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HEADING: DRUG AND ORPHAN DISEASES

Pharmacovigilance and drug-induced rare diseases: strengths of the French Network of Regional Pharmacovigilance Centres

Pharmacovigilance and drug-induced rare diseases

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Summary

The French-style organization in the field of rare diseases allows a close contact between reference centres and regional pharmacovigilance centres thanks to their implementation within the French university hospital. This collaboration leads to highlight more and more drug-induced rare diseases. Through several historical examples (eosinophilia-myalgia syndrome due to L-tryptophan, type 1 narcolepsy with H1N1 pandemic influenza vaccine, capillary leak syndrome, acquired von Willebrand syndrome), it remains clear that pharmacovigilance is the cornerstone of the alert system. Clinicians from the rare disease reference centres can easily report adverse drug reactions (ADRs) to pharmacologists from their regional pharmacovigilance centre. Through experience, collaboration between countries, large database, and sometimes pharmacoepidemiological studies, an alert can then be raised. This collaboration underlines also similarities between the two disciplines, through the frequency of ADRs and diseases, the difficulty of the diagnosis in front of scarce data, and through the unusual worsening symptoms. Patients and associations of patients play also a proactive role as research partners at different steps, to quantify and qualify symptoms and ADRs, and also to develop orphan drugs. These several collaborations are a precious tool to improve patients' outcomes. These close contacts between the different actors are important to make earlier diagnosis of rare diseases and severe ADRs. Rare disease does not have to mean overlooked diseases.

KEYWORDS

Pharmacovigilance; Rare disease; Adverse drug reactions; Drug-induced disease; Collaboration; Network

Abbreviations

ADR: adverse drug reaction

AFSSaPS: *Agence française de sécurité sanitaire des produits de santé*

ANSM: *Agence nationale de sécurité du médicament et des produits de santé*

HES: hydroxy ethyl starch

vWF: von Willebrand factor

Introduction

Pharmacovigilance plays a key role in assessing, monitoring and preventing adverse drug reactions (ADRs). Among the available methods, the reporting of suspected ADR in clinical practice is the cornerstone of pharmacovigilance monitoring. Its main purpose is the early detection of new, rare and serious ADRs with the advantage to cover the entire population without any selection. The French pharmacovigilance monitoring is among the best in the World, ranking in the first countries about the quantity of ADRs reports and also its quality linked to its informativeness [1].

In the same way, as demonstrated by the orphaned registry and the French national plans for rare disease for more than 20 years, France has had a leadership role in initiatives in the field of rare disease [2].

In the past two decades, epidemiologic, molecular, and other research that takes advantage of scientific and technological advances in the biological sciences has greatly increased the number of rare diseases that have an identified cause—usually, although not invariably, genetic. In the present paper, we will present the organization of the French pharmacovigilance system and its link to healthcare for rare diseases, the illustration of such organization to detect earlier warnings on drug-induced rare disease, the similarities between rare diseases reference centres and pharmacovigilance activities, and the importance of a collaboration between all involved actors.

The French system of pharmacovigilance and its link to healthcare for rare diseases

The French pharmacovigilance network has been first established in 1973 and consists in 31 regional pharmacovigilance centres [3]. These are part of French medical pharmacology centres exclusively implemented within the French university hospitals, public hospitals linked to a medical school, a pharmacy school and research units. In these centres, pharmacologists make evaluation of safety and surveys for post-marketing drugs via collecting and analyzing pharmacologically, clinically and biologically spontaneous reports of ADRs. Spontaneous reports come from patients and healthcare professionals who solicit pharmacovigilance clinicians to help them making a drug-induced disease diagnosis. They play a major role in the diagnosis of these under-recognized and

overlooked diseases for example heart disease and benfluorex [4], psychiatric disorders and dolutegravir [5], central nervous system disorders and cephalosporins [6]. By its implementation through the public hospital, pharmacovigilance centres have privileged relationship with medical excellence units such as rare diseases care and research units [2]. Thanks to the pharmacovigilance clinician's expertise and their large and detailed fulfilled database, several drug-induced rare diseases had also been highlighted such as pulmonary arterial hypertension associated with protein kinase inhibitors [7,8]. Detecting, understanding and preventing are the three key words of this original and unique organization. Due to their specialized and advanced expertise (reflection on pharmacological mechanisms in front of unexpected ADRs, accurate reading of literature, management of specific studies and national medications follow-ups), pharmacologists are able to detect early warning signals and launch alerts to raise clinicians' awareness. This multidimensional way of thinking is possible thanks to their specialization in fundamental and clinical pharmacology. This French-style organization aims to improve patient's outcome and contribute to warn healthcare professional, especially in case of rare diseases for which only scarce data are available. Indeed, the French pharmacovigilance network is the first in Europe to contribute to report serious pharmacological signals. French pharmacovigilance centres are certainly the most active in the world because of their structuration.

