Review

Current State and Understanding of Methamphetamine-associated Pulmonary Arterial Hypertension

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Abstract

Methamphetamine, one of the most commonly used illegal stimulants worldwide, has been recently upgraded to the definite category in association with development of pulmonary arterial hypertension (PAH). Though its incidence and prevalence in the general population and among active methamphetamine users are unknown, with the epidemic surge of methamphetamine use, we are bound to see more cases of methamphetamine-associated pulmonary arterial hypertension (Meth-APAH). Neither basic pathophysiology nor optimal treatment strategy has been well studied for Meth-APAH, which has been shown to have worse outcomes when compared with idiopathic PAH. Extrapolating experience from other conditions associated with methamphetamine, cessation of methamphetamine use remains front and center of the treatment goals of Meth-APAH, to be complemented by other pharmacological, behavioral and psychosocial therapies in a multidisciplinary approach in dealing with this complex and highly morbid condition.

Introduction

Since the late 1990's, there has been a global epidemic of amphetamine and methamphetamine use. In the United States, particularly in the Midwest and West regions, methamphetamine is a leading cause of overdose death [1,2]. Up to 3.7% (12.4 million) of the European Union population reported lifetime use of methamphetamine [3]. In the United States, the estimated annual average rate of lifetime methamphetamine use was 59.7 per 1,000 adults, or approximately 1.6 million on average used methamphetamine each year, according to the National Surveys on Drug Use and Health 2015-2018 data [4].

Due to its highly addicting nature, methamphetamine use is a serious illness and is associated with wide range of medical and mental health implications, with afflicted individuals often manifesting marked functional limitation, severe psychosocial impairment, high rate of co-occurring substance uses, and frequent relapses [5,6].

Methamphetamine can be inhaled, smoked, snorted, orally ingested, or injected via intravenous route. Cardiovascular toxicity includes hypertension, myocardial infarction, ischemic strokes and tachyarrhythmias. Through chronic sympathetic activation and other not well understood mechanisms, prolonged methamphetamine use has been associated with pulmonary arterial hypertension and dilated cardiomyopathy, two most commonly seen long-term complications of methamphetamine. The association between methamphetamine use and pulmonary arterial hypertension was first reported in a case report in 1993 [7]. Subsequently, a study by Chin and colleagues showed that methamphetamine use occurred at a much higher rate in patients with idiopathic pulmonary arterial hypertension (IPAH, 29%) than those with chronic thromboembolic pulmonary hypertension (4.3%, odds ratio 10.1) [8].

World Health Organization classification of pulmonary arterial hypertension currently designates Meth-APAH as Group 1.3 pulmonary arterial hypertension (PAH), drugs and toxins induced. The 6th World Symposium on Pulmonary Hypertension [9] has upgraded methamphetamine from "likely" to "definite" association with PAH. Despite the growing body of evidence linking methamphetamine to PAH, little is known about the prevalence and incidence of Meth-APAH among methamphetamine users.

Pathophysiology

The molecular, genetic and biochemical mechanisms of Meth-APAH are not well understood. Several theories, however, have been proposed. One study using radiolabeled methamphetamine demonstrated that the uptake was the highest in the lungs, which may explain the pulmonary toxic effects on the pulmonary vasculature [10]. Route of administration of methamphetamine may also play a role in the susceptibility of developing Meth-APAH. In California, most users smoke or inhale vaporized methamphetamine [11]. There is yet no study evaluating if a higher percentage of Meth-APAH patients inhaled rather than ingesting or injecting the drug. It would be

interesting to see if local high concentration of methamphetamine in the pulmonary vasculature directly enhances its toxic effects and propensity for the development of Meth-APAH.

At the tissue level, pathological assessment demonstrated characteristic vascular changes similar to IPAH, including angiomatoid plexiform lesions, but also proliferative capillaries, as described in pulmonary capillary hemangiomatosis or pulmonary veno-occlusive disease [9].

Biochemically, Methamphetamine stimulates the central nervous system by promoting the release of serotonin, dopamine and norepinephrine [12]. Dysregulated serotonin metabolism has been implicated in the pathogenesis of PAH induced by anorexigen [13]. Given the similarity of molecular structure between methamphetamine and anorexigens, it is plausible that the serotonin pathway also plays a role in the development of Meth-APAH.

The genetic basis of PAH has been a focus of basic research efforts in recent years. Mutations in two receptors of the transforming growth factor-beta family, bone morphogenetic protein receptor type-2 (BMPR2) and activin-like kinase type-1 (ALK-1), have been shown to be present in the majority of cases of inherited (familial) pulmonary arterial hypertension [14]. Whole exome sequencing has also identified candidate genes in rare heterozygous mutations encoding for proteins such as caveolin 1 (CAV1) [15] and the potassium channel subfamily K member 3 (KCNK3) (16). Whether these genes are implicated in the susceptibility to developing Meth-APAH remains to be elucidated.

