American Journal of Pediatrics
2020; 6(4): 495-503
http://www.sciencepublishinggroup.com/j/ajp
doi: 10.11648/j.ajp.20200604.28
ISSN: 2472-0887 (Print); ISSN: 2472-0909 (Online)

Fever as an Adverse Drug Reaction of Different Therapeutic Groups

Sergey Postnikov[1, 2], Natalia Teplova[1], Aleksey Ermilin[1, 2], Marya Kostyleva[1, 2], Anna Gratzyanskaya[1, 2], Yulia Eremina[1], Galina Chervyakova[1]

[1]Chair of Clinical Pharmacology, Russian National Research Medical University Named After Pirogov, Moscow, Russian Federation
[2]Children Clinical Hospital of Pirogov University, Moscow, Russian Federation

Email address:
salmova@mail.ru (S. Postnikov), Teplova.nv@yandex.ru (N. Teplova), elixin@list.ru (A. Ermilin), Kostyleva_m_n@rdkb.ru (M. Kostyleva), annagrats@rambler.ru (A. Gratzhianskaya)

To cite this article:
Sergey Postnikov, Natalia Teplova, Aleksey Ermilin, Marya Kostyleva, Anna Gratzyanskaya, Yulia Eremina, Galina Chervyakova. Fever as an Adverse Drug Reaction of Different Therapeutic Groups. *American Journal of Pediatrics*. Vol. 6, No. 4, 2020, pp. 495-503.
doi: 10.11648/j.ajp.20200604.28

Received: November 16, 2020; **Accepted**: December 4, 2020; **Published**: December 16, 2020

Abstract: Fever (t>38°C) developed in association with drug usage is rare but sometimes severe side effect (SE). It could manifest as single symptom or as a part of such life-threatening syndromes like malignant hyperthermia (MH), serotonin syndrome (SS), neuroleptic malignant syndrome (NMS). Fever could be caused by different therapeutic groups of drugs but the leading positions are occupied by antibiotics (mainly beta-lactams), substances acting on central nervous system (CNS) and chemotherapeutic agents. Main mechanisms are allergic and receptive. Curative measures include discontinuation of the suspected drug, introduction of agents blocking the action of the trigger factor - dantrolene (MH), bromocriptine (NMS), cyproheptadine (SS). Purpose of this review: to present the global and Russian data concerning fever as a drug-induced side effect. To distinguish the groups of patients and drugs of the highest risk. To evaluate aid measures. Results: fever as monosymptom of drug allergy is a difficult condition to be diagnosed and there are only few things that could help to recognize it such as temporal association with the suspected drug use and manifestation of fever along with the following resolution after suspected drug discontinuation and recurrence fever after suspected drug re-challenge. Among four syndromes described in this review such as serum sickness-like reaction (SSLR), NMS, SS and MH just fever at MH is not only a sign like in case of three others but it is significant and life-threatening manifestation and therefore requires additional curative methods (in addition to pharmacological support with dantrolene) – rapid cooling measures: ice-water nasogastric and rectal lavage, infusion of crystalloid solutions cooled up to 4°C, ice packs placing on main blood vessels and liver area, ventilatory measurements.

Keywords: Children, Drug Fever, Malignant Hyperthermia, Serotonin Syndrome, Neuroleptic Malignant Syndrome

1. Introduction

Normal temperature of human body is usually balanced around 37°C and its stability (temperature homeostasis) is supported by two main mechanisms: central system – anterior hypothalamus where “thermostat” is placed and peripheral part – skin blood circulation, muscular tonus and sweating.

In general understanding fever is an adaptive physiological reaction that is resulted from synchronized response of vegetative and neuroendocrinal systems for disease or other injury.

Drug-induced fever (DF) is abnormal pathological phenomenon that coincides in time with the use of drug in the absence of other reasons for its manifestation.

In accordance with data from Vigibase (2018) drug-induced fever (t>38°C) was observed in 3,1% of children with variables in frequency in different age groups, countries [1-3], out-patient or in-patient practice where the intensity and volume of drugs administration is higher.

Pharmacovigilance service of our hospital in 2006-2007 registered 22 cases of drug-induced fever (12,35% of all adverse side effects) and 18 cases from those were registered

as a result of beta-lactam use ("beta-lactam fever"): ceftriaxone, ceftazidime, meropenem, cefepime.

2. DF as Alone Manifestation of Drug Intolerance

It's considered that drug fever of this type does not have any specific signs allowing to distinguish from fever of another origin. However there are some landmarks which could help to suspect drug-induced fever: onset of fever coincides in time with prescription of the suspected drug, absence of obvious sites of infection, relative bradycardia. And the main argument in favor of drug-induced fever is its termination after discontinuation of suspected drug administration. In such a case the patient has to remain afebrile during at least three days after normalization of the temperature. Usually fever terminates in 48-72 hours but sometimes later if the drug eliminates slowly like amphotericin B that is eliminated during 3-5 days after first infusion.

Next important evidence is recurrence of fever after restarting (accidental or intentional) of offending drug.

However both evidences (drug discontinuation and re-challenge) have restrictions: in the first case – due to possible absence of the alternative treatment (in oncology, resistant flora) and in the second case – due to ethical considerations (as placebo effect in Naranjo scale).

Some patients (18-29%) have skin signs of hypersensitivity like urticaria or maculo-papular rash and eosinophilia in combination with fever that also could support the diagnosis of DF. But presence of rigor, slight increase of ESR and transaminases (less than two upper normal values), leukocytosis could be misleading signs for diagnosis of drug-induced fever [3, 4].

