Dilemma of Presymptomatic Testing in Children with History of Late Onset Neurodegenerative Spinocerebellar Ataxia in Indonesia

by Nydia Rena Benita Sihombing

Submission date: 31-Jul-2024 04:03PM (UTC+0700)
Submission ID: 2422612857
File name: SCA_JBTR.pdf (396.53K)
Word count: 3610
Character count: 20001

Indexed by : DOAJ Google Crossref Dimension sinta GARUDA

J.Biomed.Transl.Res
ISSN: 2503-2178

JOURNAL OF BIOMEDICINE AND TRANSLATIONAL RESEARCH

Available online at JBTR website: https://jbtr.fk.undip.ac.id

Case Report

Dilemma of Presymptomatic Testing in Children with History of Late Onset Neurodegenerative Spinocerebellar Ataxia in Indonesia

Nydia Rena Benita Sihombing[1], Tri Indah Winarni[1], Maria Belladonna[2], Annastasia Ediati[3], Sultana MH Faradz[1,4*]

[1]*Center for Biomedical Research (CEBIOR), Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia*
[2]*Department of Neurology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia*
[3]*Faculty of Psychology, Universitas Diponegoro, Semarang, Indonesia*
[4]*Diponegoro National Hospital, Semarang, Indonesia*

Article Info
History
Received: 03 Dec 2021
Accepted: 20 Mar 2022
Available: 28 Apr 2022

Abstract

Background: Spinocerebellar ataxia (SCA) is a late onset neurodegenerative disorder in which coordination and balance are affected. Although many international guidelines have been established regarding presymptomatic testing, it is still a grey area in Indonesia. We report two large families with advanced stages of SCA who underwent presymptomatic genetic testing in children along counseling process.

Case presentation: Thorough examination was performed, including pedigree construction, physical and neurological examination, gene mutation analyses for patients, and presymptomatic testing for family members, including children. SCA3/*MJD1* gene mutation analysis was done in both cases, and a full penetrance CAG repeat expansion was found in both affected patients. Two different outcomes were observed in the offspring, who were both children. The risk and consequences of positive results had been explained in a counseling session to family members, who decided to keep the information until the child would have reached legally adult age of 18.

Conclusions: In developing countries such as Indonesia, problems arose due to ethical issues, knowledge of genetic diseases, and inaccessible molecular diagnostics. Culture, religion and tribe diversities may create additional challenges. These cases emphasize the need for careful consideration of presymptomatic testing in children, especially in complicated situations where psychological and ethical issues should be addressed.

Keywords: *Case Report; Genetic Counseling; Presymptomatic Testing; Spinocerebellar Ataxia; Indonesia*
Permalink/ DOI: https://doi.org/10.14710/jbtr.v8i1.13032

INTRODUCTION

Spinocerebellar ataxia (SCA) is a late onset neurodegenerative autosomal dominant disorder in which the cerebellum progressively degenerates; it is accompanied by degenerative changes in brainstem, oculomotor system, pyramidal and extrapyramidal pathways, lower motor neurons, and peripheral nerves. The main clinical phenotype is a progressive ataxia in young-adult to mid-adult years with vestibular and speech difficulties. More than 30 types of spinocerebellar ataxia with heterogeneous clinical features are known.[1–3] Spinocerebellar ataxia type 3 (SCA3) or Machado-Joseph disease (MJD) is the most prevalent SCA form, comprising more than 20% of the SCA cases in USA and more than 50% in other countries. The most prevalent genetic change is a CAG repeat expansion on ataxin 3 (*ATXN3*) gene, also known as *MJD1* gene on chromosome 14q32, followed by non-protein coding repeat expansion, and conventional mutations (e.g. missense, deletion, insertion, duplication).[4,5]

* Corresponding author:
E-mail: *sultanafaradz@gmail.com*
(Sultana MH Faradz)

Nowadays, the availability of molecular genetic testing enables diagnostic accuracy and adequate genetic counseling. Therefore, pre- and posttest genetic counseling should be provided in all cases of presymptomatic testing of SCA.[6] There are some consensus and recommendations from health profession associations in developed countries regarding testing of affected individuals and presymptomatic testing, both in adults and children/minors.[7] According to the guidelines, presymptomatic diagnosis should not be performed in children unless there is a clear benefit for them, such as availability of effective intervention.[8] Testing of children for an adult onset, untreatable neurodegenerative disorder like SCA was considered a breach of the child's autonomy and its right of having an open future and therefore unethical. However, in Indonesia, there is no consensus or recommendations regarding genetic testing in general, neither regarding presymptomatic testing. Two large families with SCA3 are presented, in which the complexity regarding presymptomatic genetic testing in children is described. To the best of our knowledge, this is the first case series of SCA presymptomatic testing in Indonesian children.

