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Research Article

Oservational Study of Two Cases of Macrophagic Activation Syndrome in the General Pediatric Department of the Marc Jacquet Melun Hospital Center

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Abstract

Macrophage activation syndrome is a pathology whose diagnosis is difficult because of its rarity, its clinical variability and the absence of a specific diagnostic test. However, the delay in diagnosis weighs its prognosis.

This syndrome can be primary in children or secondary to various infections at any age. Viral infections by herpes virus (especially Epstein Barr and cytomegalovirus), by intracellular germs but also by pyogenic bacteria or with neoplasia (mainly lymphoma) and certain autoimmune diseases (lupus and still) [1].

It is characterized by a set of non-specific clinical and biological signs but the association of which should suggest the diagnosis and lead to a cytological or histological examination to confirm it.

In this observation, our objectives were to reduce the time to diagnosis and review our decision tree in the case of fever in children.

This was a single-center retrospective study of cases diagnosed with macrophage activation syndrome hospitalized in the general pediatrics department for 10 years.

Diagnosis was based on clinical and paraclinical examination of suspected cases of macrophage activation syndrome with case selection criteria.

For both patients, we calculated the macrophage activation syndrome score established by the Saint Antoine team. On admission and at diagnosis.

Patient 1 presented 5 criteria according to Henter while patient 2 presented only 4 for the diagnosis of macrophage activation syndrome. However, these criteria experienced a temporal dispersion. The diagnoses were evoked by the clinical and paraclinical aspect. However, in the absence of hemophagocytosis, the differential diagnosis is made with other diseases and is often difficult.

Keywords: Syndrome; Activation; Macrophasic; Diagnosis

Introduction

Macrophage activation syndrome is a pathology whose diagnosis is difficult because of its rarity, its clinical variability and the absence of a specific diagnostic test. However, the delay in diagnosis weighs its prognosis.

We decided to return to the cases of macrophage activation syndrome encountered in a general pediatrics department and more specifically to the diagnostic criteria, the time to diagnosis and to transfer to a hematology center in order to improve our practices.

This syndrome can be primary in children or secondary to various infections at any age. Viral infections by herpes virus (especially Epstein Barr and cytomegalovirus), by intracellular germs but also by pyogenic bacteria or with neoplasia (mainly lymphoma) and certain autoimmune diseases (lupus and still) [1].

The pathophysiology of macrophage activation syndrome is better understood thanks to the study of the primary forms. Macrophage activation syndrome is linked to excessive activation and/or lack of cytoxicity of CD8 T cells and Natural Killer (NK) cells which secrete large amounts of interferon gamma, activating macrophage cells in the bone marrow and of the reticuloendothelial system which in turn release pro-inflammatory cytokines [2].

It is characterized by a set of non-specific clinical and biological signs but the association of which should suggest the diagnosis and lead to a cytological or histological examination to confirm it.

All of the clinical and biological manifestations can be explained, on the one hand by the cytokine storm (cytokinestorm), responsible for a multi-visceral failure and, on the other hand, by the invasion of the reticuloendothelial system, and to a lesser extent other tissues (skin, lungs, central nervous system), by activated macrophages [1].

The identification of a potentially responsible infection in no way eliminates the diagnosis of primary macrophage activation syndrome, which can itself be triggered by such an event, and must therefore in principle be sought at the time of diagnosis. Epstein Barr virus infection is the most common trigger of macrophage activation syndrome [1].

Macrophage activation syndrome can respond to a wide variety of etiologies, but all of which are underpinned by the same inflammatory phenotype [2]. The average premium of any macrophage activation syndrome is a deficit of CD8+ T and/or NK cell cytotoxicity. The study of the genetic forms of the macrophage activation syndrome has made it possible in recent years, with the identification of new mutations, to better understand the physiopathology of this syndrome, in particular with deficient mouse models [3]. In addition, Epstein Barr virus infection can trigger primary forms of macrophage activation syndrome (X-linked lymphoproliferative syndrome, familial lymphohistiocytosis, congenital immune deficiencies) that are invariably fatal if left untreated [4,5].

