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Cerebral Vasospasm in Raynaud's Syndrome Manifesting as Pulsatile Tinnitus

David D Brown[1]* and Jason W Kimbel[2]

[1]Medical Director, Adjunct Professor of Neurology, Bridgepoint Neurology, University of Arkansas for Medical Science, Garden Grove, California

[2]Department of Internal Medicine, University of Arkansas for Medical Science, Tifton Regional Medical Center, Tifton, GA

ABSTRACT

Background: Pulsatile tinnitus is a pulse synchronous audible whooshing sensation that arises from turbulent flow in stenotic intracranial or upper cervical arteries, amidst other pathologies, yet is often idiopathic in origin. Raynaud's syndrome involves peripheral vasoconstriction, but possibly also cerebral vasoconstriction. The presence of cerebral vasoconstriction in Raynaud's was evaluated by ascertaining the prevalence of pulsatile tinnitus compared to a control population.

Methods: Pulsatile tinnitus was defined in this study as pulse synchronous audible sensations that were both bothersome and manifested during routine activities. Its presence was ascertained in consecutive patients with Raynaud's syndrome and compared to a consecutive control population who met the same inclusion criteria. The study consisted of 6 patients with Raynaud's and 58 control patients. Analysis was performed using Fisher's exact test.

Findings: Four of Six (4/6) patients with Raynaud's had bothersome pulsatile tinnitus compared to Zero of 58 patients without Raynaud's, with a significance level of p<0•0002. There was no correlation between pulsatile tinnitus and common vascular risk factors including hypertension (p<0•9999), hyperlipidemia (p<0•9999), diabetes mellitus (p<0•9999), coronary artery disease (p<0•9999), cerebral vascular disease (p<0•9999), as well as vasculitis (p<0•4632) or conductive hearing loss (p<0•9999).

Interpretation: Pulsatile tinnitus due to cerebral vasoconstriction appears to be a common manifestation of Raynaud's. Diagnostic evaluation of pulsatile tinnitus may also warrant an evaluation for Raynaud's syndrome.

***Corresponding author**
David D Brown, Medical Director, Bridgepoint Neurology, Garden Grove, California, USA.

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Introduction

Pulsatile tinnitus is different from typical tinnitus in that it is pulse synchronous rather than steady. It can arise from cervical and cranial vascular structures due to turbulent blood flow through narrowed vascular lumens or abnormal flow through vascular malformations. Recognized causes include intra- and extracranial carotid stenosis, arterial dissection of the extracranial cervical arteries, intracranial arterial dissection, intracranial aneurysm, glomus jugulare, glomus tympanicum, dural arteriovenous fistula, transverse venous sinus stenosis, and idiopathic intracranial hypertension, among others. For a significant fraction of patients the underlying diagnosis remains elusive, a condition referred to as idiopathic pulsatile tinnitus. A typical evaluation entails imaging of the intra-cranial and cervical vasculature with MR or CT angiogram, fundoscopic examination to evaluate for idiopathic intracranial hypertension, and otological evaluation [1].

Raynaud's syndrome is a vaso-spastic process that primarily affects the digits, and it is seen both as an isolated entity (primary Raynaud's) as well as in several rheumatologic conditions (secondary Raynaud's). It entails a cold sensitivity with color change beginning with blanching due to vasospasm, followed by cyanosis or redness, and eventually resumption of normal skin color (figure 1). Raynaud's has also been observed to affect the vasculature of the tongue, nipple and cornea [2-5].

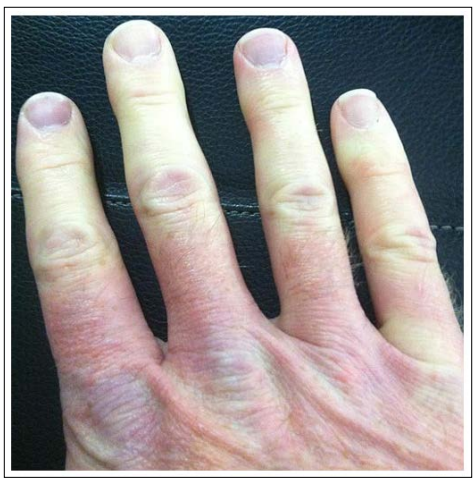

Figure 1: Raynaud's Syndrome of the Hand

Some evidence suggests Raynaud's may also cause cerebral vasoconstriction. This includes recurrent unexplained syncopal episodes in the setting of Raynaud's phenomena that completely resolved after treatment with nifedipine, cold-induced alterations in regional cerebral blood flow in secondary Raynaud's, and anecdotal angiographic and intra-operative observations [6-9].

The present study was initiated on account of a middle-aged woman presenting with intractable pulsatile tinnitus, with unremarkable cervical and cranial vascular imaging, normal otological and fundoscopic examinations, yet with a patient-noted correlation between the intensity of the pulsations and the typical manifestations of Raynaud's in her hands. She was treated with amlodipine for the underlying Raynaud's and the episodic blanching and violaceous discoloration of her hands improved. Simultaneously, her pulsatile tinnitus decreased quite substantially to no longer being bothersome or that noticeable.

