason for acute onset of psychosis may be the pharmacokinetic properties of the drug. INH is rapidly absorbed from the gastrointestinal tract and peak levels are reached within one to two hours after ingestion of a therapeutic dose [26].

Isoniazid is metabolized in the body mainly to its acetyl derivatives. Patients can be broadly classified into two groups: the slow acetylators and the rapid acetylators. The slow acetylators are at risk for drug accumulation and

consequently more side effects [18]. It has been found that about 40% of Indian population are slow acetylators, thus causing slow metabolism leading to drug accumulation and thus more side effects [27].

The risk also increases when the dose of INH is above 5 mg/ kg but has also been recorded on low dosage.10 If the dose of INH was to be calculated based on body weight, then our patient received high dose, which possibly could have increased the susceptibility to the adverse effect [28].

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A combination of drugs with a similar mechanism (e.g., cycloserine, ethambutol, and levofloxacin) is more likely to exert an additive effect in the causation of ADR [16].

The exact mechanism of delayed-onset ATT-induced psychosis and how it differs from acute onset psychosis need to be explored in future studies.

The onset of psychosis:

Most reports are from the adult population. Onset of psychosis is within days to months from drug initiation, with the majority developing symptoms in the first two weeks [14,27,28]. A typical storyline tends to occur in most reported cases with a recurring temporal association. The patient presents with convincing symptomatology, is diagnosed with pulmonary TB, is then started on combination therapy including INH, and then subsequently develops new and acute onset psychiatric symptoms which resolve once INH is discontinued. Patients were reportedly on standard recommended adult doses (300 mg/day) [14]. Pyridoxine prescription and dosing varied. Many received anxiolytics and or antipsychotics initially [14,28]. The time from discontinuation to complete resolution of symptoms ranged from 7 days to 120 days [14,27].

Usually the onset of psychiatric symptoms varies from days to months, but usually seen after few weeks of starting of isoniazid [1]. The time of onset of symptoms after the initiation of INH therapy varies roughly with the dosage. With high doses of INH, symptoms often appear within three to five weeks. In patients receiving conventional low dose INH therapy, symptoms usually do not appear until six months.

In our patient, psychotic symptoms appeared approximately two weeks after the start of the isoniazid-ethambutol-rifampicin-pyrazinamide treatment protocol and continued for more than a month after ethambutol and pyrazinamide were discontinued and treatment with isoniazid and rifampicin was continued. The temporal relationship between the administration of antituberculous therapy and the onset of psychotic symptoms, in the absence of prior psychiatric history, provided strong support for a diagnosis of drug induced psychosis. Because most of the literature concerning this effect involves isoniazid, this was the agent we first consider as the most likely responsible for the psychotic episode. There is also evidence that patients who develop psychotic symptoms on one antituberculous may be at risk of further episodes secondary to another antituberculous agent [18].

Symptoms of psychosis:

The clinical features of INH-induced psychosis are highly variable in the reported cases. A variety of psychiatric symptoms have been documented in the literature, including paranoid delusions, hallucinations (auditory, visual, and tactile), suicidal tendencies, mood symptoms, anxiety, sleep loss, muscle twitching, disorientation, loosening of associations, and echolalia [25].

Behavioral and mood alterations, memory, concentration and communication problems, sleep and appetite disturbances, hallucinations and delusions have been described [12,14].

Our patient presented with isolation and behavioral changes that had intensified within a week. He manifested emotional lability, soliloquy with verbalization of delusions, visual, tactile and auditive hallucinations, and sleep disturbances.

Diagnostic:
Menon et al. AndPrasad et al. increased the plausibility of causality by attempting toreintroduce INH which resulted in the recurrence of psychiatricsymptoms.

In Oninla et al. 's first described pediatric case, INH wasreintroduced with no recurrence of psychiatric symptoms [17]. However, the dose was modified to 5mg/kg/day and the reintroduction occurred two months after initial presentation. This may have provided adequate time for any risk factors such as malnutrition or comorbidities to improve or resolve, and thus could have altered his risk. This was not expanded on by the authors [29].

Using the Naranjo criteria for adverse reactions, we were able to conclude that INH-induced psychosis in our patient was 'probable' and not 'definitive', since we did not re-challenge him with INH to assess symptoms recurrence and we did not have an objective method to confirm the diagnosis.

Table 2. WHO-UMC Causality Categories

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

Adverse Drug Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total Score:			

Naranjo Algorithm - ADR Probability Scale

Score	Interpretation of Scores
Total Score ≥9	**Definite**. The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.
Total Score 5 to 8	**Probable**. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	**Possible**. The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	**Doubtful**. The reaction was likely related to factors other than a drug.

Causality Assessment
World health organization (WHO) causality assessment scale, and Naranjo's Causality assessment scale were used to evaluate the causal relationship between the drug and reaction.

The following score was obtained after applying the above scales for observed suspected ADR. Table 1.

Re-challenging was not done as it is not required as per WHO-UMC for probable drugs.

ADR Scale	Score	Assessment
WHO-UMC	-	Probable
Naranjo's	7	Probable

Table 1:- Causality assessment score of suspected ADR.

The psychiatric reference confirmation is the primary evidence for the confirmation of INH induced psychosis. The occurrence of the clinical condition along with drug regimen shows a robust temporal association, which strongly supports the case study.