The specific treatment of macrophage activation syndrome is based on corticosteroids, intravenous immunoglobulins and VP16 and apart from symptomatic and etiological treatments.

In the primary forms, VP16 and ciclosporin have proven their efficacy while waiting for a bone marrow allograft, the only curative treatment (appendix 1 algorithm for the management of lymphocystiocytosis). The prognosis of the macrophage activation syndrome is variable according to etiology, but the mortality is 50%. This requires early diagnosis and treatment even in the absence of an image of hemato-phagocytosis, which is sometimes difficult to find.

Patients and Methods

The patient files were selected according to the criteria for the diagnosis of macrophage activation syndrome after a detailed clinical and paraclinical examination. All of our patients were under 12 months old. We included in this study the two cases of macrophage activation syndrome diagnosed and having benefited from care in the service and whose clinical and biological data were available and those who did not meet the selection criteria were excluded.

This was a retrospective study operated in a single center concerning cases diagnosed with macrophage activation syndrome hospitalized in the general pediatrics department of MELUN for 10 years from 2007 to 2017.

The diagnosis was based on the clinical and paraclinical examination of suspected cases of macrophage activation syndrome with criteria for selecting files.

For each patient were noted:

- Sex, age at diagnosis
- Family ATCD of death in the family especially of a boy at a young age and or of SAM
- Presence of a family history
- Analysis of Henler's diagnostic criteria revised in 2004
- Results of serology and/or EBV PCR
- Results of genetic studies if performed
- Presence of neurological impairment

- Temporary dispersion of diagnostic criteria
- Treatment and evolution.

Clinical presentation

Observation #1

Patient 1

4 months old, born to full-term non-consanguineous parents, with no particular history known, born by cesarean section for maternal cause, with no notion of miscarriage, or death in the neonatal period or at a young age in the family. Birth weight 4120 grams, good neonatal adaptation, Height 55 cm PC 36.5 cm APGAR 10/10, Under mixed breastfeeding, Good height and weight growth.

Consultation for Fever at 38.6 degrees Celsius degrees Celsius the day before 06/10/2015 initially responding well to Doliprane, new febrile episode at 38.5 degrees Celsius the next night accompanied by dry cough during feedings drinks her bottles 30/90 ml every 4 hours, remains asthenic.

On admission, he weighed 6,450 kg (+130 g in 6 days), Height 65 cm Saturation at 98% in ambient air, Temperature 38.6 degrees Celsius, asthenic feverish to the touch, Clear consciousness G = 15/15, good axial tone, decrease in peripheral tone, low-intensity systolic murmur at the mitral focus, no palpated organomegaly. Good water status and stable hemodynamics. Normal cardiopulmonary auscultation. The rest of the exam is unremarkable.

The assessment on arrival at the emergency room:

THb: 9.4 g/dl, Platelets: 85000 mm/3, VGM: 62.7 fl, Leukocytes: 5610/mm^3, PNN: 30%, Lymphocytes: 67%, Reticulocytes: 0.7% i.e. 33 G/l, Eosinophils: 0%, Basophil: 0%, Monocytes: 3%, NA: 134 mmol/l, Proteins: 52 g/l, Alkaline reserve: 23 mmol/l, CRP: 26.8 mg/L, Blood sugar: 5 mmol/l, ECBU: negative and blood cultures: sterile.

In view of this assessment and given the persistence of the fever, a normochromium microcytic anemia and a biological inflammatory syndrome was retained. Treatment initiated bi probabilistic antibiotic therapy based on Claforan 200 mg/kg every 8 hours and gentamicin 5 mg/kg per day. The clinical evolution will always be marked by the persistence of the fever on a plateau and the deterioration of the general condition. This is how a control report will be carried out after 72 hours of treatment which finds: THb: 8.5 g/dl, VGM: 63.4 fl, Platelets: 45000/mm^3, Neutrophil: at 21%, Sodium: at 133 mmol/l.