Temperature elevation is non-specific reaction and due to understandable reasons drug-induced fever is the diagnosis of exclusion that is remembered at the latest that is caused among others by the known mistaken belief of health-care professionals that fever could be only related to infection and mainly bacterial requiring antibiotics (AB). In particular such situation is wide-spread among pediatricians as far as the requirements for AB indications in pediatrics are reduced in addition to the fact that this class of drugs could cause fever on its own.

2.1. DF Mechanisms

There are three mechanisms of DF caused by AB:

First mechanism is attributed to the properties of the drug itself or to procedure of its administration.

a) It's related mainly to the quality of the drug. Fever could be caused by pyrogenic contaminants not removed during manufacturing process like it was for vancomycin [5].

b) In case of infusion of amphotericin B and bleomycin manifestation of pyrogenic reactions is resulted due to release of endogenic pyrogens (interleukin-1 (IL-1), tumour necrosis factor alpha (TNF-α) from granulocytes. Special characteristic of such type of fever is its manifestation usually during drug infusion.

c) Fever could be caused by the injection itself in case of subcutaneous administration, for instance dalteparin injection (low-molecular heparin derivative) or as a result of phlebitis after infusion of irritating solution like vancomycin, cephalosporines, ciprofloxacin (local toxic reaction). According to our observations mentioned above effect of ciprofloxacin is related as well to infusion speed that is not followed by phlebitis if becomes slower.

d) Vaccines and allergic extracts could cause fever because both contain bacterial and virus pyrogens [6-8].

e) Treatment by interferons (in our hospital for laryngeal and lungs papillomatosis) is predictably followed by high fever.

f) Intrathecal introduction of cerliponase-α (own unpublished data).

Second mechanism is attributed to pharmacological effect of AB for treatment of spirochetosis (syphilis, leptospirosis, borreliosis) by penicillin or for treatment of abdominal typhoid fever by chloramphenicol and release of pyrogens by killed microbes. This type DF caused by bacteriolysis that usually develops after 6-8 days from the beginning of AB treatment. It's considered that the role of pyrogen plays endotoxin known as lipopolyssacharide being the part of cell wall of killed microbes.

Anticancer drugs (bleomycin, vincristine, daunorubicin) have similar mechanism of development. Fever followed its administration is caused by release of pyrogens from the destroyed cancer cells and their effect on hypothalamus.

Third mechanism (the most frequent) is immune, allergic reaction of III type following by the formation of immune complexes from drugs and its metabolites binding with proteins. Immune-mediated reaction is followed by release of endogenous pyrogens (IL-1, TNF-α) from leucocytes.

Leading positions in development of such reaction belong to antibacterial agents first of all beta-lactams: cephalosporins and ureidopenicillins [2, 4, 9].

2.2. Risk Factors and Risk Groups for DF of Allergic Origin in Children

Risk factors:

a) allergic and autoimmune diseases in parents (especially in mothers).

b) AB treatment by beta-lactams during pregnancy followed by antenatal sensibilization.

c) perinatal disturbances (neurovegetative instability) and early age (immaturity of center of temperature control).

d) gender characteristics: prevalence of drug-induced allergy is higher in girls (3:1000) than in boys (2:1000).

e) compromised background: protein-overloaded food, dysplasia of connective tissues, polypharmacy, irrational use of AB.

There are some patient groups more susceptible to drug allergy than others:

a) patients with cystic fibrosis due to their hyperimmune status

b) oncological patients who have seriously disturbed immunological reactivity and consequently they are more sensitive to drugs;

Allergic reactions for the injected AB could be urgent (within 1 hour) considering the clinical signs progression rate in particular the fever, sometimes even at first injection of drugs such as streptomycin, cloxacillin, isoniazid.

Subacute or delayed allergic reactions with fever develop in several hours or days and even weeks or months after AB administration as for piperacillin / tazobactam, vancomycin, tigecycline, minocycline, antituberculotics.

In addition to that the same drug, for instance isoniazid, could cause the development of acute (already after the first dose) as well as delayed fever response.

2.3. Pharmacogenetic Mechanism of DF

Some groups of drugs (AB, NSAIDS, simple analgesics, sulfonamides, malariacidal agents – totally more than 140 drugs) could cause hemolytic reaction in patients with G6PD or glutathione deficiency (Greeks, Jews, Azerbaijaneses) that is followed by release of endogenous pyrogens from destroyed erythrocytes, fever manifestation and sometimes development of hemolytic kidney and acute renal insufficiency requiring hemodialysis (own unpublished data).

Another group of drugs could contribute to fever based on two mechanisms: increase of heat production and (or) heat loss reduction.

2.3.1. Neuroendocrine Mechanism

Levothyroxine is an example of drug that could directly augment heat production through increasing the speed of basal metabolism. Excitation occurring during the treatment could play a role in the development of fever. Both effects of levothyroxine are dose-dependent and partially mediated through activation of sympathetic nervous system.

2.3.2. Neurovegetative Mechanism

Antimuscarinic effect is related mainly to two groups of drugs - antiparkinsonian agents and tricyclic antidepressants (TCA) in case of their overdose or long-term administration, and as well it could happen in case of atropine-containing drugs intoxication: it's Belloidum in Russia (own unpublished data).

But fever is related not to only TCA overdose. Enchancement of cholinomimetic action could occur if TCA and histamine-lytic agents of I generation or TCA and amantadine are used in parallel (potentiative effect of interaction).

Emergent fever in such a case is a result of decrease heat loss with sweat and increase of heat production due to patient's excitation and increase of physical activity as well.

