

The Study of Cognitive Function in Elderly

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ABSTRACT

The study of cognitive decline and mental status in elderly person showed that age, head trauma and stroke were the risk factors for dementia and mild cognitive impairment (MCI). We found that normal subjects had often habits of physical exercise while dementia person lacked physical exercise. In our survey of declined cognition in elderly we found that almost all dementia patient had stroke. Ninety-seven valid MCI cases were followed up, and about 29.9% becoming to dementia (probable Alzheimer's disease) in third year. This was similar to Dr. Peterson's predication that 12.37% of MCI deteriorated to dementia (AD) every year. 14.43% of patient with MCI developed to depression, and 9.23% recover to normal status, and around 46.3% remained in MCI status. ApoE4 allele is a known risk factor of cognitive regression to MCI and dementia. We found that ApoE4 allele in the depression and normal groups was smaller than in the dementia group with a odds ratio (OR)=5.74 and in the MCI group OR=5.5. The serum level of high-density lipoprotein cholesterol (HDL-C) was lower in the dementia group than in the MCI and normal groups. This suggests that the presence of ApoE4 allele combine with a low serum level of HDL-C could be the risk factors for Alzheimer's disease. Therefore, the prevention and treatment of dementia or others cognitive decline could be done by very earlier AD-8 dementia screening. In study of UBQLN1 (Ubiquilin 1) gene polymorphism (UBQ-8i), all 187 subjects were AA-type gene without G allele. Therefore, we concluded that this gene mutation in Taiwan was rare and the single nucleotide polymorphism (SNP) of UBQ-8i was not compatible with Hardy-Weinberg law. Since all UBQLN1 gene of rs12344615 site were AA-type allele, we suspected that there was a ethnic genetic difference between Taiwanese and Caucasians in UBQLN1 gene of UBQ-8i site. In intervention study of MCI with Art therapy, the mean age of the experimental and control groups were 82.83 ± 3.703 and 82.89 ± 3.367 respectively, $P=0.956$. After 16 weeks of intervention with visual expression art therapy, participants from the experimental group improved their cognitive function significantly, $P=0.009$, especially with the language function $P=0.001$.

Keywords : Cognitive decline、Mild cognitive impairment / MCI、ApoE4、Alzheimer's Disease / AD、Art therapy、Dementia、Ubiquilin 1