The objective of this study is to determine whether this anecdotal observation was an isolated incident or representative of a previously unidentified association between Raynaud's and cerebral vasoconstriction manifesting as pulsatile tinnitus.

Methods

Consecutive patients with and without primary or secondary Raynaud's presenting as new or follow up patients to Mercy Rheumatology Clinic were evaluated. This clinic shared common office space at Mercy Clinic with the corresponding author's neurology clinic, and the study was conducted from 11/30/15 to 12/25/15. Eligible subjects were asked if they heard pulsations or whooshing sounds in their ears that were synchronous with their pulse, if these pulsations were bothersome, and if these pulsations were present during routine activities (not during physical exertion and not only during settings of extreme quiet such as bedtime). In addition, patients were interviewed for relevant history that could possibly contribute to vascular pulsatile tinnitus, including hypertension, hyperlipidemia, diabetes mellitus, vasculitis, prior coronary artery or cerebral vascular disease, and conductive hearing loss, as well as other comorbid conditions being determined. If pulsatile tinnitus was identified, such patients were recommended to have further evaluation by an otorhinolaryngologist or neurologist for alternative underlying causes.

Inclusion and exclusion criteria for the Raynaud's and the control population included being of age 18-90 years old, no diagnosis of fibromyalgia, no diagnosis or suspicion of dementia, and no history of conversion disorder. The Raynaud's population additionally consisted of patients with primary or secondary Raynaud's syndrome diagnosed by a board-certified rheumatologist.

This study polled 96 consecutive patients. Study inclusion and exclusion criteria excluded 32 patients, leaving 64 patients for data analysis. This study was performed over the course of one month and the study size is a reflection of the number of consecutive patients polled by the research team during that time period. Responses were a categorical yes or no, and analysis was performed using Fisher's exact test with significance defined as p<0•05. These findings were reviewed and verified by the UAMS Translational Research Institute (TRI), a university medical biostatistics consulting firm.

Standard Protocol Approvals, Registrations, and Patient Consents

The inclusion criteria and study format was reviewed and approved by the Mercy Healthcare System research review and ethical committees and exempted from IRB approval because it was a cross sectional study. Informed consent was obtained from all participants in the study. There was no personal identifying information retained in this study.

Role of the Funding Source

There were no funding sources used in the writing of this manuscript nor in the decision for publication. Neither author has been paid to write this article by any pharmaceutical company or any other agency. The corresponding author had full access to all the data in the study and accepts final responsibility for the decision to submit for publication.

Results

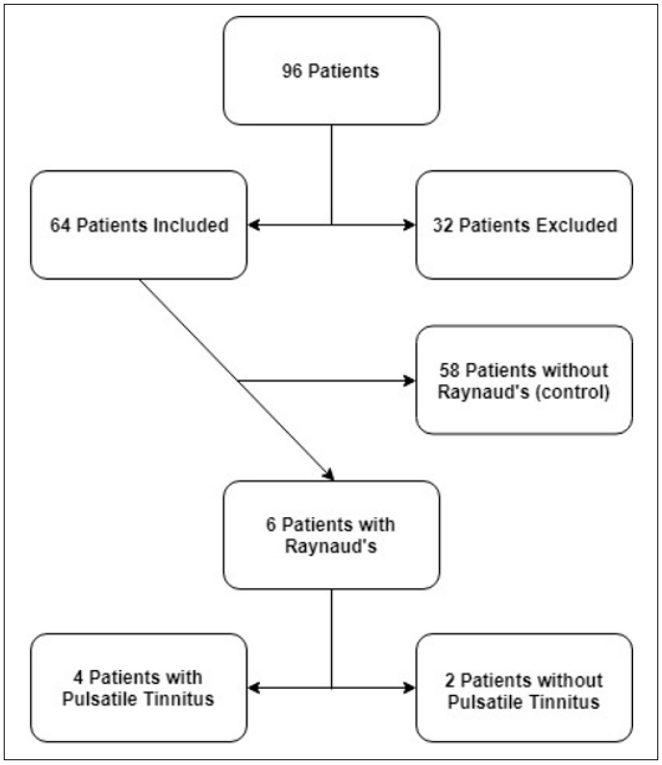

Figure 2: Flowchart of Sampling Procedure

Table 1

	Number with pulsatile tinnitus	Number without pulsatile tinnitus
Raynaud's*	4	2
Control Population	0	58

*p<0•0002 via Fisher's exact test compared to control population

Table 2

Frequency of Pulsatile Tinnitus in Primary and Secondary Raynaud's and Proposed Risk Factors				
Symptom	**Total**	**No Pulsatile Tinnitus**	**Pulsatile Tinnitus**	**Significance level (P)**
Primary or Secondary Raynaud's	6	2	4	<0•0002
HTN	26	23	3	0•9999
Hyperlipidemia	8	8	0	0•9999
DM	5	5	0	0•9999
CAD	7	7	0	0•9999
CVD	3	3	0	0•9999
Vasculitis	9	8	1	0•4632
Conductive Hearing Loss	1	1	0	0•9999