Some anticonvulsants like topiramate, valproic acid could also cause intermittent fever due to disfunction of sweat glands followed by hypohydrosis and decrease of heat loss.

Sympathomimetic effect caused by psychoactive agents (amphetamine, MDMA) and hallucinogenics (LSD) is attributable to adrenalin, noradrenalin, dopamine and serotonin release. Fever manifestation in such a case is related to significant stimulation of peripheral alpha-adrenoreceptors followed by vasoconstriction and decrease heat loss. In addition amphetamine and MDMA act like exogenous pyrogens affecting «thermostat» in hypothalamus causing temperature increase. And one else: increase of heat production is caused by neuropsychic disturbances and intensified physical activity [10].

3. Fever as a Part of Syndromes Caused by Drug Use

3.1. Serum Sickness Like Reaction (SSLR)

SSLR as well as drug fever is caused by AB mainly by beta-lactams and is developed following the same mechanism – allergic reaction of III type. Main clinical signs of SSLR (in addition to hyperthermia) are lymphoadenopathy, arthralgia (particularly in major joints), myalgia (commonly in hands and feet), rash (urticaria or morbilliform) and laboratory abnormalities (not constant) – leukocytosis, increased transaminases, alkaline phosphatase (AP) and lactic dehydrogenase (LDG) concentrations.

Prevalence of SSLR is nearly 0,2% but in children it's 0,5% and in children younger than 5 years it's 0,9% that is related to more frequent AB use in children, first of all these AB are cephaclor and ampicillin during long-term or repeated courses [11-14].

However SSLR development is related not only to AB use. We would like to pay attention to propranolol that is non-selective beta-adrenoblocker (from the list of S. Wilson, 2018) and is used currently for three indications: as antihypertensive agent, as antiarhythmic and since recently for treatment of infantile angioma (IA) because propranolol has as well antiangiogenic effect as it was revealed by French investigators. However it seems that SSLR associated with this beta-adreno-blocker is very rare complication because there were no any such complication among hundreds of patients with IA treated by propranolol in our hospital but the only notification about it is related to 1993 [1, 13].

We could say the same about acetylcysteine (from the list of S. Wilson, 2018) as a reason for SSLR. We have not revealed such effect among many hundreds of patients have been or being observed in Moscow center of mucoviscidosis with the constant use of this mucolytic.

Management of SSLR is required (besides dicontinuation of offending drug) the administration of histaminelytic agents and in case of severe course – glucocorticosteroids (GCS). In rare cases (if discontinuation of suspected drug is not possible plasmapheresis is recommended.

The common mechanism of fever development predominantly through increasing muscle tonus is typical for three other syndromes: neuroleptic malignant syndrome NMS), serotonin syndrome (SS) and malignant hyperthermia (MH).

Pathogenic similarity of these syndromes is supported by the following facts:

a) Possibility to have both MH and NMS for one patient;
b) Symptoms and signs of SS are similar to those in NMS;
c) Antipsychotic drug risperidone could cause both NMS and SS [1, 15].

3.2. Neuroleptic Malignant Syndrome (NMS)

This syndrome is called malignant not only due to severity of clinical manifestations (coma, rhabdomyolysis) and high mortality rate (in particular in patients with background organic brain affections) but also due to severe neurological deficiency that develops not rarely after NMS resolution.

NMS is characterized by symptoms tetralogy (fever, muscle rigidity, impairment of consciousness, instability of vegetative nervous system) and could be caused by any antipsychotic agent with the frequency nearly 0,2-3,23%. It is considered that early (typical) antipsychotics like fluphenazine and haloperidol (most notably) could cause NMS more frequently than later (atypical) antipsychotics like risperidone and olanzapine.

3.2.1. Mechanism NMS

Mechanism of NMS is idiosyncratic reaction as a result of dopamine receptors inhibition by antipsychotics in CNS and most likely it has pharmacogenetic basis (taking into account family cases) – predisposition to distored reactivity for antipsychotics intake. Possibly that increased expression of specific allele in gene of dopamine receptor D_2 plays a role in this mechanism of NMS development [16].

Sometimes another genetic mechanism could be involved in the development of NMS: higher occurrence of NMS as a response for haloperidol and risperidone is related to decrease activity of CYP 2D6 metabolizing these drugs (poor metabolizer) with the resulted relative overdose. In this relation it's important to notify that the most polymorphic isoenzyme of cytochrome P450 among all of them is namely CYP 2D6 and the frequency of patients with genotypes of slow metabolism in Russian population reaches 20-25% [17].

However NMS is a complex process and it is developed possibly with the participation of the receptors of different types and not only with dopamine receptors. So that in the large list of S. Wilson [1] and L. Simon [16] there is metoclopramide that blocks both dopamine and 5-HT_3 serotonin receptors.

Unfortunately domperidone that replaced metoclopramide for the treatment of functional constipation in children of early age could cause NMS as well [1, 16]. It's necessary to notify that domperidone crosses insignificantly the blood-brain barrier mainly acting for peripheral D_2–dopamine receptors because 66% of this drug is eliminated by intestinal tract.

However the effect of domperidone on CNS could be increased under two conditions: a) long-term use of this drug; b) concomitant use of inhibitors isoenzyme CYP 3A4 which metabolizes domperidone (metronidazole, omeprazole, macrolides, anti-fungal drugs of azole group).

It seems that even if NMS as a domperidone reaction is developed very rare (we did not see any case during many years of its usage) it's necessary to be warned of its possible manifestation and it additionally emphasizes the various conditions and mechanisms of NMS development. This could be confirmed by anticonvulsants presented in the list of drugs causing NMS [1]. The principal effects of phenytoin and lamotrigine are related to fast sodium channel blockade but carbamazepine has in addition GABAergic system activation effect (like valproates) and inhibition effect on neuro-mediated amino acids excitability: glutamate and aspartate [18].

