THE LABORATORY AND NEUROIMAGING INVESTIGATIONS IN THE DIAGNOSTIC APPROACH OF FEBRILE SEIZURES

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Abstract: *The opportunity of the laboratory and neuroimaging investigations in the study of febrile seizures (FS) is determined by clinical parameters such as the type and number of the FS, age, neurological status, presence of anamnestic or clinical risk factors, type of the underlying infectious disease. Biomarkers with potential role in the differential diagnosis of FS (prolactin, creatin kinases) or assessing the risk of recurrence (iron deficiency) have been identified. The lumbar puncture (LP) is not recommended in the routine evaluation of the SFS (simple febrile seizures) with normal neurological exam and complete immunization schedule, or in the case of CFC (complex febrile seizures) with absent predictors for meningitis. The LP should be considered in patients aged 6-12 months with uncertain immunological status, in the absence of vaccination for Streptococcus pneumoniae or Haemophilus influenzae and in the presence of the clinical factors suggestive of meningitis. The neuroimaging assessment is not indicated in the emergency unit for the first SFS or for the CFS associated with normal neurological exam and good general condition, but is recommended in the context of an evocative clinical picture for a neurological disorder or recurrent CFS.*

INTRODUCTION

Febrile seizures (CF) as epileptic, age dependent events, are the subject of specific studies aimed at establishing a protocol addressing the diagnostics, therapeutics and monitoring. Two of the operational definitions of FS are currently used both without excluding patients with previous neurologic disorders, differentiated by the lower age limit (one month and three months). The three basic elements for the diagnosis of FS are seizure, age and fever. FS may occur early, before the fever starts, complicating the diagnosis.(1,2,3,4,5,6,7,8) In FS, the diagnose is established by the clinical criteria. The need for complementary explorations in excluding CNS infections and other acute symptomatic seizures, in the diagnosis of atypical seizures and in establishing the therapeutic and monitoring approach or the prognosis is made by applying the exclusion criteria (history of neonatal seizures or unprovoked seizures).

The diagnosis of FS is made using the clinical criteria given the correlation of this paroxystic event with the parental anxiety (limiting an accurate anamnesis), but should be facilitated by identifying new, minimally invasive instruments (biomarkers) and by limiting the use of invasive or risky investigations (lumbar puncture, neuroimaging with sedation) for the cases where the benefits are clear. The differentiation of FS from epilepsy may prove difficult, especially in the presence of risk factors correlated with an increased incidence of epilepsy (complex febrile seizures, chronic neurological disease, and a family history of epilepsy). Recent data from literature suggest the possible benefit of certain serum enzymes in the differential diagnosis, e.g. serum prolactin which shows transient elevated values in the postictal phase in afebrile seizures or epilepsy, but not in FS or nonepileptic type events.(9,10,11,12)

Advanced researches are aiming to establish the best timing of laboratory and neuroimaging investigations in the following situations: 1.the diagnosis of FS 2. the exclusion of acute symptomatic seizures, nonepileptic paroxysmal manifestations and epilepsy. Recent data from the literature show a reassessment of the recommendations related to performing lumbar puncture in relation to the type of FS, age, clinical, immunological, or neurological status of the child.

MATERIALS AND METHODS

Our review is an analysis of the literature to determine the opportunity of the following diagnostic approaches: 1. the definition of biomarkers suggestive to differentiate between FS and other acute symptomatic seizures, epilepsy or nonepileptic events, 2. performing the lumbar puncture (LP) to exclude central nervous system infections by the FS type, 3. Using of the neuroimaging (brain CT or MRI) in the exclusion of acute intracranial pathology or pre-existing structural abnormalities.

