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Nonsteroidal anti-inflammatory drugs-induced hypersensitivity reactions: algorithm for the diagnostic and management

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ABSTRACT

The role of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in neurosurgical practice is a secondary one, however they are still constantly involved in perioperative management of pain or in nonoperative management of acute radiculopathy. Beside the well-known adverse reactions (ADRs), the neurosurgeon practitioner should also take in account the drug hypersensitivity reactions (DHRs) of NSAIDs and be able to deal with it. The aim of this paper was to review the diagnostic and management steps for NSAIDs-induced Hypersensitivity Reactions. The actual stratification of NSAIDs-induced Hypersensitivity Reactions is based on understanding of the heterogeneity of immunological/non-immunological mechanisms of reactions and complexity of clinical manifestations. Practically, this stratification allows the physician to assess suspicion of DHR, based on anamnesis and clinical analysis, and to consider further practical steps to manage and eventually confirm the diagnosis. Drug allergies are considered only the DHRs for which a definite immunological mechanism (either drug-specific antibody or T cell) is demonstrated. In conclusion, clinical analysis and anamnesis of patient with NSAIDs-induced Hypersensitivity Reactions can be realized by any physician and could be enough to diagnose, but it is not sufficient to confirm the diagnosis. In vitro tests and oral provocation challenges may be necessary to be undertaken by an allergy specialist.

INTRODUCTION

Post-operative pain management in neurosurgery is very complex because the administration of some drugs might interfere with postoperative outcomes or with the neurological evaluation[22]. Although the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in neurosurgery has been restricted due to their platelet dysfunction and risk of intracerebral bleeding, the postoperative pain is a nociceptive type pain which responds well to NSAIDs[17]. Furthermore, NSAIDs are

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effective to reduce morphine requirements by 25%–50% in a broad spectrum of postoperative (consequently decreasing adverse effects secondary to opioids administration) and for rescue analgesia in post-craniotomy pain management (may have even greater benefit when administered preemptively)[8,22]. The use of NSAIDs has been proved to be efficient also for the pain management after spine surgery[19,21]. Besides perioperatory involvement, NSAIDs are often prescribed (for short term) in addition to muscle relaxants and oral corticosteroids for nonoperative management of acute cervical radiculopathy[4,10].

A recent study from the UK, conducted by Marinho et al., in 2016, reported the use of mainly opioids (82%) by anesthesists, followed by paracetamol (56%) and NSAIDs (28%). Diclofenac was the most commonly used NSAID for perioperative pain, followed by parecoxib and ibuprofen[15]. In a survey study of 31 neurosurgical units in Great Britain, 42% of these reported prescribing NSAIDs, with 19 % prescribing NSAIDs on a regular basis for post-craniotomy analgesia[13].

Drug Hypersensitivity Reactions (DHRs) after NSAIDs administration are less taken into account by practitioners, because gastrointestinal bleeding, platelet dysfunction, increased bleeding times and cardiovascular risk are the most known and severe adverse drug reactions induced by NSAIDs[6]. Depending on the method of assessment, the analyzed population and type of reaction, the general prevalence of NSAIDs hypersensitivity ranges from 0.6 to 6% and according to the Online Latin American Survey on Anaphylaxis (OLASA), NSAIDs were the culprit agents in 73% of the drug-induced anaphylaxis[18].

NSAIDs are frequently involved in DHRs because they are frequently prescribed at all ages. Every practitioner should be aware that any drug can induce a DHR and the NSAIDs (especially Ibuprofen) beside some antibiotics are more likely to be the culprit for immediate reactions such urticaria and anaphylaxis[6]. We propose a model of clinical approach for the neurosurgical patient with suspected NSAID hypersensitivity reaction.

I. NSAIDs-induced hypersensitivity reactions - Diagnostic steps

According to WHO (World Health Organization), **Adverse Drug Reactions induced by drugs** are classified as:

- **A-type reactions:** predictable and dose dependent, with a frequency of approximately 75%;
- **B-type reactions or DHR:** unpredictable and dose-independent, with a frequency of approximately 25%; based on their mechanisms these are classified as:
  - ***immunologically mediated (allergic reactions)*:** due to a specific IgE or due to a T cell response
  - ***non-immunologically mediated* (*non-allergic reactions* or *cross-reactive*):** due to an increased release of cystenyl leukotrienes by inflammatory cells, secondary to the inhibition of COX-1 enzyme[16]; these are caused by changes of pharmacological pathways (e.g. inhibition of cyclooxygenase)[14].