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REFERENCES

- 1.人文取向藝術治療。2008。國立台中教育大學。
- 2.內政部統計處。1975~2012。戶籍登記現住人口數按五歲、十歲年齡組分。
- 3.內政部統計處。2011。內政統計通報，第二週。
- 4.江學澄譯。2004。兒童藝術治療。心理出版社。台北。
- 5.阿恩海姆 (Rudolf Arnheim) :《藝術與視知覺》，(北京:中國社會科學出版社，1984年版)
- 6.卓良珍、林志堅、關清模。1997。台中市老年人精神狀態之研究。台中榮民總醫院民國86年研究報告TCVGH-860101D。
- 7.郭乃文、劉秀枝等。1989。中文版「簡短式智能評估」(MMSE)之簡介，臨床醫學:23(1)。台北榮總。
- 8.陸雅青。2005。藝術治療繪畫詮釋，從美術進入孩子的心靈世界。心理出版社。台北。
- 9.陸雅青、周怡君、林純如、張梅地、呂照宗等譯。2008。藝術治療，心理專業者實務手冊。學富文化事業有限公司。台北。
- 10.黃月霞譯。1990。兒童諮商與實務。五南圖書出版社。台北。
- 11.楊淵韓、李明濱、劉景寬。極早期阿茲海默氏失智症之篩檢。台灣醫界，Vol.52，No.9:P8-10，2009。
- 12.蘇東平、卓良珍。1981。生活改變之壓力量化研究。中華醫學雜誌28(4):405-415。
- 13.聯合國秘書處經濟與社會事務部人口科2006年修正版，<http://esa.un.org/unpp>
- 14.聯合國世界人口預測表2000年修正版，1940年後。
- 15.American Psychiatric Association. 1994. Multiaxial Assessment. Diagnostic And Statistical Manual of Mental Disorders. 4th edition. (DSM-IV). American Psychiatric Association: 25-31.
- 16.Arieti, S. 1976. Creative: The magic synthesis, New York: Basic Books Art Therapy (n.d.) from The George Washington University Art Therapy Graduate Program: History Web site: <http://www.gwu.edu/~artx/history/index.cfm>
- 17.Barker, A., R. Jones., C. Jennison. 1995. A prevalence study of age-associated memory impairment. Br J Psychiatry 167: 642~648.
- 18.Bedford F. K., J. T. Kittler, E. Muller, P. Thomas, J. M. Uren, D. Merlo, W. Wisden, A. Triller, T. G. Smart, and S. J. Moss. 2001. GABA(A) receptor cell surface number and subunit stability are regulated by the ubiquitin-like protein Plic-1. Nat Neurosci;4:908-916.
- 19.Berg, L., 1988. Alzheimer's and Parkinson's Disease and The Aging Brain 55: 87.
- 20.Bertram L, M. Hiltunen, M. Parkinson, M. Ingelsson, C. Lange, K. Ramasamy, K. Mullin, R. Menon, A. J. Sampson, M. Y. Hsiao, K. J. Elliott, G. Velicelebi, T. Moscarillo, B. T. Hyman, S. L. Wagner, K. D. Becker, D. Blacker, and R. E. Tanzi. 2005. Family-based association between Alzheimer's disease and variants in UBQLN1. N Engl J Med. Volum352: 884-894.
- 21.Blazer, D. 1989. The Epidemiology of Psychiatric Disorder in Late Life. Geriatric Psychiatry, American Psychiatric Press 9: 235-237, 254-257.
- 22.Blessed G, B. E. Tomlinson and M. Roth. 1968. The association between quantitative measures of dementia and senile change in the cerebral grey matter of elderly subjects. British Journal of Psychiatry, 114: 797-811.
- 23.Blazer, D. G., C. David and W. Ewald. 2006. Geriatric psychiatry. American Psychiatric Publishing, Inc. USA.
- 24.Brookmeyer R, E. Johnson, K. Ziegler-Graham and M. H. Arrighi. 2007, Forecasting the global burden of Alzheimer's disease. Alzheimer's and Dementia. 3(3):186-91.
- 25.Chuo, L. J., W. Sheu, M. C. Pai, and Y. M. Kuo. 2007. Genotype and plasma concentration of cystatin C in patients with late-onset Alzheimer disease. Dement. Geriatr. Cogn. Disord. 23:251-257.
- 26.Crook T., R. T. Bartus, S. H. Ferris, P. Whitehouse, G. D. Cohen and S. G. Gershon. 1986. Age-associated memory impairment: proposed diagnostic criteria and measures of clinical change - report of a National Institute of Mental Health work group. Developmental Neuropsychology, 2, 261-76.
- 27.Dembner, A., 2005. Alzheimer's disease appears to have multiple causes, and scientists are slowly unraveling them. boston.com News.
- 28.Ebly, E. M., Hogan, D. B., Kluger, A. 1995. Cognitive impairment in the nondemented elderly. Archives of Neurology 52: 612-619.
- 29.Folstein, M. F., S. E. Folstein and P. R. McHugh. 1975. Mini-Mental State: a practical method for grading the cognitive state of patients for the Clinician. J Psychiatr Res 12: 189-198.
- 30.Galvin J. E., C. M. Roe and K. K. Powlishta. 2005. The AD8: A brief informant interview to detect dementia. Neurology, 65:559-564.
- 31.Gardner, H. 1993a. Creating minds. New York: BasicBooks.
- 32.Grasel E, S. Cameron and S. Lehl. 1990. What contribution can the Hachinski Ischemic Scale make to the differential diagnosis between multi-infarct dementia and primary degenerative dementia? Arch Gerontol Geriatr. Jul-Aug;11(1):63-75.
- 33.Hachinski V. S., L. D. Iliff and E. Zilkha. 1975. Cerebral blood flow in dementia. Arch Neurol 32: 632-637.
- 34.Huang. H.

