Journal of Pharmacy Practice and Community Medicine.2017, 3(1):27-30 • http://dx.doi.org/10.5530/jppcm.2017.1.6

BRIEF REPORT

OPEN ACCESS

Pseudocholinesterase Deficiency in an Indian Community

Maddi Ramaiah*[1], Prudhivi Ramakrishna[2]

[1]*Department of Pharmacognosy, Hindu College of Pharmacy, Guntur – 522002, AP, INDIA.*

[2]*Department of Pharmacy Practice, Dayananda Sagar University, Bangalore – 560078, Karnataka, INDIA.*

Received: 27 September 2016;

Accepted: 09 November 2016

***Correspondence to:**

Dr. Ramaiah Maddi, PhD,

Department of Pharmacognosy, Hindu College of Pharmacy, Guntur – 522002, AP, INDIA.

Email: rampharma83@gmail.com

DOI: 10.5530/jppcm.2017.1.6

ABSTRACT

Back ground: India, the seventh largest country, 3rd largest standing army and one of the oldest civilizations in the world, with a literacy rate of 74.04%. Indian population was a mixture of 46,73,034 categories of different castes and sub-caste each related to a specific occupation. Arya Vysya is a Hindu Indian caste with a total population of 22,952,000. **Methods:** Pseudocholinesterase is a glycoprotein enzyme with complex molecular structure synthesized in the liver and specifically hydrolyzes certain exogenous cholinesters. Pseudocholinesterase deficiency is a genetic enzyme abnormality or acquired alteration in the metabolism of choline esters in this patient may experience a paralysis of the respiratory muscles, to overcome this, required more time mechanically-assisted breathing. The presence of the genetic defect is not realized until one is exposed to succinylcholine or mivacurium. **Results:** Arya Vysya community people of India having deficiency of pseudocholinesterase is the most affected people than any other with homozygous mutation incidence rate of 2-4%. Very recent studies in 2016 reveal that malnutrition-induced pseudocholinesterase deficiency is also a possible etiology. **Conclusion:** It was suggested that the Arya Vysya Community people with a history of pseudocholinesterase deficiency should tell his or her doctor if when they undergo anesthesia for surgery to avoid potentially serious unwanted adverse effects.

Key words: India, Arya Vysya, Pseudocholinestase, Pseudocholinestrase deficiency, Choline esters, Acholest test paper.

INTRODUCTION

India, the 7th largest country, 3rd largest standing army and one of the oldest civilizations in the world, with 29 states and 7 union territories. India has achieved all-round socio-economic progress during the last 70 years of its Independence with a literacy rate of 74.04%. As per March 2011 census reports, India's population, stood at 1.2 billion (623.7 million males and 586.4 million females) and at present in 2016 it is 1.3 billion. Hinduism (79.8%) is the largest religion in India and a home to two major language families of Indo-Aryan (74%) and Dravidian (24%).[1-3] Socio Economic and Caste Census 2011 conducted by the Registrar General of India has reported that, Indian populations was a mixture of 46,73,034 categories of caste, sub-caste, synonyms, different surnames, gotras in the caste and clan names and each related to a specific occupation.[4,5]

Arya Vysya Community: Arya Vaishya (Arya Vysya) is an Indian caste belongs to the religion of Hinduism. Their p*opulation in India* is 22,952,000[6] with Gavara and Kalinga

subdivisions and about 80 groups and those follow rituals as per a religious text prescribed in "*Vasavi Puranam*". In India, Vysya community people are distributed in Andhra Pradesh, Karnataka, Maharashtra, Odisha, Telangana and Tamil Nadu. It is one of the notable as trading community from 1325 CE to till date. According to the "*Vasavi Puranam"*, the Vaishya's of Penugonda, West Godavari district, Andhra Pradesh, India and 17 other towns belonged to a group of Vaishya's of 714 gotras. However, the 102 gotras of Gavara's separated out, and formed the Gavara Komati community.[7,8]

Pseudocholinesterase: It was reported that, cholinesterase was of 2 types, one is acetylcholinesterase and another one is pseudocholinesterase. Acetylcholinesterases inactivates acetylcholine produced at the neuromuscular junction during neurotransmission whereas pseudocholinesterase, a glycoprotein enzyme having complex molecular structure synthesized in the liver and immediately released into the plasma with a half-life of 12 days[9,10] also found in many tissues with the exception of red blood cells, and its function is unknown, it has been suggested that it may specifically hydrolyze certain exogenous cholinesters which inhibit acetylcholinesterase. [11]

Pseudocholinesterase deficiency: It is a genetic enzyme abnormality or acquired alteration in the metabolism of choline esters such as succinylcholine, mivacurium,[12-14] and ester-linked local anesthetics including procaine, chloroprocaine, and, to a lesser extent, cocaine in which the body's production of butyrylcholinesterase (BuChE) also known as pseudocholinesterase, serum cholinesterase, plasmacholinesterase, and false cholinesterase was impaired.