Thus, we performed a meta analysis on dedicated databases (Medline, EMBASE, PubMed, Cochrane Library) taking into account all the studies published until 2015. Most of the identified studies are class II and III and a few class I studies with implications for the use of certain blood tests, LP or neuroimaging in the diagnosis of FS. The FS diagnosis has been reported by the FS type (SFS/CFC), neurological status and general clinical status and patient's age. The following inclusion criteria were considered: 1.patients with SFS or CFC with or without preexisting neurological disorders, 2.patients with different lower age limit (1 month, 3 months or 6 months), 3. different control groups (children with unprovoked seizures or nonepileptic events),(4,5)

RESULTS AND DISCUSSIONS

I. In the terms of opportunity to perform *routine laboratory tests* for the diagnosis of FS this are not needed in the SFS given the absence of studies to support a benefit in this type

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of seizures. They can be taken into consideration for determining the etiology of fever if the diagnostic suspicion of acute symptomatic seizures persists or when certain underlying conditions motivate the laboratory tests (e.g. electrolytes in acute diarrheal disease, although according to the Guidelines of the American Academy of Pediatrics the assessment of electrolytes proves be rarely useful).(13,14) The recommendations are also supported by Charmberlain et al's study describing an incidence of 5% of occult bacteremia in patients with FS and age under 2 years, similar to patients with fever but without critical events.(15)

Regarding the differential diagnosis between FS, epilepsy or nonepileptic events, a possible contribution might be made by the prolactin (postictal prolactin level).(9,10,11,12)

Based on research identifying associations between unprovoked seizures and increased prolactin serum levels immediately after the episode, the debate concerns the opportunity of this hormone determinations in FS.

Trimble et al were the first to indicate a possible increase in the prolactin level in generalized tonic-clonic seizures compared to the nonepileptic type events. They started from the hypothesis of prolactin's secretion alteration (inhibition of the pituitary prolactin secretion) due to the propagating ictal activity in the hypothalamus.(16) The results of the studies are variable, even contradictory because of the: 1. circadian variability of prolactin level depending on the transition from sleep to wakefulness, variable prolactin levels with gender (higher levels in females), 2. different serum levels considered pathological (most studies have reported a double basal level).(17,18,19)

Ahmad and Beckett have already done in 2004 the first meta analysis of studies that aimed to identify the role of prolactin in evaluating a first generalized tonic-clonic seizure without fever. Thirteen relevant studies were identified. A level at least three times higher compared to the baseline in the first 1 hour of postictal phase was correlated with a 9 times higher probability of recent tonic-clonic seizures compared to a pseudo seizure and with a 5 times higher probability compared to a syncope. A normal value does not exclude the diagnosis of seizure (20). In a meta analysis of the relevant studies carried out until 2005, Chen et al noted in the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology's report, the benefit of determining the prolactin serum level in the first 10-20 minutes after a suspect event in differentiating between the tonic-clonic and complex seizures and psychogenic seizures in older children. These identified studies (mostly Class II, only one class I study) showed a higher sensitivity for generalized tonic-clonic seizures than for the complex partial ones, but nevertheless they demonstrated identical specificity in both cases. Class II trials exclude the diagnostic advantage of serum prolactin in differentiating between epileptic seizures and syncope.(17) Sifinou et al described a transient hyperprolactinemia in patients with SFS as compared to the control group (healthy patients), but without having identified a significantly changed value compared to the basal individual value.(9)

Macooie and the collaborators conducted a study on children aged between 6 months and 5 years, involving 3 groups: 1. with FS, 2. with unprovoked seizures, 3.seizure free patients. They found that serum prolactin levels determined in the first 2 hours of the postictal phase doubles in the case of afebrile seizures or epilepsy, *but not with FS or nonepileptic events* and is positively correlated with the duration and number of seizures.(11)

The presence of postictal *high creatin kinase levels* is reflected in some studies generally 24 hours after a tonic or tonic-clonic seizure. This enzyme marker could prove to be effective in the differentiation of FS from nonepileptic events like shivering in cases with inconclusive history.(12,21) Alehan et al inserted the hypothesis of discrete increase of the total creatin kinase levels possibly due to the CK-MB fraction which would actually suggest cardiac injury associated to the critical event. Thus postictal elevated CK-MB and plasma natriuretic peptide (cerebral type) levels were identified in a study on a group of 31 children with FS and seizures without fever of generalized tonic-clonic type compared with a group of 51 healthy patients, all without cardiac, renal, metabolic or muscle pathology.(22)

The clinical criteria for diagnosis are essential. Patients with epilepsy or FS can present in febrile context, nonepileptic events like syncope or sleep disorders. These clinical entities enter into the differential diagnosis of FS, but specific biomarkers that differentiate between the two types of paroxystic events were not identified.