However fever with NMS-like symptoms could develop not only in case of dopamine receptors antagonists administration but also at abrupt discontinuation of these receptors agonists: levodopa, amantadine and bromocriptine. NMS-like symptoms could be observed after sudden discontinuation of baclofen treatment (centrally acting muscle relaxant – GABA-derivative), especially when it's injected intrathecally [1].

NMS risk factors: 1) high start dose of the provocative drugs or fast dose increase; 2) parenteral injection of antipsychotics; 3) male gender; 4) poor nutrition (dystrophy); 5) hydropenia; 6) ferrum deficiency; 7) background mental retardation; 8) sudden interruption of dopaminergic drugs; 9) concomitant use of lithium, cholinergic agonists, TCA [18]. TCA effect, in particular amitriptyline, is increased to the extent of death if one or two gene 2D6 alleles are not active [17].

Development of this syndrome is possible in any age groups starting from infants [19]. Primary symptoms of typical NMS are impairment of consciousness (from delirium to coma) and muscle rigidity in 80% of cases (these symptoms are responsible for temperature increase) and in addition blood pressure and pulse instability.

It's necessary to admit that timely diagnosing of NMS could be quite complicated due to some objective reasons: firstly due to delayed manifestation of NMS (sometimes after several years) and secondly - due to atypical course of the syndrome (for example absence of muscle rigidity) in case of risperidone and paliperidone administration [1].

3.2.2. Management of NMS

Drug of first choice is bromocriptine (dopamine receptors agonist) at starting dose 2,5 mg 3 times per day per os or per nasogastric tube with dose increasing up to 45 mg per day. Administration should be continued until onset of therapeutic effect following by tapering dose (within one week) in order to avoid recurrence of NMS [20].

Amantadine could be alternative drug (antiparkinsonian medication) that blocks glutamate NMDA receptors and the reduction of calcium delivery to the neurons decreasing thereby excitement and rigidity. Dose for children is 5-9 mg/kg/day but no more than 150 mg per day.

In case of renal insufficiency amantadine dose should be decreased as it's completely eliminated by kidneys in unchanged mode.

In addition to amantadine in case of significant muscle rigidity another antiparkinsonian (combined) medication could be administered (with caution) – levodopa/carbidopa having the ability of dopamine receptors agonist.

Dantrolene (myorelaxant) is recommended at temperature more than 40°C, suspected rhabdomyolysis and dopamine receptors agonists therapeutic failure. This drug blocks calcium outflow from endoplasmic reticulum into myoplasm that decreases the signs of rhabdomyolysis and heat production. Starting dose is 1 mg/kg four times per day intravenously up to onset of action or until cumulative dose is achieved 10 mg/kg when it starts tapering dose to avoid recurrence of NMS.

As soon as dantrolene has hepatotoxic effect it's not recommended to patients with liver disorders.

Besides this it has to be noted that there are doubts about benefit and even safety of dantrolene use at NMS [19].

Diazepam (anxiolytic-tranquillizer of benzodiazepine group) is used as adjuvant treatment. Besides sedative and anticonvulsant effect diazepam has central myorelaxation effect. Daily dose for children of early age is 0,5-2 mg and at 6-14 years old – 6-10 mg.

As soon as fever at NMS is not prostaglandin-dependent it's not recommended to use NSAIDs and acetaminophen for temperature decrease.

3.3. Serotonin Syndrome (SS)

Any drug having serotonergic activity (directly or indirectly) could cause SS in monotherapy or in combination (more likely).

Four groups of drugs have such effect: monoamine oxidase inhibitors (MOI), selective serotonin reuptake inhibitors (SSRI), TCAs, L- triptophane (precoursor of serotonin) and also prohibited psychoactive agents (MDMA, amphetamine).

Beyond that opioid analgesics (phentanyl and tramadol) more likely inhibit serotonin reuptake as well and increase SS risk in particular when they are combined with non-selective inhibitor of MOI like linezolid [21-23].

SS risk factors - SS could develop in any age including neonates whose mothers use antidepressants during pregnancy and breast-feeding. Especially it concerns SSRI as they are drugs of first choice for treatment depression in pregnant women. Among all SSRI fluoxetine and its active metabolite norfluoxetine having both long half-life 2-6 days could cause SS more likely [24, 25].

In pediatric practice serotonergic medicines could be used for treatment migraine, arterial hypertension, compulsive disorders, pain reduction and depression (2-6% of children and adolescents are suffered from depression that's the third cause of death at the age of 10-19) [19].

3.3.1. SS Mechanism

SS development depends from two conditions: a) increased serotonin concentration (absolute or relative) in presynaptic neurons in brain and vegetative ganglions; b) pharmacological sensitivity of multiple types and sub-types of serotonin receptors and functional and non-functional ratio of its isomers.

Conditions and drugs affecting serotonin level in tissues: long-term treatment bacterial infection by linezolid; slow metabolizers of serotonergic medicines (for example increase of fluoxetine toxicity in CYP 2D6 activity decrease); excessive production of serotonin in case of treatment by L-triptophane of different mood disturbances, combination of sertraline and risperidone intake, prohibited agents abuse (MDMA, amphetamine) that contribute to serotonin release in presynaptic terminals [17].

Among all serotonin receptors $5HT_1$ and $5HT_2$ types are more affinitive for serotonin, they are wide-spread in CNS and peripheral tissues (myocytes) and the status of these receptors determine the development of SS.

