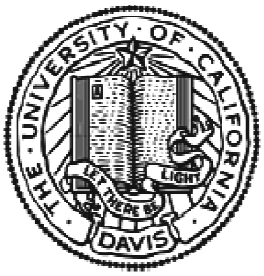
BRAIN VOLUME CHANGES AS PREDICTORS OF FXTAS PROGRESSION

PERUBAHAN VOLUME OTAK SEBAGAI PREDIKTOR PERKEMBANGAN FXTAS



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Thesis

Submitted to fulfill the assignment and fit-out requisite in passing Post-graduate Program Majoring Genetics Counseling Diponegoro University Semarang

Zukhrofi Muzar
22010111400105

Biomedical Science Post Graduate Program
Majoring Genetics Counseling
Diponegoro University Semarang
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THESIS

Brain volume changes as predictors of FXTAS progression

Arranged by

Zukhrofi Muzar

22010111400105

Has been defended in front of the defense committee and has been approved by:

UC Davis MIND Institute, USA **Principal supervisor**	**Diponegoro University, Indonesia** **Principal Supervisor,**
Prof. Randi Hagerman, M.D.	DR. Dr. Tri Indah Winarni, M.Si.Med, PA NIP. 19630128 198902 2 001
Supervisor,	**Supervisor,**
Andrea Schneider, Ph.D.	Prof. Dr. Sultana MH Faradz, Ph.D. NIP. 19520202 197901 2 001

Recognition,
Director of Graduate Programs
Masters in Biomedical Sciences, Diponegoro University

Prof. Dr. dr. Tri Nur Kristina, DMM, M.Kes
NIP. 195905271986032001

DECLARATION

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, and there is no plagiarism as defined by Permendiknas No. 17, 2010. Knowledge obtained by the product of publishing or those not or not yet published, the sources were explained in the writing and reference.

Semarang, February 2014

Zukhrofi Muzar

CURRICULUM VITAE

Name	Zukhrofi Muzar
Date of birth	06-28-1986
Place of Birth	Duri, Riau Province, Indonesia
Email	muzar.zukhrofi@gmail.com
Institution Affiliation	City Health Office, Solok, West Sumatera Province, Indonesia
Current address	Jalan lumba-lumba 130 Duri, Riau province, Indonesia 28884
Nationality	Indonesian

Education and Training

Nov 2012 – Nov 2013	Research fellow in neurodevelopmental disorders including fragile X syndrome and autism at UC Davis MIND Institute as part of master program in Biomedical Science, Diponegoro University, Indonesia
2011-present	Master's Candidate in Biomedical Science, major: Genetic Counseling at Diponegoro University, Indonesia
2008-2010	Medical Doctor, University of North Sumatera (USU), Indonesia
2004-2008	Bachelor of Medicine, University of North Sumatera (USU), Indonesia

Working Experience

2011 – present	General Practitioner (Civil servant) at Public Health Center, Tanjung Paku , Kota Solok, West Sumatera Province, Indonesia
2010 – 2011	General practitioner at Emergency Unit Helvetia General Hospital, Medan, Indonesia General Practitioner at Athika Shiddiq Clinics, Medan, Indonesia Lecturer at Midwifery School Helvetia, Medan, Indonesia General Practitioner at Sumatera Clinics, Binjai, Indonesia

General Practitioner at Budi Medical Centre, Jati Jajar, Depok, Indonesia

Publications

1. **Muzar Z**, Pasha M. The effect of the propolis on the growth of staphylococcus aureus. Abstract: 2nd Annual meeting of pharmacy, pharmacology and medicine, Medan, Indonesia, 2007
2. **Muzar, Z**., Schneider, A., Adams, P., Hagerman, R. Narcotic use in FXTAS. Abstract: 1st international conference on the *FMR1* premutation, Italy, 2013.
3. Schneider, A., **Muzar, Z**., Summers, S., Tassone, F., Seritan, A., Rivera, S., Grigsby, J., Hessl, D., Hagerman, P., Hagerman, R. Female characteristics of fragile X-associated tremor/ataxia syndrome. Abstract: 1st international conference on the *FMR1* premutation, Italy, 2013.
4. Lechpammer, M., Clegg, MS., **Muzar, Z**., Huebner, PA., Jin, LW., Gospe, SM Jr. Pathology of Inherited Manganese Transporter Deficiency (Annals of Neurology, 2014)