Carboxylesterase 1 (CES1), a gene involved in drug metabolism that codes for an enzyme involved in the detoxification of several drugs including methamphetamine, amphetamine, methylphenidate, heroin, and cocaine, was found to be predominantly expressed in healthy but not Meth-APAH patients. Reduction of CES1 increases methamphetamine-induced apoptosis through the generation of harmful reactive oxygen species (ROS) and deranged (autophagy responses in cells autophagy is a stress-related response by cells to allow repair) (17). CES1 holds the potential as a biomarker to identify methamphetamine users at risk of developing Meth-APAH and also as a potential therapeutic target to increase cell viability and reduce disease progression.

Like other disease entities with proposed genetic mechanisms, gene-gene or gene-environment interactions exist that enhance the development of the irreversible pulmonary vascular changes in susceptible methamphetamine users carrying a particular candidate mutation. How to identify, modify and harness such patterns of genetic susceptibility remains an urgent focus of basic, translational and clinical research endeavors.

Clinical Presentation and Outcomes

Similar to other subtypes of PAH, Meth-APAH patients often remain free from symptoms in the early phase, the diagnosis is therefore often delayed until late in the course, when irreversible obliteration of pulmonary arterioles has occurred. When patients with Meth-APAH present for clinical attention, initial symptoms may be non-specific such as declining functional capacity, worsening exercise tolerance, chest pain, dizziness or dyspnea. Late stage symptoms include syncope, arrhythmias, edema, congestive hepatopathy/cardiac cirrhosis from low cardiac output and congestion due to severe right heart failure.

PAH itself is a devastating disease with poor outcomes. In the REVEAL registry (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management), a multicenter USA based longitudinal registry, the estimated 1, 3, 5, and 7-year survival rates from time of diagnostic right heart catheterization were 85%, 68%, 57%, and 49%, respectively [18].The prognosis of patients with Meth-APAH appears to be even worse than for those with IPAH [19]. Meth-APAH when compared to IPAH is less likely to be females, reported more advanced heart failure symptoms, with higher right atrial pressures and lower stroke volume index and associated with more than double the risk of death or clinical worsening.

In a large retrospective cohort analysis, our group compared the clinical characteristics and outcomes of methamphetamine associated cardiomyopathy and Meth-APAH and found that the unadjusted mortality rate at 20 months was higher in the Meth-APAH cohort than in the methamphetamine-induced cardiomyopathy cohort (18% vs 15.2% respectively), as compared to 4.5% in the control group (Control group: methamphetamine users without either cardiomyopathy or pulmonary hypertension phenotype) [20]. Even more alarming than the higher mortality and poorer prognosis of Meth-APAH than methamphetamine cardiomyopathy patients, and perhaps not at all surprising, is the high mortality rate of MUD individuals without demonstrable cardiac conditions (the control group). With 4.5% unadjusted mortality rate at 20 months follow-up, methamphetamine use in and by itself, in the absence of cardiomyopathy or PAH, carries a much higher mortality rate than the general population. Methamphetamine use contributes to the excess mortality either through direct pathophysiological mechanisms or as a marker of associated high-risk conditions such as mental disorders, polysubstance abuse, homelessness and other psychosocial impediments to optimal self care. Consequently, the observed higher mortality and poorer outcomes in Meth-APAH patients may also be at least partially due to the many other facets of methamphetamine's negative impact on Meth-APAH individuals' health and condition.

Prevention and Treatment

Optimal treatment strategies are not known for Meth-APAH as these patients were excluded from randomized trials and most observational studies. Management of Meth-APAH patients is largely extrapolated from other subtypes of PAH. After initial diagnosis by echocardiography, right heart catheterization is required to confirm the diagnosis of Meth-APAH, assess the severity of hemodynamic impairment and to test for vaso-reactivity. Other than right heart catheterization, other tests commonly employed include 6-minute walking test(a submaximal exercise test) to assess exercise capacity, and Cardiopulmonary exercise testing (a maximal exercise test), which provides important information on gas exchange, ventilatory efficacy and cardiac function during exercise. For a group notable for high rates of homelessness, mental illnesses, co-abuse of other substances and low health literacy, navigating through the myriad diagnostic testing and healthcare system can prove to be challenging to Meth-APAH patients. At our center, they are not infrequently lost to follow-up due to failed urinary drug testing needed to proceed to right heart catheterization.

Treatment goals of Meth-APAH, therefore, follow a distinct algorithm apart from other forms of PAH, with psychosocial support and methamphetamine cessation counseling taking a prerequisite and central role.

One must not think of managing Meth-APAH, a condition that is presumably rare even among MUD cohort, outside the larger context of MUD itself. To date, there is no medication approved by the Food and Drug Administration for the treatment of MUD. Timely development of effective treatment(s) has been identified as an essential public health goal given the magnitude of the problem in the US and globally. A recent randomized, double blind, placebo-controlled trial has shown that MUD individuals receiving extended-release injectable naltrexone plus oral extended-release bupropion for up to 12 weeks had a overall treatment effect of 11.1% (13.6% over 2.5% in the control group, p<0.001) [21]. The response rate was overall low but was statistically higher than MUD individuals in the control arm. This landmark study, the first of its kind with pharmacological therapy targeting MUD, the parent disorder of Meth-APAH, offers a glimmer of hope for Meth-APAH. Emerging therapies, either pharmacological or behavioral, will hopefully ameliorate the extent and impact of MUD, the upstream condition from which Meth-APAH develops.