Practical implementation: illustration and lessons learned with several warnings on drug-induced rare disease

Rare diseases affect a limited number of individuals, defined as no more than 2000 individuals in the European Union, and consequently lead to specific difficulties [9]. With more than 7000 discovered ones, rare diseases are numerous and new ones are steadily discovered and published.

Drug-induced rare diseases can be split into 2 different categories: specific drug-induced diseases, for whom drug exposition is the solely etiology (for example the fetal valproate syndrome, the eosinophilia-myalgia syndrome due to L-tryptophan ...), and diseases for whom drug is one of the possible etiologies (in most of cases). For the first category of disease, clinicians often react quickly. For the second category, it can lead to serious outcomes because of a late recognition of the drug involved. Moreover, new drug-induced rare diseases are regularly reported to the

pharmacovigilance network of clinical pharmacologists (such as narcolepsy induced by H1N1 vaccines). For these rare diseases, only European and even international pharmacoepidemiological studies can confirm the link with the drug and sometimes, can describe the clinical and biological specificities to further better understand the pathology. Beside the publication as case reports, notification of cases of drug-induced rare disease to the regional pharmacovigilance centres is mandatory and helpful. First, better describing their particularities and understanding their pathophysiology can lead to therapeutic hypothesis for these rare diseases (as for example for interleukine-2-induced capillary leak syndrome). Secondly, the notification allows a validation of the case, which can lead to a signal emit by the regional pharmacovigilance centre, and if validated (search for similar cases and pharmacoepidemiology studies), will launch the alert and trigger health measures.

The following historical examples have been selected to illustrate the phenomenon because of specific highlighting modalities or specific characteristics. These examples are not exhaustive, all drugs can induce all diseases (or so). That's why pharmacovigilance clinicians play a major role. They first help clinicians to make a drug-induced disease diagnosis, then they raise a signal and lead to an alert.

Eosinophilia-myalgia syndrome due to L-tryptophan

This syndrome is an excellent illustration of a drug-induced rare disease. L-tryptophan is an amino-acid normally present in dietary proteins, as a serotonin precursor. L-tryptophan has been commercialized for depressive syndrome or insomnia without proof of efficacy, at a daily dose of 3 to 9 grams. Its main adverse drug reactions were dizziness, headache, nausea and digestive disorders in a dose-dependent manner. In 1989, in New Mexico, several patients exhibited a couple of symptoms associating severe myalgia and hyper eosinophilia. Other similar cases were then reported to the Centre for Disease Control. The Centre then described this new syndrome as "eosinophilia-myalgia syndrome" when eosinophilia $>1000/\text{mm}^3$ and generalized and disabled myalgia were associated, and when a parasitological etiology (in particular trichinosis) or even infectious and neoplastic conditions were excluded [10,11]. To elucidate the apparent association between L-tryptophan-containing products (medications and dietary supplements) and eosinophilia-

myalgia syndrome, a case-control study was done with 11 case reports. This pharmacoepidemiological study led to a recall of all L-tryptophan-containing products in January 1990 and to their end of commercialization by the Food and Drug Administration [12]. This “epidemic syndrome”, with a multiplication of case reported since July 1989, has led to evoke a contamination of the amino acid by a toxic compound when manufactured [13]. Another hypothesis was of a tryptophan metabolism abnormality revealed or triggered by the ingestion of L-tryptophan-containing products and its contaminant because one of the manufacturers had recently changed the fermentation process (with another bacteria strain) and purification system [14]. In France, 24 cases of eosinophilia-myalgia syndrome were reported to the 31 regional pharmacovigilance centres [15].