On debate referring to identifying patients with FS with risk of recurrence is the screening for *iron deficiency* and the opportunity of using blood iron and ferritin levels as biomarkers. Meta analysis studies are linking the iron deficiency with a decrease of the seizure threshold and high ferritin levels in the glial cells in mice with epilepsy and the involvement of these biomarkers in the temporal lobe epilepsy.(23,24,25)

In terms of differentiation between the two types of FS (SFS/CFC) Goksugur et al propose the determination of neutrophil/lymphocyte ratio and RDW, given the higher values of these biomarkers in CFC compared to SFS.(26).

II. Recent data from the literature show a reassessment of lumbar puncture recommendations in the exclusion of CNS infections as a cause of the epileptic events in febrile context.

The lumbar puncture (LP) was strongly recommended in assessing cases of FS, reported to the age because of the subtle, less specific symptoms of meningitis in the age category of under 18 months.(14) Recent retrospective studies offer a challenge of this age threshold.(27,28)

The need of performing the LP in SFS is controversial. According to revised guidelines from the American Academy of Pediatrics (2011), routine LP is not recommended in patients with SFS, normal neurological exam and complete immunization schedule, because of the low incidence of meningitis (<5%) in febrile context seizures. Hom and Medvid's study indicate a bacterial meningitis rate of 0% in patients aged 6-12 months, with a history and physical exam without significant changes.(14,28)

It should be considered in patients *aged 6-12 months with uncertain immune status or without immunization for Streptococcus pneumoniae and Haemophilus influenzae* or for those who have other factors suggestive of possible meningitis: 1. abnormal neurological exam, 2. previous antibiotic, 3. seizures still unfolding in the ICU, 4. focal seizure with abnormalities on the physical exam (petechiae, rash, cyanosis, hypotension), 5. recent visit to a medical facility.(29,30)

Although reasoned by the possible subtle and masking symptoms in patients with previous antibiotic presentation, the LP should not be performed routinely in the absence of other meningitis symptoms, contrary to previous recommendations.

The risk is low for patients with a first episode of CFC (Fletcher and Sharieff), so is the need to perform LP for patients with CFS, even though the incidence of meningitis in the seizures facilitated by febrile (suggestive for CFC) is superior to that of SFS (4.81% versus 0.86%)(31). In a study of 309 children with febrile seizures associated with meningitis, Offringa et al identify clinical factors suggestive for the

infectious context (nuchal rigidity, petechiae, coma, drowsiness, paresis / motor deficit and unfolding seizures). The absence of these symptoms are rarely associated with meningitis.(32,33)

Joffe et al demonstrated that the clinical examination has a higher sensitivity and specificity comparing to the LP, in identifying CNS infections. The predictive value of a normal clinical history and clinical exam is 100%.(34)

The LP is not recommended in the routine evaluation of all CFS if they are not associated with possible predictors namely: altered mental status, persistent neurological deficits, and status epilepticus).(14,31,35,36) Kimia suggests that patients with 2 seizures in 24 hours, short, generalized episodes and no other symptoms associated have a decreased risk for meningitis.(37)

In the FEBSTAT study, 77% of patients with status epilepticus are undergoing LP procedure motivated by the young age, duration of status, focal aspect. The predominantly normal (95%) CSF examination does not contradict the recommendation of conservative approach for the patient with SFS and normal neurological exam.(38)

In a retrospective study including 157 patients with first FS aged under 18 months Casasoprana et al recommend this diagnostic tool based on the following criteria: 1. absolutely necessary in the clinical suspicion of CNS infection and 2. relatively in patients with incomplete vaccination, CFS or previous antibiotic therapy.(27)

An interesting meta analysis of studies in Medline, Cochrane, Inist databases, suggests a reduced benefit of the LP in the routine diagnosis of CNS infection. For instance it was necessary to make a LP in the case of 1109 cases of SFS or 180 cases of CFS to identify one patient with meningitis.(39)