Alkaline reserve

18 mmol/l, AST: 387 IU/L, ALT: 82 IU/L, GGT: 144 IU/L, CPK: 52 IU/l, LDH: 712 IU/l, Alkaline phosphatase: 148 IU/L, Triglyceride: 3.41 g/l, Ferri tin: 4976 micrograms/l, Fibrinogen: 0.68 g/l, Albuminemia: 28.9 g/l.

Faced with a persistent plateau fever, deterioration of general condition with pancytopenia, hyper triglyceridemia, hyperferritinemia, hypo fibrinogenemia, hepatic cytolysis, high LDH, hyponatremia, the hypothesis of macrophage activation syndrome is evoked after 3 days of hospitalization and probabilistic treatment with dual antibiotic therapy, the transfer was carried out on 09/10/2015 in pediatric intensive care at NECKER Hospital.

Management in the immunology department of Necker Hospital.

Inclusion in the C-HLH protocol before the transplant:

Campath IV 0.5 mg/kg/d, Corticosteroid therapy 2 mg/kg/d and Ciclosporin with clinico-biological remission after the second course of Campath, intrathecal chemotherapy due to neurological impairment.

Haplo-identical transplant with his mother on 19/11/2015, T repeated by Endoxan.

Donor/recipient pair

EBV+/- CMV+/-.

Prevention

Of graft-versus-host reaction (GVH) by Ciclosporin (stopped on D39. Faced with the stigma of thrombotic microangiopathy) and Lymphocyte phenotyping: note immune reconstitution: CD3+ = 558/micro liter, CD4+ = 252/micro litre, CD8+ = 189/micro liter CD19+ = 54/micro liter CD16+CD56+ = 207/micro liter and excess activated T lymphocyte.

Digestive stage II and cutaneous stage I post-transplant GVH on D38.

Locoregional BCGitis evolving under Rifampicin and Isoniazid, addition of Moxifloxacin and Myambutol.

CMV disease

Bilateral necrotizing chorioretinitis with retinal detachment treated with Cymevan+Foscarnet dual therapy in 4 injections, favorable evolution with improvement of the fundus, more marked involvement of the right eye without obvious clinical visual repercussions, prevention of amblyopia of the right eye.

On the dermatological level, there is a frank well-defined, diffuse depigmentation with periorbital, abdominal and extremity involvement without involvement of the skin appendages. Lesions suggestive of post-transplant vitiligo, compatible with post-chemotherapy depigmentation.

Skin biopsy of 06/17/2016.

Very frank hypopigmentation of the epidermis combined with dermal pigmentation. This is not the image of vitiligo it is probably a post inflammatory pigmentation. This pigmentation could be a sequela of toxemia, as well as a sequela of GVH>>.

Etiological diagnosis

Familial lymphohistiocytosis due to Perforine deficiency.

In total

Patient 1 aged 4 months suffering from familial lymphohisticytosis diagnosed on day 3 of fever, start of treatment on day 4 at Necker included in the C-HLH protocol and responding well to treatment before its transplant, then repeated intrafamilial haplo identical T marrow transplant, is in good hematological reconstitution and immunological under immunoglobulin treatment without BCG lesion itis, vitiligo in slow regression under Protopic.

OBSERVATION #2

Patient 2

9 months old of parents of African origin, the carrier mother of heterozygous AS sickle cell disease, unremarkable pregnancy at 38 SA+2, term vaginal delivery. Birth weight 3480 grams, Height 48 cm PC 35 cm, APGAR 10/10. Known sickle cell heterozygous AS and having had two episodes of bronchiolitis, without notion of miscarriage, or death in the neonatal period or at a young age in the family. Up-to-date vaccination, born in metropolitan France and has never travelled. The age of care at 9 months.

Admitted to the emergency room for Fever at 39.8 degrees Celsius evolving for 4 days and 3 to 4 diarrheal stools per day justify her hospitalization in the pediatric department of the Center Hospitalier de Melun on 14/10/2007.

Assessment in the emergency room and initial care in General Pediatrics:

THb: 9.6 g/dl, MCV: 72 fl, White blood cell: 17,500 including 60% neutrophils, platelets: 506,000/mm^3, normal blood ionogram, CRP: 107 mg/l, higher pro calcitonin 10 ng/l, ECBU: shows leucocyturia 8000 leuco/ml without germ on direct examination or culture. The chest X-ray is normal.