The significance of reception for SS development is described by H. Phan [26] in clinical case when 9-years old child demonstrated SS development in 30 minutes after single dose of sertraline (even increased dose) that contributes to treatment stop. In this case side effect developed before therapeutic effect. This case could be considered as "first dose effect" that means increased organism response at first drug intake as well as hypersensitivity syndrome (like idiocrasy) that is not dependent from drug concentration. It's notably that sertraline pharmacokinetic ability is slow accumulation because of first pass metabolism and slow elimination (T ½ 22-36 hours) and therefore more or less significant sertraline concentration in brain is not reached during 30 minutes after sertraline intake.

It is supported by data from S. Wilson list [1]: in 232 patients treated by TCAs (90% monotherapy) or in combination with SSRI (10%) (that's more important) there were no SS cases that's indicative of low sensitivity of serotonin receptors to toxic effect of such drugs.

Thus within the spectrum of low-high sensitivity of serotonin receptors SS variety could manifest: starting from slight course up to life-threatening events with fatal outcome (2-12%), cases with full-scale clinical picture of SS or abortive course (without pyrexia and rhabdomyolysis); cases with early and late onset.

Clinical presentations of SS include the signs in large measure similar to those at NMS: consciousness disturbances till coma, vegetative instability (fever, diaphoresis, tachycardia, variability of pulse and BP), neuromuscular hyperactivity (myoclonus, tremor, hyperreflexia).

Muscle rigidity presenting at both syndromes has some special characteristics in case of SS: it's less noticeable and manifests itself mainly in low extremities.

Similarity of clinical signs of SS and NMS is not occasional. It's explained by closeness of serotonin and dopamine subcortical nucleuses, the transmission of signals pass by the same pathways. That is why some drugs (risperidone and metoclopramide) having two directional actions (serotonin and dopamine receptors blockage) could cause both NMS and SS.

3.3.2. SS Diagnostics

Diagnostics in children in particular of early age is more difficult than in adults as children could not verbally explain exacerbation of their health status but the adolescents trend to keep in secret psychoactive agents intake because they could

be used on top of everything else for suicide attempts [28].

3.3.3. SS Treatment

Besides discontinuation of offending (that could be enough in case of slight course of the event) most commonly it's necessary to introduce specific pharmacotherapeutic intervention for SS management.

Cyproheptadine – non-selective $5HT_{2A}$-receptors blocker in CNS and in periphery. Unfortunately, cyproheptadine like others histaminolytics of first generation has antimuscarinic activity and inhibits sweating that is compensatory reaction at NMS. Dose for children is 0,25 mg/kg/day in 2-3 intakes per os or by nasal gastric tube.

Chlorpromazine – neuroleptic agent with slight anti-serotonin activity and own antipyretic effect. It is used in case of cyproheptadine treatment failure, unresolved pyrexia and behavior disturbances. Initial dose is 1 mg/kg every 6 hours and then up to 40-75 mg/day (age-dependent dose) if necessary.

Benzodiazepine (oxazepam, lorazepam) in monotherapy or in combination with propranolol (slight $5HT_{1A}$-receptors blocker) or propofol (sedative agent) are used for significant anxiety and excitation. However propofol is contraindicated in children under 3 years old.

Despite of similarity of clinical picture and some mechanisms of NMS and SS it's considered mistaken to administer bromocriptine for SS [1].

3.4. Malignant Hyperthermia (MH)

MH – idiosyncratic (pharmacogenetic) reaction for inhalation anesthetics (most frequently for halothane and except nitrous oxide) in combination (or without it) with succinilcholine (depolarizing neuromuscular relaxant of short action) that increases risk and severity of MH and shortens time until symptoms manifestation as well.

In addition to that MH is not only idiosyncratic reaction being a result of enhanced individual patient's sensitivity to toxic action of anesthetics and neuromuscular relaxants but at the same time MH is a paradoxical reaction for medications because not expected myorelaxation is manifested in succinylcholine administration but muscular rigidity.

Unfortunately, since Denborough's description of MH in 1960 the list of triggered drugs was enlarged [27]: non-polarizable neuromuscular relaxant D-tubocurarine, local anesthetics ropivacaine and lidocaine, narcotic non-inhaled agent ketamine having myotoxic effect.

MH risk groups - MH manifests more often (sometimes in the absence of inhalation anesthetic use) in children under 15 years old (52,18%) with frequency 1:8000-1:15000 [1], in accordance with other data with frequency 1:10000-1:250000 with 2:1 prevalence in male. Besides age other risk factors include operations in the area of head and neck, background diseases of muscular system and high level of stigmatization [29]. In Russia in accordance with spontaneous reporting data covering 2009-2014 8 cases of MH were registered in children 3-12 years old with 3:1 prevalence in male [30].

By the way there was no any case of MH during 35 years since our hospital foundation. Our anesthesiologists are aware of such kind of complications and they have dantrolene at their disposal.

Mechanism: MH is rare inherited disturbance of calcium metabolism in skeletal muscles that has latent course and could be revealed only during (or after) surgical intervention, strenuous exercises or high temperature of the environment and also after emotional stress [27-29].