In the general medical practice, when a drug allergic reaction is suspected, DHR is the used term, according to international consensus on drug allergy[5]. Drug allergies are considered only the DHRs for which a definite immunological mechanism (either drug-specific antibody or T cell) is demonstrated.

Cross hypersensitivity represents the majority of DHRs induced by NSAIDs compared to specific immunological mediated-reactions (76 vs. 24%)[14].

Based on the time-lapse between the last drug administration and the onset of the reaction, the DHRs of NSAIDs are classified as[5]:

- **immediate reactions** (usually immediate to several hours after the drug exposure):
  - **IgE-mediated (immunological):**
    - **single-NSAID-induced urticarial / angioedema / anaphylaxis (SNIUAA)** manifested as urticaria, angioedema and/or anaphylaxis induced by a single NSAID or by several NSAIDs belonging to the same chemical group in subjects that tolerate other chemically nonrelated NSAIDs and usually do not have a history of chronic urticaria or asthma → labeled as;
  - **Non IgE-mediated (non-immunological or cross-reactive):**
    - **NSAIDs-exacerbated respiratory disease (NERD)** manifested as bronchial obstruction, dyspnea, and nasal congestion/rhinorrhea induced by aspirin or other NSAIDs in patients with an

underlying chronic airway respiratory disease (asthma/rhinosinusitis/nasal polyps);
    - **NSAIDs-exacerbated cutaneous disease (NECD)** manifested as wheals and/or angioedema – induced by aspirin or other NSAIDs in patients with a history of chronic spontaneous urticaria;
    - **NSAIDs-induced urticaria/angioedema (NIUA)** manifested as wheals and/or angioedema – induced by aspirin or other NSAIDs (at least two NSAIDs with different chemical structure - not belonging to the same chemical group) in healthy subjects (without history of chronic spontaneous urticaria);
- **non-immediate reactions** (usually more than 24 h after exposure):
    - **Single-NSAID-induced delayed hypersensitivity reactions (SNIDR)** are T cell – mediated, manifested as cutaneous symptoms (exanthema), fixed drug eruption, Drug Reaction with Eosinophilia and Systemic Symptoms, acute generalized exanthematous pustulosis, Stevens-Johnson Syndrome/toxic epidermal necrolysis, severe organ-specific or systemic symptom – induced by a single NSAID.

Immediate to several hours after the drug exposure, as a chronological stratification, has limitations:

- the exact onset of initial symptoms might be hard to pinpoint;
- the route of administration can influence the time interval in which the reaction occurs.
- cofactors such as co-medications, food intake, alcohol and exercise, can speed up or slow down the onset or progression of a reaction[2].

	NSAIDs-induced hypersensitivity				
	NSAIDs-Exacerbated Respiratory Disease (NERD)	**NSAIDs-Exacerbated Cutaneous Disease (NECD)**	**NSAIDs-Induced Urticaria/ Angioedema (NIUA)**	**Single-NSAID-Induced Urticaria/ Angioedema or Anaphylaxis (SNIUAA)**	**Single-NSAID-Induced Delayed Hypersensitivity Reactions (SNIDR)**
Clinical manifestations?					
	respiratory symptoms (bronchial obstruction, cough, wheezing dyspnea, and nasal congestion/rhinorrhea)	wheals and/or angioedema		urticaria, angioedema and/or anaphylaxis	very diverse symptoms – from cutaneous symptoms (with different degree of severity) to severe organ-specific or systemic symptoms
Onset time of the reaction?					
	1-2 hours after drug intake, up to 24 hours (when reaction occurs within minutes or during the 1st hour there is highly susceptible for SNIUAA or NERD/NECD)				more than 24 hours after drug intake
History/relapse of symptoms?					
	history of similar symptoms caused by other strong COX-1 inhibitor and/or history of good tolerance of selective COX-2	history of reaction to more than one chemically unrelated COX-1 inhibitor		history of cutaneous (urticaria and/or angioedema) and/or anaphylactic reactions to a single NSAID	usually no typical history
Underlying chronic diseases?					
	asthma and/or rhinosinusitis with nasal polyps	episodes of spontaneous chronic urticaria / angioedema, unrelated to NSAIDs	typical no underlying diseases		