On admission, faced with this severe septic syndrome, with a sensitive abdomen and diarrhoea, as a warning sign, she was put on ROCEPHINE: 50 mg/kg/day, she remained very febrile with peaks of more than 40 degrees Celsius.

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on ROCEPHINE: 50 mg/kg/day, she remained very febrile with peaks of more than 40 degrees Celsius.

A check-up carried out on day 4 of antibiotic therapy shows hemoglobin at 8.2 g/dl with a VGM at 69 fl, whites at 13,900/mm^3, CRP at 77 mg/l, platelets at 352,000/mm^3, pro calcitonin between 2 and 10 ng/ml, negative blood cultures, negative ECBU, a control of the chest x-ray is normal.

Faced with this unexplained fever with a significant inflammatory syndrome on D 9 is discussed, KAWASAKI's diagnosis, the sedimentation rate is 78 mm.

Faced with this hypothesis, it was decided to infuse TEGELINE 2g/kg on 10/19/2007, treatment with ASPEGIC 75 mg/kg/day was also started.

Despite this infusion, she is still very febrile with the persistence of febrile peaks at 40 degrees Celsius. On clinical examination, she weighs 10 kg, height 70 cm, erythematous throat, some cervical and bilateral axillary and inguinal lymphadenopathy. At the cutaneous level, she presents a micro papular eruption of the folds of the neck and axillary appeared on D5 of the fever, dermatologist opinion evokes a sudamina. She also presents a slight edema of the feet which appeared 48 hours after the infusion of TEGELINE, no lesions of the extremities nor erythema nor cheilitis. The joints are free, the spleen is palpated.

The cardiac ultrasound of 10/22/2007 is normal with a minimal posterior pericardial blade remaining in the physiological data. Abdominal ultrasound at the entrance showed the presence of an anterior cortical zone of its upper pole with a triangular morphology and more echogenic than the rest of the parenchyma measuring 19 mm in diameter at the level of the right kidney, which could correspond to a focus of acute pyelonephritis. The control of the abdominal echo is carried out on 22/10//2007 shows two kidneys with good cortico-medullary differentiation, this image is not found, the gallbladder of less than 4cm in length has a thin wall not alithiasic but finds a spleen of more than 8 cm in length which is homogeneous.

The control blood test carried out found hemoglobin at 7.4 g/l, platelets at 142,000/mm^3, WBC at 24,900/mm^3, a normal blood ionogram, a CRP at 56 mg/l, a normal liver test, a pro calcitonin >10 ng/ml, ESR at 46 mm. The EBV serology is negative, the enterovirus and adenovirus serology pending, as well as the HIV serology and the search for adenovirus on the nasal secretions.

Faced with the persistence of the fever on D13 of treatment without aetiology found with this disturbed biological assessment which highlights anemia and thrombocytopenia, he was transferred on 23/10/2007 to KREMLIN BICETRE to continue treatment.

Clinically, throughout her hospitalization, she presented fever peaks of up to 40 degrees Celsius once or twice a day. During the febrile episodes, she is tired, grumpy, whiny with a bloated and sensitive abdomen that is difficult to examine, presence of cervical and axillary lymphadenopathy and intracentric femoral lymphadenopathy.

Various additional examinations carried out during his hospitalization at KREMLIN BICETRE:

- **Hematology:** Microcytic anemia with several episodes of acute hemolysis, requiring 4 transfusions (the last on 28/11/2007).

Assessment of 11/30/2007: THB = 10.6 g/l VGM = 79.5 fl., Coombs direct negative on 11/25/2007 and weakly positive for anti-IgG (negative for anti-C3D), folates increased serum = 32 n mol/l (N: 5-25), Vitamin B12 serum = 755, Dosage of glucose 6 phosphatase dehydrogenase = 7.7 IU/g of hemoglobin (N: 11-17). Assay in favor of a heterozygous deficiency in G6PD, pyruvate kinase = 13.4 IU/g of hemoglobin (N: 14-19), GB = 16999/mm^3 PNN = 11210 lymphocytes = 3910/mm^3 monocytes = 1870/mm^3, thrombocytopenia relative the lowest rate of platelets 126000/mm^3 on 11/27/2007 and 171000/mm^3 on 110/30/2007.