Table 3

Patient Characteristics		
	Pulsatile tinnitus	**No pulsatile tinnitus**
Average Age	52	62•9
Males	0%	25%
Females	100%	75%
Rheumatologic comorbidity prevalence		
Rheumatoid Arthritis	0%	39.7%
Sjogren's Disease	0%	6.8%
SLE	25%	6.8%
MCTD	0%	1.7%

We found a strong positive association between Raynaud's and bothersome pulsatile tinnitus with a p <0•0002 significance level. There was no correlation between the selected vascular risk factors and bothersome pulsatile tinnitus, including hypertension (p<0•9999), hyperlipidemia (p<0•9999), diabetes mellitus (p<0•9999), coronary artery disease (p<0•9999), cerebral vascular disease (p<0•9999), as well as no correlation with vasculitis (p<0•4632), and conductive hearing loss (p<0.9999).

Discussion

A significantly higher prevalence of bothersome pulsatile tinnitus was identified in individuals with Raynaud's compared to a control population meeting the same inclusion criteria (Table 1 and Table 2). One weakness of the study is the small sample size of the Raynaud's group, yet statistical evaluation indicates the association observed is very unlikely to be due to chance (p<0•0002). Another limitation of this study is that the follow up diagnostic evaluation of these patients to determine alternative causes of pulsatile tinnitus is unknown, and any recognized underlying causes of pulsatile tinnitus could confound the results. Nevertheless, given a reported prevalence of pulsatile tinnitus of only 1.2% in the general population, this is considered an improbable confounding factor [10].

The study was performed on consecutive patients who met strict inclusion/exclusion criteria to limit bias. However, the generalizability of our findings to all patients with Raynaud's is limited due to evaluating patients in a rheumatology clinic who likely have more severe underlying Raynaud's disease. The population studied presumably also has a higher incidence of secondary Raynaud's, and this study was not powered to detect a difference in symptom prevalence rates between primary and secondary disease.

It is likely that occasional audible pulsations that are present with exercise or extreme quiet are common in healthy adults. This potential confounder was addressed by requiring audible pulsations to be both bothersome and present during routine physical activities in order to be considered positive.

The pulsatile tinnitus sufferers in our study had a lower average age than the rest of the study group (52 vs. 62•9), and none of them were male (0% male vs. 25% male) (Table 3), likely related to the common causes of secondary Raynaud's being significantly more frequent in females. However, only a modest difference between the prevalence of primary Raynaud's in males versus females is seen in larger epidemiological studies. In addition, our study group included only Caucasians due to local population demographics. Another possible weakness of this study is a lack of objective confirmation of subjective symptoms [11].

In light of this study and other observations of cerebrovascular manifestations of Raynaud's, it can be inferred that cerebral vasospasm is a manifestation of Raynaud's [6-9]. Interestingly, in this study patients with Raynaud's and pulsatile tinnitus experienced the pulsatile tinnitus consistently, rather than only at times they were experiencing clinically evident peripheral vasospasm. It is therefore interesting to speculate that some patients with idiopathic pulsatile tinnitus may have cerebrovascular manifestations of the vasospasm that occurs in Raynaud's, without peripheral vascular manifestations, and this would require further study.

From a diagnostic standpoint, existing case series in which the causes of pulsatile tinnitus have been determined after extensive diagnostic evaluation, including catheter angiography, have not been able to identify causes in from 9% to 27% of patients. Even in the more contemporary case series in which intracranial venous abnormalities as a potential cause of pulsatile tinnitus are more frequently identified, idiopathic cases have ranged from 15% to 24% of patients [12-15]. We propose that primary and secondary Raynaud's enter the differential diagnosis for pulsatile tinnitus in which imaging, otological and fundoscopic evaluations are unrevealing [14, 15].

Since the conduct of this study, two more patients with idiopathic pulsatile tinnitus and associated Raynaud's syndrome have been treated with amlodipine, with a significant reduction in the audible sensations. It would therefore also be of interest to see how patients with cerebral vasospasm related to Raynaud's respond to amlodipine or other vasodilatory agents in a controlled trial.

Research in Context

Evidence before this Study

Pulsatile tinnitus is well known to result from structural vascular abnormalities as well as idiopathic intracranial hypertension. However, a significant percentage of patients have pulsatile tinnitus of an undetermined origin.

Added Value of this Study

This study reveals that pulsatile tinnitus is a clinical manifestation of Raynaud's disease, and that Raynaud's should enter the differential diagnosis of pulsatile tinnitus.

Implications of all the Available Evidence

Raynaud's may have cerebrovascular manifestations in addition to peripheral vascular manifestations. Findings also suggest vasodilatory agents might be effective for idiopathic pulsatile tinnitus, or pulsatile tinnitus in Raynaud's and this requires further investigation.

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Author Contributions

Dr. David Brown, study concept and design, study supervision, critical manuscript revision

Dr. Jason Kimbel, assist with study design, perform acquistion and interpretation of data, literature searches, manuscript revision

Declarations of Interest

Dr. David Brown – Reports no conflicts of interest.

Dr. Jason Kimbel – Reports no conflicts of interest.

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