Thanks to these reports, specific clinical manifestations could be defined: generalized myalgia sufficiently severe to affect a patient's ability to pursue daily activities, hypereosinophilia (sometimes major), asthenia, early and fleeting cutaneous manifestations (cutaneous induration) and most rarely fever, loss of weight, arthralgia, digestive disorders, pulmonary disorders (cough, dyspnea) or neurological ones (paresthesia, neuropathy) [15]. One third of patients were hospitalized with a corticosteroid treatment and one third suffered from sequelae. In January 1990, the French Ministry of Health quickly stopped the manufacture, the importation and the commercialization authorization of L-tryptophan-containing products, after the reports of the first two cases in France in December 1989 (more than 15 products were commercialized at that time) [16]. As this new syndrome has been quickly recognized by the American health regulatory authorities and rapidly linked to a drug, it is a good example of pharmacoepidemiologic studies early set up to confirm the hypothesis and to establish quick health measures.

Type 1 narcolepsy with H1N1 pandemic influenza vaccine

Narcolepsy following pandemic H1N1 vaccination is another example of drug-induced rare disease. Narcolepsy is a consequence of a loss of hypocretin production by specialized hypothalamic neurons. It is a chronic affection characterized by excessive daytime sleepiness with irresistible sleep attacks, abrupt loss of muscle tone and sleep disturbances. Pediatric incidence is three times rarer than in adults. Narcolepsy etiology has probably a genetic origin and before 2010, no cases of drug-induced narcolepsy has been yet reported. Nevertheless, a relationship between narcolepsy and

Pandemrix[®] vaccination was evoked in Finland in August 2010 after 15 cases were reported to the National Institute for Health and Welfare. The same year, 12 cases were also reported to the Medical Products Agency of Sweden [17,18]. In September 2010, the three major centres of reference for narcolepsy (Montpellier, France; Montreal, Canada; and Stanford University, United States) collaborated to publish a case series of 16 reports of narcolepsy following H1N1 influenza vaccination [19]. The median time to onset was 7.4 weeks. The most striking features of the reports were the abrupt onset and the unusual severity of both sleepiness and cataplexy. During the same time, Finland and Sweden continued to report an increase of type 1 narcolepsy cases [20]. The increase of narcolepsy incidence during the H1N1 pandemic influenza vaccination campaign with a similar chronology between the different case reports, 1 to 2 months after Pandemrix[®] injection in children and adolescents, led to suspect a relationship between the two events. Four different vaccines had been used in Europe: Pandemrix[®], Panenza[®], Focetria[®] and Celvapan[®]. About 650 cases of narcolepsy were reported to the European pharmacovigilance after the vaccination campaign for more than 19 million people vaccinated. In France, 4.1 million people were vaccinated with 59 reports of narcolepsy identified on 21 adults and 38 children (from 4 to 17 years old); 54 were vaccinated by Pandemrix[®] and 3 with Panenza[®]. After the emergence of this signal, the European Medical Agency asked for a reevaluation of the benefit/risk balance of this vaccine. In Finland, a pharmacoepidemiological study concluded that the use of Pandemrix[®] was associated with an increase narcolepsy incidence factor of 12.7 for children and young adults who received the vaccine. The incidence of narcolepsy was 9.0 in the vaccinated as compared to 0.7/100,000 person-years in the unvaccinated individuals [21,22]. This association between narcolepsy and Pandemrix[®] use was quickly confirmed by other countries data using the same product such as Ireland, Great-Britain and France [19,23,24]. In a specific and complete analysis of the French data through a case-control study called “NarcoFlu-VF”, H1N1 vaccination was strongly associated with an increased risk of narcolepsy-cataplexy in both children and adults in France [25]. This case-control study managed in 15 expert centres (83 cases and 202 control subjects) also showed an association between H1N1 vaccination (Pandemrix[®] for 90%) including adults, with an Odds Ratio of 4.6 [2.3-8.9]. The vaccinated patients more often exhibited cataplexy (91% vs 57%).