Myelogram carried out on 10/24/2007: very rich granular marrow, the myeloid precursors are numerous, hyper granular, with slowing down of terminal maturation. The erythroblast line is balanced but there are clear signs of terminal deerythropoiesis with an exfoliated appearance of the nuclei. Presence of active-looking cells of medium size with extensive basophilic cytoplasm. Small histiocytic expansion with the presence of a few images of cytophagocytosis in a marrow with an overall reactive appearance with exclusion of acute hemopathy.

Lymph node biopsy on 11/15/2007: little contributory with small left spinal lymphadenopathy, poorly stimulated with mild

nonspecific chronic lymphadenitis. No epithelioid granuloma, no plasmacytosis, no tumor infiltration.

Osteo-medullary biopsy of 11/15/2015: little contributory with a cortical and subcortical fragment containing only very rare hematopoietic elements of the erythrocyte granular line without atypia, without megakaryocytes. There is no inflammatory infiltrate, no plasmacytosis, no epithelioid granuloma. No tumor infiltration.

Lumbar puncture of control carried out one month after the persistence of the fever, finds an acellular liquid, sterile with absence of visible germ was normal, which was negative beforehand.

Disturbed haemostasis: factor II = 54%, factor VII+X = 46%, factor V = 97%, fibrinogen = 1.7g/l Highly increased ferritin = 12810 micros g/l (N: 100-300), hyponatremia (Na = 134 mmol/l).

Impaired hepatic assessment: ASAT 129 IU/l, ALAT 56 IU/l, GAMMA GT 243 IU/l, Total bilirubin = 58 micromol/l, Conjugated bilirubin = 17 micromol/l, Triglycerides increased = 1.97 mmol/, CRP between 30-105 mg/l, PCT between 2-2.8 ng/ml, blood lead level normal, dosage of normal catecholamines.

Serology performed after immunoglobulin infusion

PCR: Adenovirus and marrow DNA is undetectable.

Positive hepatitis A and negative hepatitis C serology.

HIV 1 and 2 screening test negative.

CMV serology and parvovirus B 19 IgG positive, anti-CMV IgM negative.

Search for viral antigens by direct immunofluorescence: negative for influenza virus A and B, para influenzae 1, 2,3, adenovirus a RSV.

Negative search for malaria (thick blood smear and NOW malaria), Mycological culture on marrow: negative.

Search for leishmania by PCR and mycoplasma pneumoniae negative.

Decreased IgA toxoplasmosis serology and negative stool culture.

Serodiagnosis of Vidal and Félix: negative and Search for anti-Brucella antibodies: negative.

Search for anti-chlamydia antibodies: negative and serology coxiella burnetii negative, rickettsia conorii negative, rickettsia mooseri negative, sterile lymph node biopsy culture and IDR negative.

Imaging

- **Whole-body MRI:** Multiple cervical axillary and inguinal lymphadenopathy, homogeneous splenomegaly. Bilateral intra-articular effusion at the level of the two knees, predominantly on the left. Infiltrated appearance of subcutaneous fat in the entero-external regions of the lower half of both thighs.
- **Cardiac ultrasound:** Low abundance pericardial effusion without haemodynamic impact.
- **Scintigraphy:** Bone scintigraphic appearance within normal limits
- **At the therapeutic level:** Treatment with corticosteroids started on 20/11 in view of the suspicion of Still's disease, ferritin at 12000 micrograms/ml. Then the diagnosis of SAM at the end of November in front of a hypertriglyceridemia, a hypofibrinogenemia and a phenotyping of the lymphocytes on 28/11. Ciclosporin treatment started on 11/30 and transferred to immunology at NECKER hospital.