Symptoms: Unless an affected person was given choline ester drugs and ester-linked local anesthetics, pseudocholinesterase deficiency does not produce any symptoms. Mostly, the patient may experience a paralysis of the respiratory muscles, to overcome this, required more time mechanically-assisted breathing.

Causes: Pseudocholinesterase deficiency can be inherited (genetic) or acquired. Genetic pseudocholinesterase deficiency is due to abnormal alleles that code for the synthesis of pseudocholinesterase and this known as faulty gene which results in abnormal or inadequate levels of plasma enzyme. This faulty gene known as BCHE gene, located on chromosome 3 (3q26.1-q26.2) and its region spans about 70 kb and has 4 exons and3 introns.[15,16] Acquired pseudocholinesterase deficiency due to having physiological conditions like chronic infections (tuberculosis), severe burn injuries, liver diseases, malignancy, malnutrition, organophosphate pesticide poisoning, uremia, pregnancy, cardiopulmonary bypass, leprosy and all these conditions may cause lower levels of plasma pseudocholinesterase.[17,10]

Pathophysiology: In normal healthy persons, about 90% of i.v. administered succinylcholine was inactivated before it reaches to the neuromuscular junction. The left over 10% succinylcholine dose then acts as an acetylcholine receptor agonist and causes depolarization results in initiation of skeletal muscle twitching with in one minute and it was again normal within five minutes. In people with pseudocholinesterase deficiency having very high levels of succinylcholine results in too much and too long depolarization can be taken place and it will be continued may be upto eight hours.

Epidemiology: Pseudocholinesterase deficiency is most common in Arya Vysya community people of India[18-20] and Persian Jews.[21]

Complications: People who have pseudocholinesterase deficiency may be sensitive to certain anesthetic drugs and muscle relaxants. The majorly reported consequences of pseudocholinesterase deficiency are respiratory failure, prolonged paralysis and apnea after administration of succinylcholine or mivacurium. The presence of the genetic defect is not realized until one is exposed to succinylcholine or mivacurium.[22]

Case Reports of Affected Hindu Arya Vysya Community

Arya Vysya community people of India having deficiency of pseudocholinesterase is the most affected groups than any other people with homozygous mutation incidence rate of 2-4%.[23] A study was performed on 22 men and women of Arya Vysya community belonging to Coimbatore, Tamil Nadu state of India showed that 9 of them had pseudocholinesterase deficiency;[24] The gene mutations responsible for absence of pseudocholinesterase activity were identified[25] and it was associated with 58 different mutations, including frame shift mutations, deletions, substitutions, insertions of alu repeats, and mutations affecting intron/exon splicing. The silent phenotype of human pseudocholinesterase has a frequency of 1 in100,000 in European and American populations, but an extremely high frequency of 1 in24 in the Vysya community of India[24]; Literature review revealed a total of 40 pseudocholinesterase deficiency cases were being reported in USA from 1956 to 2011;[10] A very recent studies in 2016 reveals that malnutrition-induced pseudocholinesterase deficiency is also a possible etiology;[26,27] A 36-year-old correctional officer with pseudocholinesterase deficiency when exposed

to organophosphate toxicity he immediately developed abdominal cramps, diarrhea, sweating, excessive salivation, frequent urination, and increased bronchial secretions;[28] A 19 year old girl underwent her first experience of general anesthesia for 30 minute dentoalveolar procedure and unexpectedly met extubation requirement for 5 hours due to pseudocholinesterase deficiency;[29] The four patients in the Mostas Private Health Hospital, Turkey was identified with positive pseudocholinesterase deficiency. In all four of the patients, the prolonged blocks are deteriorated due to mivacurium use;[9] A 72-year-old male underwent neck dissection and parotidectomy with facial nerve preservation. Endotracheal intubation was facilitated with succinylcholine. Prolonged muscle paralysis which was first detected after failure to stimulate the facial nerve with electrocautery, lasted five hours and it is due to pseudocholinesterase deficiency.[10]

Prognosis: Administration of succinylcholine along with proper medical support particularly respiratory support measures like mechanical ventilation. In nonmedical condition in which subjects with pseudocholinesterase deficiency are exposed to cocaine, sudden cardiac death can occur.