A homology in sequences of virus proteins and hypocretin-producing neurons is among the different hypothesis raised to explain this unknown ADR and the possible association with the Pandemrix[®] vaccine [26]. In fact, type I narcolepsy is a rare cause of hypersomnia which is characterized by the destruction of hypocretin-producing neurons in genetically predisposed patients. It is an auto-immune, multi factorial pathology involving genetic and environmental

factors. Because among cases reported, narcolepsy occurred almost exclusively with Pandemrix®, the involvement of a specific adjuvant in Pandemrix® (ASO3) was questioned. This hypothesis is also supported by another observation: in other countries such as United States, Australia or China, no narcolepsy had been reported after the H1N1 vaccination using vaccine without this adjuvant. The role of a genetic predisposition was also raised in front of a majority of patient vaccinated who also exhibited a particular genetic mutation [27]. The lonely mutation could not be sufficient to express the disease but it could be revealed by a vaccination or an infectious condition and lead to narcolepsy [28].

Even if the number of case reports was not very high, a relationship with the vaccination was established. Nevertheless, numerous interrogations about vaccine-induced narcolepsy etiology subsist. Since then, Pandemrix® has no longer been commercialized and the French health authorities now preconizes the manufacture of vaccines without that adjuvant [29].

Capillary leak syndrome

The capillary leak syndrome was first described in the 60s, characterized by weight gain with edema, oliguria, hypotension which could lead to a shock condition. These clinical symptoms were also associated with biological features like hemoconcentration and hypoalbuminemia [30]. Several types of the syndrome are described. The idiopathic capillary leak syndrome or Clarkson syndrome is mostly caused by malignant hemopathy and viral infections, rarely drug-induced. Numerous drugs, especially oncologic ones, are involved in secondary capillary leak syndrome such as interleukin-2 with more than 75 case reports published [30]. Studies concerning the pathophysiology of the interleukin-2-induced capillary leak syndrome showed alterations of the post-capillary endothelium promoting the adhesion and extravasation of activated leukocytes [31]. Endothelium could be then damaged by leukocytes, attracting inflammatory cells and increasing capillary permeability thanks to a cytokines release. Moreover, studies in mice showed that recombinant interleukin-2-induced capillary leak syndrome were enhanced by TNF-alpha blockade [32]. Hematopoietic growth factors are in the second position in providing capillary leak syndrome, which is not surprising because the endogenous granulocyte-colony-stimulating factor seems to be involved in the pathology [33]. In France, the *Agence nationale de sécurité du médicament et des*

produits de santé (ANSM) had raised an alert concerning hematopoietic growth factors and capillary leak syndrome several times [34,35]. In the literature, cases are more often published with the use of oncology drugs such as gemcitabine, bortezomib, taxanes (docetaxel, paclitaxel), ciclosporin, doxorubicin, clofarabine and trastuzumab [36]. Nevertheless, beside these sporadic case reports, pharmacovigilance plays a major role in detecting new drugs involved in capillary leak syndrome to alert healthcare professionals. Indeed, a recent French publication has reported 576 cases of capillary leak syndrome collected by national drug authorities of 29 countries using data from the international pharmacovigilance [37]. The median age was 57 years old and the most frequent clinical manifestations were edema, hypotension or shock, renal failure, pulmonary edema and pleural effusion. Compared to the idiopathic form, hypoalbuminemia was less severe in the drug-induced syndrome but pulmonary edema was frequent. The mean time of onset was 8 days, and 27% led to fatal outcomes. Concerning drugs, oncology or immunomodulatory drugs were involved at 86% with mostly gemcitabine and clofarabine. A disproportionality analysis highlighted an increased risk of capillary leak syndrome with 52 drugs, which was a new adverse drug effect for 32 drugs (not yet published nor listed) [38].

This study underlines the importance of notification to the regional pharmacovigilance centres, especially in drug-induced rare diseases. All these data contribute to feed the international pharmacovigilance database allowing international pharmacoepidemiologic studies. Indeed, with only a few French cases, specific analysis can then be performed on the international database to highlight an association and raise an alert.