In total

Probable familial lymphohistiocytosis with macrophage activation syndrome comprising prolonged fever with splenomegaly, damage to the erythrocyte line associated with relative thrombocytopenia, hypo fibrinogenemia, hypertriglyceridemia, hyponatremia and hyperferritinemia, the child is transferred to immunology to NECKER for further support.

Management in the immunology department of the Necker hospital:

The evolution before the transplant was marked by a new flare of the lymphocyte activation syndrome which did not yield to the immunosuppressive treatment associating ciclosporin, solumedrol as well as a SAL cure stopping at 40 mg in total. Faced with this poor response to treatment with SAL, a course of campath at 0.2 mg/kg/day was instituted for 5 days.

In March 2008, the clinical evolution remains worrying, the indication of a bone marrow transplant will be evaluated. The donor balance sheet for both parents in order to be able to choose according to the typing and the serologies, the father was chosen since there is an advantage on the HLA level being homozygous, on the other hand, he presents the serology of a cured hepatitis B, injections of specific immunoglobulins for hepatitis B before the transplant. The CMV, EBV and Adenovirus PCRs remain negative, absence of hepatic cytolysis.

The haplo-identical bone marrow transplant with his father on April 24, 2008, 5 months after the diagnosis.

The evolution of the graft was characterized by febrile outbreaks above 40 degrees Celsius little argument in favor of GVH, absence of eruption in favor of cutaneous involvement, immunosuppressive treatment was instituted very transient way was able to lower the fever without obtaining prolonged apyrexia. Analysis of the myelogram found an erythroblastic marrow with no sign of lymphoid or macrophage infiltration, no image of hemophagocytosis. Neutropenic remains with 300 PNN and 1200/mm^3. She still presents with symptomatic reactivation of CMV following treatment with THYMOGLOBULINE

In total, therefore, she presented with a macrophage activation syndrome probably triggered or favored by an unnoticed salmonella typhirium infection. The various examinations did not make it possible to characterize the most frequent etiologies of familial or congenital lymphohistiocytosis predisposing to macrophage activation syndrome.

In September 2008, 5 months after the transplant, worsening of the respiratory situation, realization of a thoracic scanner found multiple interstitial alveolar lesions. A bronchial fibroscopy was performed which revealed grade III inflammation of the entire bronchial tree without pus, with the presence of a whitish layer in the left main bronchus. All the anatomopathological and microbiological samples will not make it possible to find a precise etiology for the dyspnea, will be followed by a massive alveolar hemorrhage justifying a transfer to general intensive care. Respiratory evolution will be rapidly unfavorable despite broad-spectrum probabilistic anti-infective treatment, and the secondary addition of immunosuppressive treatment with high-dose corticosteroids, leading to death.

Main characteristics of the two patients observed

Characteristics	Patient #1	Patient #2
Persistent fever	Yes	Yes
Hepatomegaly	Yes	Yes
Splenomegaly	Yes	Yes
Anemia < 9 g/dl	Yes	Yes
Thrombocytopenia< 100,000/mm^3	Yes	No
Neutropenia < 1000/mm^3	Yes	No
Fibrinogen < 1.5 g/l	Yes	No
Ferritin > = 500 g/l	Yes	Yes
Hemophagocytosis	Yes	No
NK activity in vitro	NR	NR
Number of criteria Henter	5	4
Time dispersion	Yes	Yes
EBV serological profile	Negative	+(old)
EBV genome	NR	NR
Perforin study	Deficit	Normal
CNS involvement	Yes	Yes
family history	Negative	Negative
Specific treatment: corticosteroids,	Yes	Yes
Immunosuppressants and IT	Yes	Yes
Marrow transplant	4 months	9 months
Age at first symptoms	2 days	1 month and a half
Pick-up time delay	2 years and over	10 months

Discussion

We were able to conduct a single-center study on two pediatric cases of macrophage activation syndrome in a context of persistent fever in the general pediatrics department of CH de Melun. The main objective of this study was to review our decision tree in the management of fevers in children in order to reduce the time to diagnosis of SAM whose prognosis is sometimes poor.