The main hypothesis relates MH development with genetic defect of ryahodine receptors RYR1, RYR2, RYR3 with the major significance of RYR1 that presents mainly in skeletal muscles. Receptors work like intracellular calcium channels in sarcoplasmic reticulum of skeletal muscles and support calcium homeostasis. Abnormal receptors (RYR1-«sleeping» gene) could support such balance only at low level. Thus calcium metabolism could be disturbed as a result of provocative factors, calcium is accumulated inside the cell due to its coming out of sarcoplasmic reticulum into myoplasm following by catabolic reactions and production of big amount of heat resulted in hyperthermia, rhabdomyolysis, acute renal insufficiency, acidosis, hypercarbia. There are two types of testing for MH: genetic test and contracture test (gold standard).

3.4.1. Clinical Presentations

First symptoms (rigidity of m. masseter and sustained hypercarbia are typical for children) could manifest already in several minutes or hours since the surgical intervention start or after its completion, these symptoms aggravate rapidly resulting in brain, renal, lung and heart insufficiencies with high mortality rate (hyperkalemic heart arrest) in the absence of timely medical aid: before dantrolene appearance in clinical practice – 84%, with the use of dantrolene – 9% [31, 32].

However full-scale clinical picture of MH is not always present that makes diagnosis more difficult if halothane-caffeine contracture test in vitro or genetic investigation (RYR mutation search) were not organized before. Variability of clinical manifestations takes place not rarely – from light course till fulminant forms with incomplete set of signs (for example absence of pyrexia) or presence of m. masseter spasm instead of wide-spread muscle rigidity, MH with fatal outcome or rapid recovering without dantrolene administration, manifestation of MH during first or repeated surgical operations [31, 33].

To our opinion such variability of MH manifestations is conditioned by many circumstances.

First of all it's explained by the fact that different alleles of RYR1 gene and its combinations display significant variability of expression and therefore variable sensitivity to toxic effect of anesthetics and muscular relaxants.

In addition it's important to take into account different degrees of family history of MH, type of anesthetics used (general - local) and muscular relaxants (succinylcholine - tubocurarin chloride), type of surgical intervention (MH manifests more often in case of head or neck surgical intervention), background diseases of muscular system,

patient's gender (male – female) and age (early childhood – adolescence).

Higher frequency of MH in male patients is related to more developed muscular mass than in women. Differentiation in muscular mass between boys and girls starts since prepubertal period (8-9 years). That is why it's supposed that starting from this age MH risk is higher in male besides young athletes whose MH risk is likely to be the same for boys and girls.

3.4.2. MH Management

For MH management (besides discontinuation of triggering agents) dantrolene is used as antidote which is specific RYR1-receptors antagonist blocking calcium outcome from endoplasmic reticulum into myoplasm of skeletal muscles that contributes to reduction of muscular rigidity and therefore heat production.

Dantrolene infusion starts within 10 minutes after first signs of MH. Starting dose is 1 mg/kg each 4 hours. Dantrolene infusion could be interrupted or the intervals between infusions increased (each 8-12 hours) if the central temperature decreases up to 38°C, muscular rigidity disappears, creatine phosphokinase and myoglobinuria continue to decrease, respiratory acidosis and hypercapnia are compensated [34].

However dantrolene is not registered in all countries that is why the object of great value is the possibility to treat MH without this antidote with the use mainly non-specific cooling measures [35, 36].

While managing arrhythmia developing at MH it's recommended to avoid administration of slow calcium channel blockers (verapamil, nifedipine) as these drugs could cause hyperkaliemia and even cardiac arrest with a background of dantrolene use [31].

Fever at MH is not simply a symptom but it's determined the prognosis. The most dangerous sign is its extremely rise, in particular it's important to control temperature below critical level of 42°C at which it's impossible to save the patient's life. Therefore fever is required individual and aggressive treatment including pharmacological therapy – antipyretics (acetaminophen, NSAID) and cooling measures: invasive (ice water nasogastric, rectal, peritoneal lavage, infusion of crystalloid solution (4°C) and noninvasive (ice-packing neck, groins and axillae, special cooling blankets, ice-cold water immersion), 75% medical alcohol wiped on body surface.

In addition in case of refractory course of MH it's recommended to use benzodiazepines, opioid narcotic analgesics, chlorpromazine as soon as these drugs have antipyretic effect as well.

It's necessary to notify that there are reasonable doubts in relation to rational use of antipyretics (acetaminophen, NSAID) for MH management as fever in this context is not attributable by prostaglandin-dependent mechanism [37-39].

Cooling of body should be stopped if the body temperature decreases below 38°C [40, 41].

4. Conclusion

As is evident from the foregoing the list of drugs able to cause fever like alone manifestation or in the complex of syndromes is quite large.

Upon that SS, NMS and MH are distinguished among others by their consequences (not rarely fatal). Thus, in 5 out of 8 cases registered in Russia had fatal outcome in children of 3-12 years old [30].

However statistical accounting of evidenced MH cases is not organized in Russia, there is no center for diagnostics and consultation of suspected MH cases and therefore dantrolene is not registered.

But along with that it's necessary to hope that the last amendments to Federal Law "About circulation of drugs" related to orphan drugs will contribute to the earliest entry to the pharmaceutical market of dantrolene that helps to increase effectiveness of MH treatment [30].

The appearance of linezolid in the list of drugs caused SS couldn't be not alerting for health care professionals as well.

Linezolid is non-selective inhibitor of MOI used initially for treatment of depression but at present time widely used in clinical practice for treatment of S. aureus, E. faecalis and E. faecium resistant to vancomycin.

But it seems that own capacities of linezolid to cause SS is not too high: we did not observe any case of SS during long-term antibiotics use in our clinical practice. Therefore, this syndrome is developed more likely in case of concomitant treatment of linezolid and other serotoninergic drugs (principally SSRI).