Acquired von Willebrand syndrome

Acquired von Willebrand syndrome is a rare hemorrhagic disorder, which is similar to congenital von Willebrand disease regarding the clinical and laboratory features. It is found in individuals without hemorrhagic or family history [39]. Three major pathogenic mechanisms are suggested to explain this syndrome: auto-immune disorder with auto-antibodies and von Willebrand factor (vWF) complexes (like in auto-immune pathologies and in monoclonal gammopathies); absorption of vWF by malignant cells clones (link in neoplasia); excessive proteolysis of high molecular weight vWF multimers in congenital heart defects (like aortic stenosis). Hereditary Willebrand

disease is a well-known disease, it is the most frequent constitutional hemorrhagic disease with a prevalence of 1% in the whole population whereas acquired von Willebrand syndrome is a rare disease (almost 300 case reports in the literature) probably underdiagnosed. This pathology is mostly reported in case of auto-immune disorder and lymphoproliferative or myeloproliferative syndromes. Nevertheless, a drug etiology can also be involved [40] and the most frequently ones are interferon alpha, penicillin derivatives, paclitaxel, fludarabine, phenytoin, clopidogrel, alphamethyl dopa, levodopa but also more common medications like for example sulfonamide antimicrobial agents, fluoroquinolones or griseofulvin [40–43]. In some reports with a drug etiology, mechanism could be different, without antibodies anti-FVIII or anti-vWF. Then Conrad and al. described a case of an acquired von Willebrand syndrome in a 51-years-old-male treated by griseofulvine for 2 months. His biological results showed a severe deficit of FVIIIc (10%) and vWF (8%). Clinical and biological manifestations disappeared a few days after stopping the griseofulvine treatment [44]. Another author described two cases of ciprofloxacin-induced acquired von Willebrand syndrome. Abnormalities disappeared during the follow-up, without any specific therapy. No inhibition of FVIIIc or vWF was detected but a proteolysis mechanism was among hypothesis [45].

More interesting is that the pharmacological and physicochemical characteristics of a colloid, named hydroxyethyl starch (HES), explain the occurrence or not of a vWF deficiency. Colloids can lead to two consequences on the homeostasis: non-specific ones linked to hemodilution (provoked by the perfusion of high volumes), and specific ones due to macromolecular solutes effect on coagulation and/or fibrinolysis. At the beginning of the 60s, studies showed that first generation high-molecular-weight HES had an impact on homeostasis, independent of the hemodilution. Because their high-molecular-weight was associated with a longer life time, this observation led to a decrease of the recommended dose [46]. Medium-molecular-weight HES were then manufactured. Nonetheless, a dozen of years after their commercialization, a case series of acquired von Willebrand syndrome was reported by a French pharmacovigilance team [47], with twelve reports of hemostatic disorders. All patients were treated with Elohes® as hemodilution therapy (for vasospasm secondary to subarachnoid hemorrhage). Eight patients exhibited an acquired von Willebrand disease, 6 with neurological complications, and 3 fatal outcomes. They had no medical history and biological parameters were normal at the admission day. Patients exhibited symptoms after a more than 4 day therapy. HES are natural polysaccharides which substitution slows hydrolysis by alpha-amylase, thus it increases the effect duration, as the high-molecular-weight and the elevated substitution ratio. The more the HES hydrolysis is slowed,

the more the drug can accumulate. Yet an absorption of the vWF on the HES exists, the complex is thus eliminated through urines which induces a quantitative vWF decrease; this phenomenon leads to a type I-like von Willebrand syndrome. Studies showed that first and second HES generations decreased circulating FVIII and vWF for more than 80%, even for doses from 25 to 50 ml/kg [48,49]. When there were commercialized, low-molecular-weight HES were presented without any risk of hemorrhage, because their use was only perioperative and very short. The structure modifications realized to increase their effectiveness were associated with an increase of accumulation explaining that during prolonged used, the risk of hemorrhage was the same as high-molecular-weight HES. Treib and al. demonstrates that after 10 days of hemodilution, vWF activity decreased for almost 45% at day 5 and for 60% at day 10 with a long-time elimination HES like Elohes[®], whereas with a short-time elimination HES, vWF activity was the same [50]. Thus, in April 1999, the *Agence française de sécurité sanitaire des produits de santé* (AFSSaPS) informed healthcare professionals about the risk of serious hematological disorders reported after prolonged Elohes[®] administration due to its physico-chemical properties leading to an accumulation of the product. AFSSaPS made also a contraindication of the HES when acquired or constitutional hemostatic disorders are known or suspected. The daily dose was limited to 33 mL/kg/d and the duration to 4 days with a maximal dose at 80 ml/kg. A specific hemostatic monitoring was also recommended [51].