We will discuss the decision tree in case of fever, see the diagnostic hypotheses in the face of a persistent or prolonged fever of more than five days in an infant despite a well-conducted probabilistic treatment.

For both patients, we calculated the SAM score established by the Saint Antoine team (see appendix 2). On admission and at the time of diagnosis for patient number 1, the score was respectively 49, i.e. a probability of 0.064% at the onset of his symptoms, and a score of 224, i.e. a probability of 97% at the time of confirmation of the diagnosis. The items provided increasing the probability from 0.064% to 97% are the results of fibrinogen, triglycerides, ferritinemia and liver function tests carried out on day 3 of fever.

Case number 2 brought together a score of 72 points or 0.26% at the start and 196 points or a probability of 85% at the time of diagnosis confirmation. It is also the results of ferritin, triglycerides, fibrinogen and liver function tests that modify the score significantly.

Patient 1 presented 5 criteria according to Henter while patient 2 presented only 4 for the diagnosis of SAM. However, these criteria experienced a temporal dispersion. The diagnoses were evoked by the clinical and paraclinical aspect. However, in the absence of hemophagocytosis, the differential diagnosis is made with other diseases and is often difficult.

Long-term fever in pediatrics is a difficult situation and often a thorny problem. Clues to the diagnosis are often present in the history and physical examination. The rigor and repetition of examinations are of vital importance.

There is no pediatric definition for long-term fever, so in pediatric publications the adult definition prevails. Nevertheless, in pediatrics, specific explorations must begin as soon as the duration of the fever exceeds the expected duration of the evolution of a classic viral or bacterial infection (for example 10 days for an upper respiratory viral infection and 3 weeks for infectious mononucleosis, etc..), which explains the variable delay of 15 to 21 days to be able to speak of prolonged fever in children.

Some consider as prolonged fever an unexplained fever in children under 2 years of more than 5 days and more than 7 days in children over 2 years old.

What is currently practiced in the face of prolonged fever in infants

Prolonged fevers are classified as long-term fevers, classic, nosocomial or associated with an immune deficiency.

In the absence of immune deficiency, which is a special situation, a first complete infectious assessment will be prescribed with blood cultures, NFS CRP ECBU Chest X-ray and liver assessment in search of a bacterial infection.

In the absence of signs of infectious etiology to follow up on this assessment, a 2nd intention assessment with EBV CMV HIV Toxo serologies and tuberculosis research with IDR and quantification is generally requested and supplemented by an abdominal and cardiac ultrasound.

We can also wonder about the possibility of a drug fever and we will look at the interrogation for the drugs most frequently implicated.

Following our observations, in view of the simplicity of the assays such as fibrinogen, ferritin and triglycerides possibly suggesting MAS, the temporal dispersion of the signs and the urgency of the diagnosis of this pathology, we propose to add these examinations to the assessment of second intention previously discussed in the absence of etiological orientation such as could be in the hypothesis of an infectious origin a recent trip for example, headaches or other neurological signs which would require performing a brain scan and a lumbar puncture, unexplained pain or lameness that would lead us to perform a bone scan or the presence of digestive signs and/or growth curve abnormality in front of which tests for an inflammatory disease of the digestive tract would be prescribed such as fecal calprotectin and a ultrasound of the digestive tract, or even superficial lymphadenopathy or cu abnormalities tanned for which a puncture/biopsy would be performed.

This would be all the more to be discussed since it is currently accepted that only 3 to 4 criteria can be enough to diagnose the disease and raise the question of the specific treatment. The myelogram may be normal without eliminating the diagnosis.

Conclusion

Macrophage Activation Syndrome is a severe medical condition with a poor prognosis, which must be detected and treated without delay, sometimes even before having the etiological diagnosis.

But for that it is necessary to give oneself the means to make the diagnosis by carrying out examinations such as ferritin the dosage of triglycerides and fibrinogen earlier in the face of a fever in infants without etiological orientation.

This work encourages us to recommend these examinations in the face of a picture of fever without etiology in an infant in order to make it possible to evoke the diagnosis earlier and to transfer the child to a specialized service in order to initiate a specific treatment for this condition as soon as possible. as soon as possible.

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