Training / Workshop

1. Animal Care and Use 101 at UC Davis, USA 2013
2. Use of Controlled Substances at UC Davis, USA 2013
3. Biological safety and medical waste management at UC Davis, USA 2013
4. Collaborative Institutional Training Initiative at UC Davis, USA 2013
5. 10th Medical Genetic Course: from basic to clinic. Faculty of Medicine Diponegoro University in collaboration with Department of Human Genetics, Radboud University Nijmegen Medical Centre, The Netherlands. Semarang, Indonesia, 2012
6. Workshop on Neurogenetics. Faculty of Medicine Diponegoro University. Semarang, Indonesia, 2012
7. National training on HIV AIDS. The Indonesian Doctor Association, Medan, Indonesia, 2010
8. Airway Management Workshop. 9th National Congress of Indonesia Society of Anesthesiologists, Medan, Indonesia, 2010
9. One Asia Forum. Asean foundation, Kuala Lumpur, Malaysia, 2009
10. Workshop on Youth and Multiculturalism, SEAMEO-SPAFA, Chiang Mai, Thailand, 2008
11. International Training on Disaster Management, World Youth Foundation, Melaka Malaysia, 2008
12. International Workshop Research Exchange, International Federation of Medical Students' Association (IFMSA), Osaka, Japan, 2007
13. PCR and DNA Sequencing. Rajawali Hospital, Bandung, Indonesia, 2006

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CONTENTS

LIST OF ABBREVIATIONS

BET	Brain extraction tool
CCP	Corpus callosum splenium
CNS	Central nervous system
CSF	Cerebrospinal fluid
DTI	Diffusion tensor imaging
FAST	FMRIB's automated segmentation tool
FLAIR	Fluid attenuated inversion recovery
FLIRT	FMRIB's linear image registration tool
FMR1	Fragile X mental retardation 1
FMRIB	Functional magnetic resonance imaging of the brain
FMRP	Fragile X mental retardation protein
FSL	FMRIB's software library
FSL	FMRIB software library
FXTAS	Fragile X associated tremor/ataxia syndrome
GMV	Grey matter volume (total)
HC	Healthy Control
MCP	Middle cerebellar peduncles
MNI152	Montreal Neurological Institute 152
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
PGMV	Peripheral grey matter volume (cortical)
PolyQ	Polyglutamine
RNA-BP	RNA binding protein
SD	Standard Deviation
SIENA	Structural image evaluation, using normalization, of atrophy
UTR	Untranslated region
VCSFV	Ventricular cerebrospinal fluid
WBV	Whole brain volume
WMH	White matter hyperintensities
WMV	White matter volume

GLOSSARY

1.	FXTAS	Fragile X-associated tremor/ataxia syndrome (FXTAS); a neurodegenerative disorder associated with the premutation in the *FMR1* gene
2.	Fragile X premutation	CGG repeat length of 55 to 200 in the *FMR1* gene
3.	Grey matter	A major component of the central nervous system, consisting of neuronal cell bodies, neuropil (dendrites and myelinated as well as unmyelinated axons), glial cells (astroglia and oligodendrocytes) and capillaries; total grey matter in the brain
4.	Head coil	A special device that is placed around the person's head to help produce very detailed pictures of the brain
5.	Peripheral grey matter	Grey matter in cortex
6.	SIENAX	A package for estimation of whole brain volume (WBV), white matter volume (WMV), peripheral grey matter volume (PGMV), grey matter volume (GMV), and ventricular cerebrospinal fluid volume (VCSFV), normalized for subject head size
7.	Ventricular Cerebrospinal fluid	Cerebrospinal fluid in the ventricles of the brain
8.	White matter	Nerve fibers in the brain consists mostly of glial cells and myelinated axons that transmit signals from one region of the cerebrum to another and between the cerebrum and lower brain centers
9.	Whole brain	Total brain tissue

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ABSTRACT

Background: Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that has a pathological effect on the brain. Hypothesis of the study is that the neuronal dysregulation leading to neuronal loss and white matter hyperintensity (WMH) in FXTAS may cause brain volume changes, and may be used as a measure of disease progression in FXTAS.