M. and L. J. Chuo. 2002. Apolipoprotein E polymorphism in various dementias in Taiwan Chinese population. *Journal of Neural Transmission* 109: 1415-1421.

35. Hughes, C. P., L. Berg, W. L. Danziger, L. A. Coben and R. L. Martin. 1982. A new clinical scale for the staging of dementia. *Br J Psychiatry* 140: 566-572.

36. Kahn-Denis, B. K. 1997. Art Therapy with Geriatric Dementia Clients. *Art Therapy Journal of the American Art Therapy Association* 14(3): 194-199.

37. Koenig, H. G., K. G. Mcador, H. J. Cohen and D. G. Blazer. 1988. Self-rated depression scales and screening for major depression in the older hospitalized patient with medical illness. *Journal of the American Geriatrics Society*, 36, 699-706.

38. Kral, V. A. 1958. Neuro-Psychiatric Observations In An Old People ' s Home. *Journal of Gerontology*. 13(2): 169-176

39. Kral, V. A. 1962. Senescent forgetfulness: Benign and malignant. *Canadian Medical Association Journal*. vol. 86: 257-260.

40. Lane, F. and J. Snowdon. 1989. Memory and dementia: A longitudinal survey of suburban elderly: Lovibond P, Wilson P(eds). *Clinical and abnormal psychology*, Elsevier, Amsterdam: 365-376.

41. Launer, L. J. 2002. Demonstrating the case that AD is a vascular disease: epidemiologic evidence. *Ageing Res. Rev* 1: 61-77.

42. Lawton, M. P. and E. M. Brody. 1969. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*. 9:179-186.

43. Lawton, M. P. 1972. The dimensions of morale. In Kent, D.P., Kastenbaum, R., & Sherwood, S. (Eds.). *Research, planning and action for the elderly*, pp. 144-165. New York: Behavioral Publications, Inc.

44. Levy, R. 1994. Aging-associated cognitive decline. *International Psychogeriatrics*. 6(1): 63-68.

45. Lin, C., S. T. Wang., C. W. Wu., L. J. Chuo and Y. M. Kuo. 2003. The association of cystatin C gene polymorphism with late-onset Alzheimer ' s disease and vascular dementia. *Chinese Journal of Physiology* 46(3).

46. Liu C. K., M. C. Chou and C. L. Lai. 2009. Application of AD-8 to screen very mild dementia in Taiwan. *International Conference of Alzheimer ' s Disease*, 1-51.

47. Loeb, C and C. Gandolfo. 1983. Diagnostic evaluation of degenerative and vascular dementia. *Stroke*. 14:399-401.

48. Mah A. L., G. Perry, M. A. Smith and M. J. Monteiro. 2000. Identification of ubiquilin, a novel presenilin interactor that increases presenilin protein accumulation. *J Cell Biol*;151:847-862.

49. Mondell, E. J. 2005. Gene Mutation May Help Cause Alzheimer ' s disease-it ' s only the second gene with proven links to late-onset disease. *HON-News*, Health On the Net Foundation.

50. Massey, L. K., A. L. Mah and M. J. Monteiro. 2004. Ubiquilin Regulates Presenilin Endoproteolysis and Modulates -secretase Components, Pen-2 and Nicastrin, *Biochemical Journal* as manuscript BJ20050491.

51. Mondell, E. J. 2005. Gene Mutation May Help Cause Alzheimer ' s disease-it ' s only the second gene with proven links to late-onset disease. *HON-News*, Health On the Net Foundation.

52. Morris, J. C., D. W. McKeel, and M. Storandt. 1991. Very mild Alzheimer ' s disease: informant-based clinical, psychometric, and pathological distinction from normal aging. *Neurology* 41: 469-478.

53. National Center for Health Statistics, Data Warehouse on Trends in Health and Aging. [http:// www.senescence.info/definitions.html](http://www.senescence.info/definitions.html)

54. Naumburg, M. 1974. Studies of " free " art expression of behavior problem children and adolescents as a Means of Diagnosis and therapy. New York: Grune & Stratton.