Patient Education: Administration of pseudocholinesterase itself to the deficient people is one of the possible options. Behringwerke, a German pharmaceutical company, created a purified, injectable form of human pseudocholinesterase.[30,23] Another, USA-based pharma company PharmAthene has begun using genetically modified goats to create pseudocholinesterase in large quantities.[11] Treatment or management involves the avoidance of following class of drugs like drugs containing succinylcholine: quelicin, anectine; drugs containing mivacurium: mivacron; drugs containing pilocarpine: salagen; drugs containing butyrylcholine; drugs containing huperzine A and donepezil; drugs containing propionylcholine and acetylcholine; drugs containing parathion; procaine drugs: novocaine.

Diagnosis: Polymerase chain reaction (PCR) was used to identify the mutations or variants exist on a particular piece of DNA. Testing for pseudocholinesterase deficiency before surgery was also useful for diagnosis. "Normal" is described as 3,200 to 6,600 IU/L (19). A plasma assay of pseudocholinesterase enzyme activity was used for diagnosis of pseudocholinesterase deficiency. Apart from that, pseudocholinesterase enzyme activity can be determined byusing "Acholest Test Paper". When a drop of the patient's plasma was applied to the substrate-impregnated test paper, a colorimetric reaction occurs. The time taken by the exposed Acholest Test Paper to turn from green to yellow is inversely proportional to the pseudocholinesterase enzyme activity in the plasma sample.

Table 1: Reaction Times for Acholest Test Paper

S.No.	RT	PE Activity
1.	< 5 min.	Above normal
2.	5-20 min.	Normal
3.	20-30 min.	Borderline low
4.	>30 min.	Below normal

RT: Reaction Time
PE Activity: Pseudocholinesterase Enzyme Activity

CONCLUSION

Pseudocholinesterase deficiency results in delayed metabolism of only a few compounds of clinical significance like succinylcholine, mivacurium, procaine, and cocaine. Indian Hindu Arya Vysya Community people with a history of pseudocholinesterase deficiency should tell his or her doctor if when they undergo anesthesia for surgery to avoid potentially serious unwanted adverse effects. Because pseudocholinesterase deficiency is rare, it is not tested for prior to surgery. This means that most patients are not diagnosed until they have an adverse reaction to medication during surgery, or unless they have a family history of the disorder.

ACKNOWLEDGEMENT

I Sincerely acknowledges to Prof. S. Ganapaty, Dean & Principal, GITAM Institute of Pharmacy, Visakhapatnam, A.P., and the Management, Principal, Vice Principal of Hindu college of Pharmacy, Guntur, A.P., for their encouragement and support.

REFERENCE

1. World Economic Outlook Database April 2016. Available from: http://www.imf.org/external/pubs/ft/weo/2016/01/weodata/index.aspx.
2. Office of the Registrar General & Census Commissioner, New Delhi, Available from http://www.censusindia.gov.in/2011census/c-01.html.
3. National Informatics Centre (NIC), Ministry of Electronics & Information Technology, Government of India. Available from: https://india.gov.in/india-glance/profile.
4. Annapurna S. Socio-economic census 2011 reveals 46 lakh castes, sub-castes. Deccan Herald, Delhi, India, Available from: http://www.deccanherald.com/content/489752/socio-economic-census-2011-reveals.html.
5. Kumar KSS. History of Arya Vysyas. Arya Vysyas srisms, Vijayawada, India, 2012. Available from: http://aryavysyas.srisms.com/ourhistory.html.
6. Gupta DC, Bhaskar S. Vysyas: a sociological study. Ashish Publishing House – APH (1992) Publishing Corporation, New Delhi, India. ISBN 8170244501.
7. Andhra Historical Research Society, Rajahmundry, AP, India. J Andhra Hist Soc. 1964;30(1-4):207-9.
8. Kendrick K. Prolonged paralysis related to mivacurium: a case study. J Peri Anesthesia Nurs. 2005;20(1):7-12.