This last example highlights the necessity of a quickly declaration to the Regional Centre of Pharmacovigilance, of any suspicion of adverse effect, even if the link with the drug is not certain. In that example, the alert was raised after collecting cases by asking all neuro-anesthetists about the hemorrhagic adverse effect observed with this product. Several of them had noticed some hemorrhagic syndrome with prolonged use of the infusion of this HES and had changed their practices (decreased duration of use), but very few had thought to declare them to a CRPV, which would have allowed earlier health measures.

Similarities between rare diseases reference centres and pharmacovigilance activities, importance of a collaboration between all involved actors

Through these different examples, we can easily recognize similarities between rare diseases reference centres and pharmacovigilance activities. Most of the time, severe ADRs are as rare as rare diseases, even if many drug side effects are unfortunately frequent. Clinical trials usually concern a restricted number of people and that is why all ADRs are not detected. Indeed, ADRs occur in only one patient over 1 million treated patients, or even less.

The second similarity concerns difficulties among diagnosis. Some new rare diseases or ADRs are discovered through an unknown symptom or syndrome. To discover the etiology and the pathophysiology in these cases, it can be time spending before confirmation. A small or a big percentage of rare disease causes may be due to a sole pharmacological substance.

The third similarity is the frequent occurrence of unusual worsening symptoms. For example, Charcot-Marie-Tooth disease may be worsened by sleep disorders or by neurotoxic drugs. An estimated innocuous drug in a country population may worsen the syndrome in a rare disease patient.

In the future, we may find new rare diseases or new ADRs as we have found new syndromes in the recent past. Anti-NMDA receptor encephalitis, a rare case of encephalitis was diagnosed only in 2007 with immunology progress. Frequently used anesthetic ketamine was synthesized in 1956 but ketamine induced bladder fibrosis in ketamine abusers has only been recently discovered and confirmed by experimental studies on a mouse model [52]. Bladder effects of ketamine have not been detected by experimental preclinical and clinical studies. Pharmacovigilance and addictovigilance are useful in new and also in old substances surveys. We may ask the crucial question: in the past decades, was the association of ketamine use and bladder fibrosis underdiagnosed? Early detection of ADRs will always need more collaborations between patients and different caregivers.

There is still an important lack of information in the field of rare diseases and ADRs, even if there are great (but rare) specialists and even if the internet provides a large choice of data. In both cases, there is a need of informed clinicians, pharmacists, nurses and helping families.

Rare diseases need a multi-disciplinary expertise. Pharmacologists of the French pharmacovigilance centres network could increase their collaboration with rare disease organization to help in the evaluation of the association of drugs and rare diseases. The pharmacologists may try to discover the potential mechanism of drug effect on rare diseases. It could be useful to improve the knowledge of rare diseases, and to prevent ADRs.

In 2014-2015, an experiment was conducted thanks to the collaboration of the association “*maladies rares info service*”, the French pharmacovigilance network and the ANSM. This experiment has permitted to elaborate a close contact between patients and clinicians from the Regional Pharmacovigilance centres. It may be pursued in order to answer to most of the patient’s questions. It is important to maintain a regional and a national organization to provide the best expertise to patients.

Patients may directly contact the nearest regional pharmacovigilance centre or indirectly through the “*portail national de signalement des évènements indésirables*”. This close contact with the patient, his/her family or friends remains useful and may be associated with the different caregivers. A close collaboration is important to gather accurate informations about the disease and its evolution. The French pharmacovigilance network provides a practical and a close help for patients and their families. Nevertheless, there is also an increasing need of a close relationship between pharmacologists of this network and rare diseases centres clinicians to manage specialized cooperative works.

Rare disease patients are particularly concerned by an early warning system at the national level, like the French-style organization. Rare disease reference centres are an important link to give decompartmentalized informations. These useful warnings are identified and shared at national, European (European Medicinal Agency) and at an international level (World Health Organization).

Conclusion

In order to reach a better knowledge of rare diseases, pharmacologists from the regional pharmacovigilance centres, clinicians from the reference centres of rare diseases, patients and French drug agency have to pursue their collaboration. Through the previous examples, it remains clear that this close relationship allows to raise signals, make an alert and to improve patients’ outcomes but it offers also a proposed mechanism for the new and potential scientific hypothesis for the rare diseases.

Disclosure of interest

Authors have no competing interest to declare

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