Table 1. Diagnosis steps for NSAIDs-induced hypersensitivity

After the physician has gone through previous anamnesis and corroborates the obtained clinical data with DHRs classification represented in Table 1, there is a high probability to clinically diagnose a DHR as follows:

- the typical form of **SNIDR** can be clinically diagnosed (heterogenic reactions, mainly cutaneous symptoms, 24 h or more after last drug administration), but in clinical practice, in time-lapse between the intake of culprit drug and onset of delayed reactions other drugs are administrated, which can make the diagnosis assessment difficult;
- **NERD** can be suspected when a patient with asthma and/or rhinosinusitis with nasal polyps accuses respiratory symptoms (cough, wheezing, dyspnea, nasal congestion, nasal discharge). The diagnosis of NERD is confirmed if he reports a history of similar symptoms after other strong COX-1 inhibitors and/or history of good tolerance of selective COX-2;
- in the case of acute cutaneous symptoms (urticaria/angioedema) and/or anaphylactic symptoms after intake of NSAIDs, we have to distinguish between three subtypes of hypersensitivity: NECD, NIUA or SNIUAA. The detailed history of previous reactions establishes whether the patient is sensitized to a single drug or is the case of a cross-reactive type of NSAIDs hypersensitivity:
  - allergic type I reaction (SNIUAA) is based on a history of cutaneous (urticaria and/or angioedema) and/or anaphylactic reactions to a single NSAID.
  - nonallergic type reaction (cross-reactive) is suspected in a patient with history of more than one chemically unrelated COX-1 inhibitor. The diagnosis of NECD is based on history of episodes of spontaneous chronic urticaria/angioedema to several chemically unrelated NSAIDs. The diagnosis of NIUA is based on history of hypersensitivity cutaneous reactions to several chemically unrelated NSAIDs concomitant and a negative history of spontaneous urticaria/angioedema.

The clinical reality may not always look like in the above description – 10% of patients with NECD have respiratory symptoms (bronchoconstriction) that resembles the NERD23. Moreover than this, concomitant rhino-conjunctivitis in patients with NSAID-induced cutaneous reactions are reported3.

II. NSAIDs-induced hypersensitivity reactions - management

The main indication in case of an already diagnosed NSAID DHR is the avoidance of drugs from the same family. However, the neurosurgeon has the possibility of an alternative NSAID related on type of DHR:

- in the case of SNIUAA, when the specific NSAID has been identified, it can be replaced by another NSAID with similar anti-inflammatory potency but an unrelated chemical structure;
- in the case of NERD/NECD, preferential COX-2 inhibitors (around 91 to 99% of patients with hypersensitivity NSAIDs tolerate meloxicam - doses higher than 15 mg daily should be avoided) and highly selective COX-2 inhibitors (celecoxib with a rate of only 4% positive reactions and etoricoxib with a rate of reactions ranging from 2,9% to 4%) are generally well tolerated9,11,12; leukotriene-modifying drugs may bring benefits in correlation with standard chronic urticaria management1;
- NIUA – avoidance of NSAIDs (desensitization done by allergolog).

In case of patients who have taken multiple drugs (in addition to an NSAID), the administration of alternative drugs has to be suspended firstly; drugs continuously taken for months are not suspected (exception is angiotensin-converting-enzyme which can develop angioedema after months or even years of intake).

Particularly when a patient, with known DHR to a COX-1 inhibitor, needs urgently analgesic medication, the opioids should be recommended due to the differences in structure. Also the selective COX-2 might be an alternative, but a benefit – risk analysis is imperative.

III. NSAIDs-induced hypersensitivity reactions with potential of severe progression

In the case of a suspected DHR, a severe progression should always be taken into account. According to Scherer K et. al and to the more recently task force report of European Academy of Allergy and Clinical Immunology, the severe progression could be

indicated by the presence of some clinical signs [20,7] (Table 2).