Currently, international guidelines [22] and expert consensus have not considered screening for PAH in asymptomatic MUD individuals, largely due to the unknown prevalence of PAH in this population and as such adversely affects the cost-effectiveness of any screening procedure. The ongoing Screening of Pulmonary Hypertension in Methamphetamine Abusers (SOPHMA) study [23], a cross-sectional screening study employing current guideline-recommended echocardiography-based PAH screening algorithm to a large unselected MUD cohort in Hong Kong, is a step in the right direction for early detection and proactive management of Meth-APAH.

Is Meth-APAH reversible? Anecdotal cases have been observed, as in our clinical practice. Its twin entity of Methamphetamine-associated cardiomyopathy has been shown to demonstrate degree of reversibility if cessation of methamphetamine use is coupled with compliance with standard heart failure therapy during its early disease phase, i.e., when the right ventricle has not undergone irreversible remodeling as is typical in the late phase of the natural history of the disease [24]. Is Meth-APAH also reversible within the same context of early intervention, methamphetamine cessation and compliance with PAH therapy? We eagerly await reports on this topic of reversibility of Meth-APAH.

Once abstinence is achieved, Meth-APAH patients management generally follows the same framework as other PAH subgroups. The three-step treatment goals for PAH as per the 2015 European Society of Cardiology/European Respiratory Society guidelines [22] include: general measures in counseling, psychosocial support, O2 therapy and referral to expert centers for right heart catheterization; high-dose calcium channel blockers in patient with vasoreactivity; and initiation of combination therapy and lung transplantation evaluation in advanced cases.

Vasoreactivity in PAH is rare and confirmed in only approximately 10% in IPAH and <5% in those with PAH associated with connective tissue disease [25], and even rarer in Meth-APAH. In the Stanford cohort [19], 1.5% (1/68) Meth-APAH had acute vasoreactivity to inhaled nitric oxide, as compared to 9.6% (7/73) in the IPAH cohort. In the Zhao et al. study [20], 0/20 Meth-APAH patients demonstrated positive vasoreactivity. The vast majority of patients with Meth-APAH, therefore, will not be candidate for high dose calcium channel blocker either due to lack of acute vasoreactivity or due to advanced state of disease at time of diagnosis and inability to tolerate high dose calcium channel blockers.

The development and approval of 14 medications from three major drug classes, either monotherapy or in combination, have altered the landscape of PAH management over the past several decades [25]: endothelin receptor antagonists (Ambrisentan, Bosentan, Macitentan), phosphodiesterase type 5 inhibitors and guanylate cyclase stimulators (Sildenafil, Todalafil, Vardenafil, Riociguat), and prostacyclin analogues/prostacyclin receptor agonists (Iloprost [iv or inhaled], Beraprost [oral], Epoprostenol [intravenous, available in pH neutral-Flolan, or pH alkaline-Veletri diluent], Treprostinil [subcutaneous, inhaled, intravenous and oral], Selexipag [oral]). Are these drugs effective in treating Meth-APAH? The answer is uncertain. There has been no study specifically examining the efficacy and safety of these PAH agents on Meth-APAH. In clinical practice, PAH therapies are often offered to Meth-APAH patients, albeit with more challenges and problems.

Though continued use of methamphetamine is not an absolute contraindication for these therapies, many institutions require negative urine toxicology testing. The nature of PAH also necessitates close outpatient follow-ups with periodic blood tests, Six-minute walk test, echocardiogram and right heart catheterizations. Endothelin receptor antagonist class drugs require biweekly or monthly liver function testing and in female patients, monthly pregnancy testing while on therapy. Intravenous prostanoid therapy runs the risk of deadly consequences if stopped suddenly. All these tasks may appear arduous to active methamphetamine users. Care coordination, adequate psychosocial support and a collaborative, individualized approach are instrumental for patient retention and treatment progress. For Meth-APAH patients in particular, an adequate support structure incorporating personal and health system resources will prove to be essential for cessation from methamphetamine use and improved engagement with therapeutic interventions.

Conclusions

As the number of people with methamphetamine exposure continues to surge worldwide, Meth-APAH is expected to grow proportionally and will feature more prominently in the overall makeup of Group 1 PAH. Existing data demonstrate worse prognosis and outcomes of Meth-APAH as compared to IPAH. Despite a lack of high quality data and consensus strategies for patients with Meth-APAH, the cornerstone for its management resides with cessation of methamphetamine use under the guidance of a comprehensive, multidisciplinary care team. PAH specific therapies with the current three major classes of drugs have not been tested in Meth-APAH, but are frequently used in these patients with unique challenges and unknown outcomes. There is hence an urgent need to establish national and international collaborations towards setting up a clinical registry to pool our knowledge and experience to combat this highly morbid subtype of PAH.

Abbreviations

MUD: methamphetamine use disorder; PAH: pulmonary arterial hypertension; Meth-APAH: methamphetamine-associated pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension.

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