Thus, fever manifestation in the course of the treatment of infection by antibiotics (associated with improving health state) and in case of treatment by psychotropic medications or surgical intervention with inhalation anesthesia has to alert doctors of drug-induced hyperthermia.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

References

[1] Wilson S. M., Ross J. A. «Temperature disregulation». Drug-induced diseases. Prevention, detection and management. Chapter 54, p 1185-1232. Betesda, 2018.

[2] Romanov B. K., Olefir Yu. V., Alyautdin R. N., Glagolev S. V., Polivanov V. A., Ilienko L. I., Alpatov S. P., Bogush N. V., Buyanova N. M., Ganshina I. V., Dibirova G. O., Dmitrieva N. B., Zhukova I. B., Kalinina E. V., Kirillova A. V., Kiseleva N. M., Kukushkin G. V., Leonteva T. I., Maximov M. L., Markina E. V., Mileshina S. E., Yurov D. E. Drug Safety for Children — International Monitoring Data for 50 Years. *Safety and Risk of Pharmacotherapy*. 2019; 7 (2): 57-64. (In Russ.) https://doi.org/10.30895/2312-7821-2019-7-2-57-64.

[3] Jugtawat S, Daulatabadkar B, Pande S. Drug-induced fever versus infection-induced fever. Indian J Drugs Dermatol 2016; 2: 115-6.

[4] Patel, R. A. and Gallagher, J. C. (2010), Drug Fever. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 30: 57-69. doi: 10.1592/phco.30.1.57.

[5] Dominique Vodovar, Christine Le Beller, Bruno Mégarbane, Agnès Lillo-Le Louet, Drug fever, Adverse Drug Reaction Bulletin, 10.1097/FAD.0000000000000002, 284, 1, (1-4), (2014).

[6] Jake Laun, Katie Laun, Adeel Farooqi, David J Smith, Heparin-Induced Fever: A Case Report and Literature Review, Journal of Burn Care & Research, 10.1093/jbcr/irz064, (2019).

[7] Kenichiro Yaita, Yoshiro Sakai, Kenji Masunaga, Hiroshi Watanabe, A Retrospective Analysis of Drug Fever Diagnosed during Infectious Disease Consultation, Internal Medicine, 10.2169/internalmedicine.55.5740, 55, 6, (605-608), (2016).

[8] Sharif S, Kong MW, Drakakis J, Cunha BA. Fever of unknown origin (FUO) in a renal transplant recipient due to drug fever from sirolimus. *Infection*. 2016; 44 (4): 559-561.

[9] Martha Belete, Colin Bigham, Beta-lactam-induced pyrexia, Journal of the Intensive Care Society, 10.1177/1751143715594628, 17, 1, (84-84), (2016).

[10] Jamshidi N, Dawson A. The hot patient: acute drug-induced hyperthermia [published correction appears in Aust Prescr. 2019 Apr; 42 (2): 79]. *Aust Prescr*. 2019; 42 (1): 24-28. doi: 10.18773/austprescr.2019.006.

[11] Fang Y, Xiao H, Tang S, et al. Clinical features andtreatment of drug fever caused by anti-tuberculosis drugs. Clin Resp J 2016; 10: 449-54.

[12] Shao QQ, Qin L, Ruan GR, Chen RX, Luan ZJ, Ma XJ. Tigecycline-induced Drug Fever and Leukemoid Reaction: A Case Report. *Medicine (Baltimore)*. 2015; 94 (45): e1869. doi: 10.1097/MD.0000000000001869.

[13] Gu W, Shi D, Mi N, Pang X, Liu W. Physician, Beware! Drug Fever Without Skin Rashes Can Be Caused by Minocycline. *J Investig Allergol Clin Immunol*. 2017; 27 (4): 268-269. doi: 10.18176/jiaci.0164.

[14] Swe T, Ali M, Naing AT. Drug fever induced by piperacillin/tazobactam in an elderly patient with underlying human immunodeficiency virus (HIV) infection. *BMJ Case Rep*. 2016; 2016: bcr 2016215814. Published 2016 Jul 20. doi: 10.1136/bcr-2016-215814.

[15] Portel L, Hilbert G, Gruson D, Favier JC, Gbikpi-Benissan G, Cardinaud JP. Malignant hyperthermia and neuroleptic malignant syndrome in a patient during treatment for acute asthma. *Acta Anaesthesiol Scand*. 1999; 43 (1): 107-110. doi: 10.1034/j.1399-6576.1999.430123.x.

[16] Simon LV, Hashmi MF, Callahan AL. Neuroleptic Malignant Syndrome. In: *Stat Pearls*. Treasure Island (FL): Stat Pearls Publishing; June 3, 2020.

[17] Psareva N. V. "Analysis of the relationship between the efficacy and safety of amitriptyline and pipofezine in patients with depressive disorders with the influence of genetic polymorphism of CYP2D6". Drugs and rational pharmacotherapy. 2014, №2, pp. 26-31.

[18] Yıldırım V, Direk MÇ, Güneş S, Okuyaz Ç, Toros F. Neuroleptic Malignant Syndrome Associated with Valproate in an Adolescent. *Clin Psychopharmacol Neurosci*. 2017; 15 (1): 76-78. doi: 10.9758/cpn.2017.15.1.76.

[19] Silva RR, Munoz DM, Alpert M, Perlmutter IR, Diaz J. Neuroleptic malignant syndrome in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1999; 38 (2): 187-194. doi: 10.1097/00004583-199902000-00018.

[20] Westfall C, Mullett CJ, Nield LS. Index of suspicion. Case 2: Fever and Irritability in a 15-year-old Boy With Autism. *Pediatr Rev*. 2015; 36 (7): 313-315. doi: 10.1542/pir.36-7-313.