55. Ohm T. G., M. Kirca., J. Bohl, H. Scharnagl, W. Gross and W. M/irz. 1995. Apolipoprotein E polymorphism influences not only cerebral senile plaque load but also Alzheimer-type neurofibrillary tangle formation. *Neuroscience* 66, 583-587.

56. Pantoni, L. and D. Inzitari. 1983. Hachinski's ischemic score and the diagnosis of vascular dementia: a review. *Ital J Neurol Sci*, 14, 539-546.

57. Pasley, B. N. and R. D. Freeman. 2008. *Scholarpedia*, 3(3):5340.

58. Petersen, R. C. 2004. Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine* 256: 183-94.

59. Petersen, R.C. and S. Negash. 2008. Mild cognitive impairment: an overview. *CNS Spectr*. Jan;13(1):45-53. Review.

60. Petersen, R. C., G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos and E. Kokmen. 1999. Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology* 56: 303-308.

61. Ravid-Horesh, R. H. 2004. " A temporary guest " : the use of art therapy in life review with an elderly woman. *The Arts in Psychotherapy* 31: 303-319.

62. Regier D. A. , J. H. Boyd, J. D. Burke, D. S. Rae, J. K. Myers, M. Kramer, L. N. Robins, L. K. George, M. Karno and B. Z. Locke. 1988. One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. *Arch Gen Psychiatry*. Nov; 45(11): 977 – 986.

63. Reisberg, B., S. H. de Ferris, and M. J. Leon. 1998. Stage specific behavioral, cognitive, and in vivo changes in community residing subjects with age-associated memory impairment (AAMI) and primary degenerative dementia of the Alzheimer type. *Drug Development Research* 15: 101-114.

64. Reisberg, B., S. H. de Ferris, M. J. Leon and T. Crook. 1982. The global deterioration scale for assessment of primary degenerative dementia. *American Journal of Psychiatry* 139: 1136-1139.

65. Rosen, W. G., R. D. Terry, P. A. Fuld, R. Katzman and A. Peck. 1980. Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol*. 7:486-488.

66. Shore, A. 1997. Promoting Wisdom: The Role of Art Therapy in Geriatric Setting. *Art Therapy Journal of the American Art Therapy Association* 14(3): 172-177.

67. Spaniol, S. 1997. Guest Editorial-Art Therapy with Older Adults: Challenging Myths, Building Competencies. *Art Therapy Journal of the American Art Therapy Association*: 158-160.

68. Stephen, M. S. 2008. *Stahl ' s Essential Psychopharmacology*. Third Edition. Cambridge University Press. New York.

69. Wald, J. 1989. Art Therapy for patients with Alzheimer ' s Disease and Related Disorders. *Advances in Art Therapy*: 204-221.

70. Waller, D. and A. Gilroy. 1994. *Art therapy: a handbook*, Buckingham & Philadelphia: Open University Press.

71. Wadson, H. 1980. *Art psychotherapy*.

72. Wimo A. 2007. An estimate of the total worldwide societal costs of dementia in 2005. *Alzheimers Dement* 3:81-91.

73. Wu A. L. , J. Wang, A. Zheleznyak and E. J. Brown. 1999. Ubiquitin-related proteins regulate interaction of vimentin intermediate filaments with the plasma membrane. *Mol Cell*;4:619-625.

74. Wu, S, A. Mikhailov, H. Kallo-Hosein, K. Hara, K. Yonezawa and J. Avruch. 2002. Characterization of ubiquilin 1, an mTOR-interacting protein. *Biochim Biophys Acta*;1542:41-56.

75. Yang Y.H., S. H. Chen and C. L. Lai. 2009. Concentration of donepezil tp therapeutic response in Alzheimer ' s disease. *International Conference of Alzheimer ' s Disease*, 2-218.

76. Zeiger, B. L. 1976. Life review in art therapy with the aged. *American Journal of art Therapy* 15: 47-50.

77. Zhan, L. 1992. Quality of life: Conceptual and measurement issue. *Journal of Advanced Nursing* 17(7): 795-800.

78. Zlokovic, B. and M. Apuzzo. 1998. Strategies to Circumvent Vascular Barriers of the Central Nervous System. *Neurosurgery* 43, 877-878.