III. In terms of neuroimaging, depending on the type of seizure, the CT or MRI scan, are not appropriate for the routine evaluation of patients with a first SFS. These procedures have no diagnostic or prognostic value and should not be performed in the routine evaluation of a first CFS with a normal neurological exam given the reduced risk of intracranial pathology.(8,14,37,40,41,42) Regarding the brain CT scan, it should be considered in CFS but the evaluation has to be individualized and integrated in the clinical context (the presence of other severity factors). On the other hand up to date studies correlate rarely a first CFS with pathological intracranial conditions requiring emergent medical or neurosurgical intervention and they have a safety range that does not exclude the risk of intracranial pathology.(43) Crustas al recommend assessing brain imaging and EEG in patients with abnormal neurological exam or with recurrent FS.(44)

Warden and the collaborators demonstrate the absence of intracranial anomalies in the CT scans done in the emergency units for patients with seizures in febrile context or with unprovoked seizures. These patients did not belong to any of the categories at high risk (hydrocephalus, malignancies, phacomatoses, head trauma), had their age over 6 months, and the seizure episode lasted less than 15 minutes in the context of no recent neurological deficits.(45,46,47)

The brain neuroimaging is indicated in children with FS of intracranial hypertension symptoms, history or examination suggestive of trauma or possible structural defects (eg in cases of spasticity, microcephaly). In these cases the preferred investigation is the MRI.(48,49,50)

The most important predictor for the presence of abnormalities of brain imaging is the postictal neurological deficit. The brain MRI does not bring any benefit compared to the CT scan in the course of the treatment in the emergency services. In a retrospective study including 45 patients with first episode of CFS, 165 neuroimaging abnormalities where found but none required emergency intervention.(37,51,52,53) Although in the emergency units only 36% of the physicians are performing imaging for patients with CFS, the conducted studies indicated no significant benefit for the routinely performed MRI in the absence of trauma or intracranial hypertension syndrome.(54,55)

In a retrospective cohort study over a period of 7 years, Kimia and collaborators evaluated the medical records of 526 patients, aged between 6 and 60 months, without other chronic conditions having presented a first CFS in a tertiary emergency department. From the 526 patients evaluated, 268 patients had CT scans, 6 patients performed MRI scans and 8 patients underwent both investigations. Severe imaging abnormalities were identified in 4 patients: 2 cases of intracranial hemorrhage, 1 case of acute disseminated encephalomyelitis and 1 case of cerebellar abnormality. None of the 4 patients had CFC of recurrent FS type within 24 hours.(37)

CONCLUSIONS

In SFS, routine laboratory tests and neuroimaging are usually not indicated. The determination of the postictal serum prolactin levels may be useful in assessing the prognosis of epilepsy. The screening to identify iron deficiency may be important in assessing the likelihood of FS recurrence. Routine LP is not recommended in patients with SFS, normal neurological exam and complete immunization schedule. This should be considered in patients of 6-12 months of age with an uncertain immune status, patients without immunization for Streptococcus pneumoniae and Haemophilus Influenzae or in patients with other clinical factors suggestive of meningitis.

The LP is not recommended in the routine evaluation of all CFS if they are not associated with possible predictors for meningitis (persistent alteration in mental status, neurologic deficits, and status epilepticus).

The brain neuroimaging is not recommended after a first SFS, but may be considered in the context of a clinical picture evocative for a neurological condition (micro/ macrocephaly, preexisting or acute persistent neurological deficits , abnormalities of skin, or in the case of recurring CFS) especially if the diagnose of FS is uncertain.

Emergent brain neuroimaging is not necessary to be carried out in patients with first CFC, normal neurological exam and general wellbeing, especially in those patients with a single diagnostic criterion of CFC, consisting of recurrence in the first 24 hours.

Although the current recommendations regarding the diagnostic approach are restrictive, the opportunity of the investigations is determined by the clinician, with the clinical decision being patient adapted and integrated in the clinical context.

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