Immediate reaction (anaphylaxis)	Non-Immediate reaction (delayed reaction)
• Severe urticaria • Rapid onset of extensive pruritus (especially scalp and palmo-plantar) • Angioedema of the oral mucosa (especially pharynx and larynx) • Hypotension • Conjunctivitis and rhinitis with flush on face and neck • Dyspnea with bronchospasm (particularly in asthmatics)	Cutaneous symptoms: • Hemorrhagic necrotizing lesions • Centrofacial edema (diffuse erythematous swelling) • Purpura • Involvement of large body surfaces or erythroderma • Painful skin • Atypical target lesions • Nikolsky sign positive • Erosive stomatitis • Mucositis (involving more than one mucosal area)
	Symptoms suggesting internal organ involvement: • Unexplained rapid onset of high fever (> 39 °C) • Arthritis and arthralgias • Disseminated lymphadenopathy

Table 2. Clinical signs for a potential severe progression of NSAIDs-induced hypersensitivity reactions.

IV. Criteria to refer a patient with DHS to allergist

First steps that include a clinical analysis and anamnesis of patient can be realized by a non-specialist and could be enough to diagnose in some cases, but frequently NSAID hypersensitivity, is not sufficient to confirm the diagnosis (Fig. 1). In vitro tests and oral provocation challenges may be necessary to be undertaken by an allergy specialist.

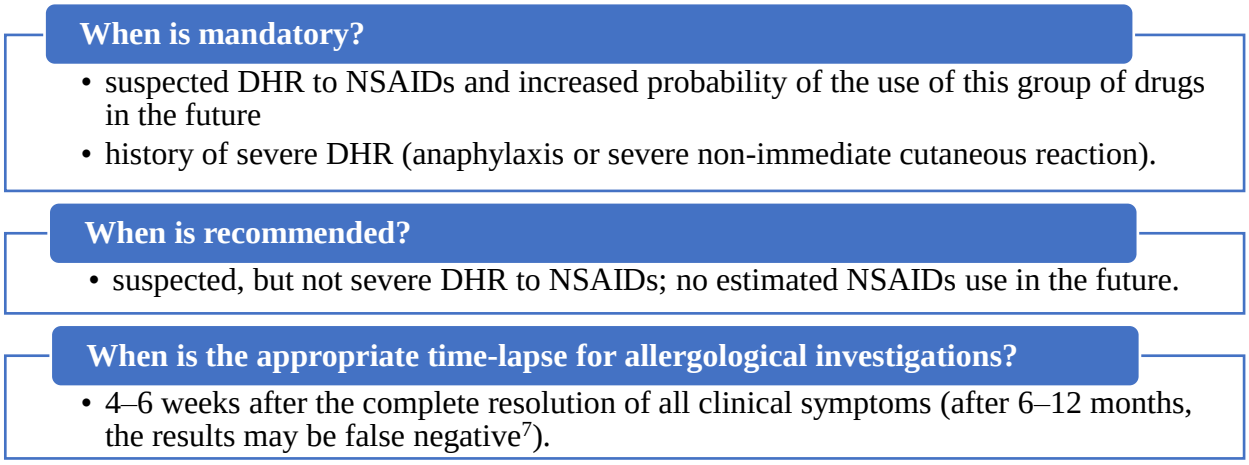

Figure 1. Criteria to refer a patient with DHS to allergist

Up to 1/3 of patients with chronic spontaneous urticarial report exacerbations of cutaneous symptoms upon ingestion of NSAIDs. The level of sensitivity could temporary variate in relation to coexisting chronic spontaneous urticaria and consequently, sensitivity may decrease and even disappear – therefore reassessing the tolerance to NSAIDs is appropriate14.

Conclusions

The neurosurgical practice implies often moderate-to-severe postoperative pain in a multitude of procedures such as craniotomies for aneurysm clipping, craniotomies for tumor resections and epilepsy surgery, neuroradiological procedures and penetrating traumatic brain injury. Post-operative pain management is very complex due to interference of drugs with postoperative outcomes or with the neurological evaluation22. Nociceptive type pain responds well to NSAIDs, even their use in neurosurgery has been restricted due to the platelet dysfunction and risk of intracerebral bleeding17.

Diagnosing DHRs is a complex issue. Clinical analysis and diagnostic of a DHR can be realized by any physician, but the confirmation of the diagnosis needs in vitro tests and oral provocation challenges which should be undertaken by an allergy specialist. If the NSAID-induced hypersensitivity is confirmed,

recommendations based on the current classification for drug avoidance, use of alternative NSAIDs, and other management modalities, including aspirin desensitization, can be implemented.

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