Consensus on therapeutic approach:
There is no consensus on how patients suspected to have INH induced psychosis should be managed. The majority consider stopping INH the most important step. Most reports include the initial addition of anxiolytics and antipsychotics in order to manage acute symptoms, though the duration of such medications varied from days to months. For a patient presenting with acute onset psychosis who has recently been started on INH and who is suspected of having INH-induced psychosis, we recommend discontinuing

INH, as long as there are alternative choices for TB therapy. The role of pyridoxine remains unclear and the option to give a daily dose is left up to the treating physician. Short courses of anxiolytics and antipsychotics can help alleviate initial symptoms. Input from the infectious diseases services, pediatric psychiatry, and neurology is strongly recommended for diagnosis, management, and follow up.

Vitamin B6 supplement is recommended with the initiation of TB therapy in certain populations at risk of vitamin deficiency (pregnancy, HIV seropositive, renal failure, diabetes mellitus, and malnutrition), to avoid peripheral neuropathy [6]. The WHO recommends a dose of 10 mg/day [6]. Children with malnutrition or with HIV on antiretrovirals are considered at risk and are recommended to receive 5e10 mg/day [30] or 1mg/kg/day [10]. Despite several authors reporting supplementing from the beginning of treatment [14] or starting higher doses (40e100mg/day) at thetime of psychotic symptomatology [15], there has not been a clear association between vitamin B6 deficiency and INH-induced psychosis at this point.

The usual approach in treating patients with isoniazid induced psychosis includes withdrawing the drug first, treating the psychosis and then to gradually reintroduce at a lower dosage one the psychosis completely settles [31]. Some authors have also suggested restarting isoniazid with higher doses of pyridoxine while others have recommended using antipsychotic drugs along with high doses of pyridoxine [32]. In cases where psychiatric symptoms are not very severe, INH can be continued along with novel antipsychotics like risperidone and olanzapine.

Thus, Treatment for isoniazid-induced psychosis includes discontinuation of isoniazid, addition of an antipsychotic, or a combination of both.

For our patient, and in collaboration with his pulmonologist, we opted for the continuation of isoniazid treatment in combination with risperidone, based on the following arguments

1. The advanced stage of the anti-tuberculosis treatment protocol, as our patient had approximately 2 and a half months of isoniazid and rifampicin treatment remaining.
2. The favorable evolution of the patient with this protocol.
3. The good improvement of psychotic symptoms at low dose of risperidone.
4. The good tolerance of risperidone by the patient
5. The positive cooperation of the parents in the management of the child

Of Pediatric cases reported in the literature:
Oninla et al. report two pediatric cases in undernourished children [17]. In the first case, a 14-year-old, severely undernourished boy developed auditory hallucinations, echolalia, food refusal, and insomnia eight days after starting TB therapy for extensive pulmonary disease. He received 13mg/kg/day of INH without a vitamin B6 supplement. After discontinuing INH and starting vitamin B6 (100 mg) and haloperidol, his symptoms gradually improved. Two months later, INH was reintroduced at 5mg/kg/day with no recurrence of symptoms.

Their second case was of a 5-year-old girl who was HIV positive with failure to thrive and severe malnutrition. She developed disorientation and bizarre behaviors (scratching her body, attempting to cut her hair, wandering aimlessly) two weeks after starting TB therapy (with INH at 5mg/kg/day). An initial attempt to stop ethambutol did not improve her condition and only when INH was stopped did her symptoms resolve. In her case, she did not receive vitamin B6, anxiolytics, or antipsychotics and INH was not reintroduced.

A few reports describe INH-associated psychosis in patients on INH prophylaxis therapy for latent TB. Sharawat et al. report a 3-year-old girl who developed episodes of aggression, social withdrawal, and what is thought to be visual hallucinations two weeks after starting INH (10 mg/kg/day) as prophylaxis for a confirmed household case of pulmonary TB [21].

Iannaccone et al. describe a 14-year-old girl who, one day after starting latent TB therapy (INH 300 mg and pyridoxine 50 mg), developed auditory hallucinations that urged her to attempt suicide by drug overdose [26]. She did not receive an antipsychotic agent initially and follow up psychiatric evaluation after discontinuing INH revealed no previous psychiatric illness and no recurrence of psychiatric symptoms or suicidal ideation.

Conclusion:-
In developing countries, the burden of TB is enormous and the use of anti-TB drugs is increasing. TB is one of the most common infectious diseases in Morocco. As INH is one of the main first-line drugs in the treatment of active and latent TB, pediatricians should be aware of this rare adverse effect.

We report a case of acute onset psychiatric symptoms in a pediatric patient with a temporal association strongly supporting INH-induced psychosis. The acute onset of psychotic symptoms in a patient taking isoniazid should lead to suspicion of this psychiatric side effect and prompt intervention, involving discontinuation of isoniazid and/or trial of an antipsychotic.

As protective measures, the authors suggest adjusting the dose of isoniazid to weight, possibly performing genetic testing if slow acetylation is suspected, and closely monitoring patients with the above-mentioned risk factors.

Thus, this type of case study highlighting drug-induced injury/disease certainly adds to the literature on drug-induced conditions. Continuous monitoring of disease progression and clinical outcomes is the inexpensive, most accessible, and quickest method of detecting any drug-related injury.

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