9. Patrick JH, Tetsuro S. Pseudocholinesterase Deficiency: A Case Report and Literature Review. Open J Anest. 2012;2:188-94.
10. Matthew W, Demetri K. Pseudocholinesterase Deficiency in an Octogenarian Undergoing Total Intravenous Anesthesia; Implications for Neuromonitoring. Midd East J Anest. 2015;23(2):157-62.
11. Lehmann H, Liddell J. The Cholinesterase Variants, in: The Metabolic Basis of Inherited Diseases, 3d ed., Stanbury JB, Wyngaarden JB, and Fredericksen DS (eds.), New York: McGraw-Hill, 1972;173.
12. Hemadri M, Purva M, Trakova V. Unexpected prolonged neuromuscular block after mivacurium: a case report. Med Princi Pract 2002;11(1):50-2.
13. Cerf C, Mesguiah M, Gabriel I, *et al*. Screening patients with prolonged neuromuscular blockade after succinylcholine and mivacurium. Anesthesia & Analgesia, 2002;94(2):461-6.
14. Allderdice PW, Gardner HA, Galutira D, Lockridge O, LaDu BN, Mc Alpine PJ. The cloned butyrylcholinesterase (BCHE) gene maps to a single chromosome site, 3q26. Genomics, 1991;11(2):452-4.
15. Hodgkin WE, Giblett ER, Levine H, Bauer W, Motulsky AG. Complete Pseudocholinesterase Deficiency: Genetic and Immunologic Characterization. J Clini Invest. 1965;44(3):486-93.
16. Pandit JJ, Gopa S, Arora J. A hypothesis to explain the high prevalence of pseudocholinesterase deficiency in specific population groups. Eur J Anaesthesiol. 2011;28(8):550-2.
17. Bin Li, Ellen G. Duysen, Michaela Carlson, Oksana Lockridge. The Butyrylcholinesterase Knockout Mouse as a Model for Human Butyrylcholinesterase Deficiency. J Pharmacol Expe Thera, 2008;324(3):1146-54.
18. Manoharan I, Boopathy R, Darvesh S, *et al*. A medical health report on individuals with silent butyrylcholinesterase in the Vysya community of India. Clinica Chimica Acta, 2007;378(1):128-35.
19. Kaback M, Lopatequi J, Portuges A, Quindipan C, Pariani M, Salimpour-Davidov N *et al*. Genetic screening in the Persian Jewish community: A pilot study. Genetics in Medicine. 2010;12(10):628-33.
20. Manoharan I, Wieseler S, Layer PG, Lockridge O, Boopathy R. Naturally occurring mutation Leu307Pro of human butyrylcholinesterase in the Vysya community of India. Pharmacog Geno. 2006;16(7):461-8.
21. Lockridge O. Genetic variants of human serum cholinesterase influence metabolism of the muscle relaxant succinylcholine. Pharmacol Ther.1990;47(1):35-60.
22. Flanna KS, Yvette PC, Richard H. Pseudocholinesterase Deficiency: A Comprehensive Review of Genetic, Acquired, and Drug Influences. AANA Journal, 2010;78(4):313-20.
23. Ellen GD, Cynthia FB, Oksana L. Wild-Type and A 328 W Mutant Human Butyrylcholinesterase Tetramers Expressed in Chinese Hamster Ovary Cells Have a 16-Hour Half-Life in the Circulation and Protect Mice from Cocaine Toxicity. J Pharmacol Expe Ther. 2002;302(2):751-8.
24. Primo-Parmo SL, Bartels CF, Wiersema B, Spek AF, Innis JW and La Du BN. Characterization of 12 silent alleles of the human butyrylcholinesterase gene. Ame J Hum Genetics. 1996;58(1):52-64.
25. LaRocca CJ, Beilman GJ, Birch M. A Case of Pseudocholinesterase Deficiency Resulting From Malnutrition. A & A Case Reports. 2016;7(5):112-4.
26. Niazi A, Leonard IE, O'Kelly B. Prolonged neuromuscular blockade as a result of malnutrition-induced pseudocholinesterase deficiency. J Clini Anes. 2004;16(1):40-2.
27. Lurati A. Organophosphate Exposure with Pseudocholinesterase Deficiency. Workplace Health & Safety. 2013;61(6):243-5.
28. Antbony M, Rober BR. Heterozygous Pseudocholinesterase Deficiency: A Case Report and Review of Literature. J Oral and Maxill Sur. 2003;61(7):845-7.
29. Beyazit Z. Pseudocholinesterase enzyme deficiency: a case series and review of the literature. Cases J. 2009;2(1):9148-56.
30. Huang Y, Huang Y, Baldassarre H, Wang B, Lazaris A, Leduc M *et al*. Recombinant human butyrylcholinesterase from milk of transgenic animals to protect against organophosphate poisoning. Proce Nat Aca Sci. 2007;104(34):13603-8.

Cite this article as: Ramaiah M, Ramakrishna P. Pseudocholinesterase Deficiency in an Indian Community. J Pharm Pract Community Med. 2017;3(1):27-30.