[21] Wigen CL, Goetz MB. Serotonin syndrome and linezolid. *Clin Infect Dis*. 2002; 34 (12): 1651-1652. doi: 10.1086/340710.

[22] Packer S, Berman SA. Serotonin syndrome precipitated by the monoamine oxidase inhibitor linezolid. *Am J Psychiatry*. 2007; 164 (2): 346-347. doi: 10.1176/ajp.2007.164.2.346b.

[23] Foong AL, Grindrod KA, Patel T, Kellar J. Demystifying serotonin syndrome (or *serotonin toxicity*). *Can Fam Physician*. 2018; 64 (10): 720-727.

[24] Morris R, Matthes J. Serotonin syndrome in a breast-fed neonate. *BMJ Case Rep*. 2015; 2015: bcr2015209418. Published 2015 May 6. doi: 10.1136/bcr-2015-209418.

[25] Fischer Fumeaux CJ, Morisod Harari M, Weisskopf E, et al. Risk-benefit balance assessment of SSRI antidepressant use during pregnancy and lactation based on best available evidence - an update. *Expert Opin Drug Saf*. 2019; 18 (10): 949-963. doi: 10.1080/14740338.2019.1658740.

[26] Phan H, Casavant MJ, Crockett S, Lee A, Hall MW, Nahata MC. Serotonin syndrome following a single 50 mg dose of sertraline in a child. *Clin Toxicol (Phila)*. 2008; 46 (9): 845-849. doi: 10.1080/15563650801938654.

[27] Direk MÇ, Yıldırım V, Güneş S, Bozlu G, Okuyaz Ç. Serotonin Syndrome after Clomipramine Overdose in a Child. *Clin Psychopharmacol Neurosci*. 2016; 14 (4): 388-390. doi: 10.9758/cpn.2016.14.4.388.

[28] Werneke U, Jamshidi F, Taylor DM, Ott M. Conundrums in neurology: diagnosing serotonin syndrome - a meta-analysis of cases. *BMC Neurol*. 2016; 16: 97. Published 2016 Jul 12. doi: 10.1186/s12883-016-0616-1.

[29] Laha S, Giri PP, Saha A, Gupta PP, De A. Life-threatening Episodes of Malignant Hyperthermia Following Halothane Anesthesia in Three Children: A Case Series and Review of Literature. *Indian J Crit Care Med*. 2019; 23 (1): 47-50. doi: 10.5005/jp-journals-10071-23112.

[30] Kolesnikova E. Yu., Zhuravleva E. O., Asetskaya I. L., Zatolochina K. E. Identification and assessment of cases of malignant hyperthermia triggering under anaesthetic management: analysis of spontaneous reporting database. *Safety and Risk of Pharmacotherapy*. 2015; (3): 5-12. (In Russ.)

[31] Yang L, Tautz T, Zhang S, Fomina A, Liu H. The current status of malignant hyperthermia. *J Biomed Res*. 2019; 34 (2): 75-85. doi: 10.7555/JBR.33.20180089.

[32] Chan TY, Bulger TF, Stowell KM, et al. Evidence of malignant hyperthermia in patients administered triggering agents before malignant hyperthermia susceptibility identified: missed opportunities prior to diagnosis. *Anaesth Intensive Care*. 2017; 45 (6): 707-713. doi: 10.1177/0310057X1704500610.

[33] Sinha AK, Kumari P, Vaghela MM, Sinha C, Kumar B. Postoperative Malignant Hyperthermia- A Medical Emergency: A Case Report and Review of Literature. *J Clin Diagn Res*. 2017; 11 (4): PD01-PD02. doi: 10.7860/JCDR/2017/20531.9493.

[34] Şahin SH, İnan M, Aksu B, Öner N, Çolak A, Güzel A. Post-Operative Malignant Hyperthermia in a Child after Colon Interposition. *Turk J Anaesthesiol Reanim*. 2015; 43 (6): 431-433. doi: 10.5152/TJAR.2015.04809.

[35] Liu ST, Liu LF, Wang SY. Treatment of Malignant Hyperthermia without Dantrolene in a 14-year-old Boy. *Chin Med J (Engl)*. 2017; 130 (6): 755-756. doi: 10.4103/0366-6999.201616.

[36] Mathur PR, Rundla M, Jain N, Mathur V. Malignant hyperthermia in a 6-month-old infant. *Saudi J Anaesth*. 2016; 10 (3): 353-355. doi: 10.4103/1658-354X.174915.

[37] Litman RS, Smith VI, Larach MG, et al. Consensus Statement of the Malignant Hyperthermia Association of the United States on Unresolved Clinical Questions Concerning the Management of Patients With Malignant Hyperthermia. *Anesth Analg*. 2019; 128 (4): 652-659. doi: 10.1213/ANE.0000000000004039.

[38] Turhan KS, Baytaş V, Batislam Y, Ozatamer O. Delayed onset malignant hyperthermia after sevoflurane. *Case Rep Anesthesiol*. 2013; 2013: 712710. doi: 10.1155/2013/712710.

[39] Wackernagel D, Obaya S, Nydert P. Dalteparin-sodium induced drug fever in a neonate. *BMJ Case Rep*. 2016; 2016: bcr2016217621. Published 2016 Oct 13. doi: 10.1136/bcr-2016-217621.

[40] Rosenberg H, Sambuughin N, Riazi S, Dirksen R. Malignant Hyperthermia Susceptibility. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews®*. Seattle (WA): University of Washington, Seattle; December 19, 2003.