Methods: Brain volume changes in FXTAS were analyzed longitudinally on two separate time points using SIENAX (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA). This study included 21 patients with FXTAS (mean age: 67.1y; SD = 6.2; 15 males and 6 females) with two MRI scans following initial diagnosis of FXTAS. The average interval between measurements was 2.2 years (SD = 1.2) with an interval range of 0.7-5 years. The patients were ascertained from families with and without a fragile X syndrome proband at the University of California at Davis Medical Center. Healthy control subjects (mean age: 70.9y SD = 6.7; 15 males and 9 females) were matched by age and gender to patients with FXTAS at their time 2 measurements, but the controls were assessed only once.

Results: Both annualized WBV and VCSFV change are predictors of occurrence of higher FXTAS stage. PGMV, GMV, WBV and VCSFV in the FXTAS subjects at time 2 were statistically different from healthy controls. The mean rates of WBV and VCSFV change in individuals with FXTAS were -1.5%/year and 3.05%/year respectively. There were no correlations of annualized VCSFV change and WBV change with both *FMR1* CGG repeat size and *FMR1* mRNA levels.

Conclusion: The results of our study revealed the importance of WBV and VCSFV measurements in the progression of FXTAS. Further study is needed to evaluate the rate of brain volume change with age in FXTAS and to investigate its benefit for making prognoses, monitoring disease progression, and determining the effectiveness of therapeutic treatment of FXTAS.

Keywords: FXTAS, fragile X premutation, longitudinal MRI, brain volume, White Matter Volume, Grey Matter Volume, Ventricular Cerebrospinal Fluid Volume

ABSTRAK

Latar belakang: *Fragile X-associated tremor/ataxia syndrome* (FXTAS) adalah penyakit neurodegeneratif dengan efek patologis pada otak. Hipotesis dari studi ini adalah disregulasi saraf yang menyebabkan hilangnya neuron dan bertambahnya hiperintensitas *white matter* di FXTAS dapat menyebabkan perubahan volume otak, sehingga mungkin dapat digunakan sebagai ukuran perkembangan penyakit pada FXTAS.

Metode: Perubahan volume otak pada FXTAS dianalisis secara longitudinal pada dua titik waktu yang terpisah dengan menggunakan SIENAX (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA). Penelitian ini melibatkan 21 pasien dengan FXTAS (rerata usia: 67,1 tahun SD = 6.2; 15 laki-laki dan 6 perempuan) yang memiliki 2 MRI otak setelah diagnosis FXTAS. Rerata interval antara pengukuran adalah 2,2 tahun (SD = 1.2) dengan *range* 0,7-5 tahun. Pasien diambil dari keluarga dengan dan tanpa *fragile X syndrome* di *University of California Davis Medical Center*. Subyek kontrol sehat (rerata umur: 70,9 tahun; SD = 6.7; 15 laki-laki dan 9 perempuan) dicocokkan sesuai dengan usia, jenis kelamin dengan subjek FXTAS pada pengukuran kedua, tetapi kontrol hanya dievaluasi satu kali.

Hasil: Perubahan WBV dan VCSFV tahunan adalah prediktor kejadian FXTAS stadium tinggi. PGMV, GMV, WBV dan VCSFV pada subjek FXTAS waktu ke dua berbeda signifikan secara statistik dibandingkan subjek kontrol. Rerata perubahan WBV dan VCSFV pada FXTAS masing masing adalah -1.5%/tahun dan 3.05%/tahun. Tidak ada hubungan antara perubahan WBV dan VCSFV dengan *FMR1* CGG *repeats* dan *FMR1* mRNA.

Kesimpulan: Penelitian ini membuktikan pentingnya pengukuran WBV dan VCSFV dalam perkembangan penyakit FXTAS. Penelitian lanjutan dibutuhkan untuk mengevaluasi tingkat perubahan volume otak sesuai dengan bertambahnya umur pada FXTAS dan untuk menginvestigasi keuntungannya dalam membuat prognosis, pengawasan perkembangan penyakit, dan menentukan terapi efektif untuk FXTAS.

Keywords: FXTAS, *fragile X premutation, longitudinal MRI, brain volume, White Matter Volume, Grey Matter Volume, Ventricular Cerebrospinal Fluid Volume*