CASE REPORTS

Case 1

A 35-year-old wheelchair-bound man came to our hospital with balance and movement problems. The symptoms occurred since he was 27 years old, and at the age of 30, he experienced stiffness in his hands and feet, as well as dysarthria. A magnetic resonance imaging (MRI) showed severe cerebellar atrophy. Aside of his symptoms, he came for a consultation because he was aware of a possible inherited disorder, since 3 of his brothers were also affected of whom 2 already passed away, and his father died too due to the same condition, as shown in figure 1. Based upon history, family pedigree, physical examination and the MRI, the provisional diagnosis was autosomal dominant SCA. The patient [III.14] wished to have genetic testing for himself, as well as presymptomatic testing for both of his children, who were 11 [IV.11] and 8 years [IV.12] old. Informed consent was obtained from the patient.

Genetic and presymptomatic tests were done in a Dutch licensed DNA diagnostic laboratory under the parents' request. However, the results were suspended because testing of children for adult-onset disease was considered unethical. Eventually, the results were shared after members of Indonesian national and local ethical committees, taking into account the Indonesian legal and cultural context where parents have the right to decide for their children's wellbeing until they reach adulthood,[9] gave the green light. The results revealed an expanded CAG repeat in one allele (73 repeats) of the *ATXN3* gene in III.14, and normal CAG repeat expansion for both children.

Case 2

A 44-year-old wheelchair-bound female with ataxia, dysarthria, and dysphagia, came to our hospital for genetic consultation. She was referred by a neurologist with no definitive diagnosis except ataxia. Clinical manifestations of a neurological disorder began at the age of 27 years. At first, she often suffered from vertigo and imbalance disturbances. Three years later, motor impairment started to develop. She often fell unintentionally, and she had difficulties in swallowing food. At the age of 39, she became wheelchair-bound. The family history indicated that the patient [III.13] had an older brother [III.11, 34 years] and younger brother [III.14, 36 years] who suffered from a similar neurological disorder. Her 62-years old paternal aunt [II.8] also had a less progressive neurological disorder, since she had been wheelchair-bound since the age of 60 and with later age of onset. Based on pedigree (see Fig. 2), the mode of inheritance is autosomal dominant, therefore it was suggestive of SCA.

During her visit, the most notable symptom was dysarthria. Neurological examination showed multiple cranial nerves palsy (VII, IX, X, and XII). Visual acuity was >1/60. She also showed right eye tic, lower limb spastic paraplegia, atrophy in upper and lower limbs, numbness in lower limb, and bowel-bladder incontinence. Non-contrast brain CT scan revealed cerebellar atrophy. Based on the history, physical examination and additional workup, patient was diagnosed with SCA, with the differential diagnosis of familial spastic paraplegia. During counseling session, further genetic work up was proposed. Informed consent was obtained from patient and family.

Genetic counseling was provided for the patient and her younger brother, III.14 and his wife, III.15. The patient requested her daughter not to be included during the pretest counseling session. Risk for offspring to carry the mutation and become affected in the future, as well as ethical considerations of testing minors (age < 18 years old) were explained. After hearing and understanding about her probable cause of disease, the patient and her younger brother insisted to do genetic testing for the patient, her 15 years-old daughters [IV.9], 12 years-old nephew [IV.10], and 10 years-old niece [IV.11]) who had not yet attained the legal age of 18 years for consent. Taking prior experience in Case 1 into consideration and parent request, we agreed to do the testing. Informed consent to test the children was obtained from both the mother and her younger brother.

Genetic analyses were performed in a commercial laboratory which revealed a CAG repeat expansion of the *MJD1* gene in the patient (28/76 repeats alleles, as shown in figure 3), confirming the diagnosis of SCA type 3 (SCA3). Her daughter also had a CAG repeat expansion (27/77 repeats alleles), while her nephew and niece had normal alleles (20/22 repeats alleles in both).

Due to their divorce, the patient's husband was absent during the pretest genetic counseling and played no further role. Unfortunately, before the results came back, the patient died leaving her daughter (IV-9) an orphan. Posttest genetic counseling was performed for the couple III.14 and III.15. The consequences of positive results were explained to her uncle (III-14) who became her guardian. Considering her condition who was still in high school, we decided to keep the information until she has turned 18 and ready to have consultation to disclose the laboratory results.

DISCUSSION

Decision making in presymptomatic testing

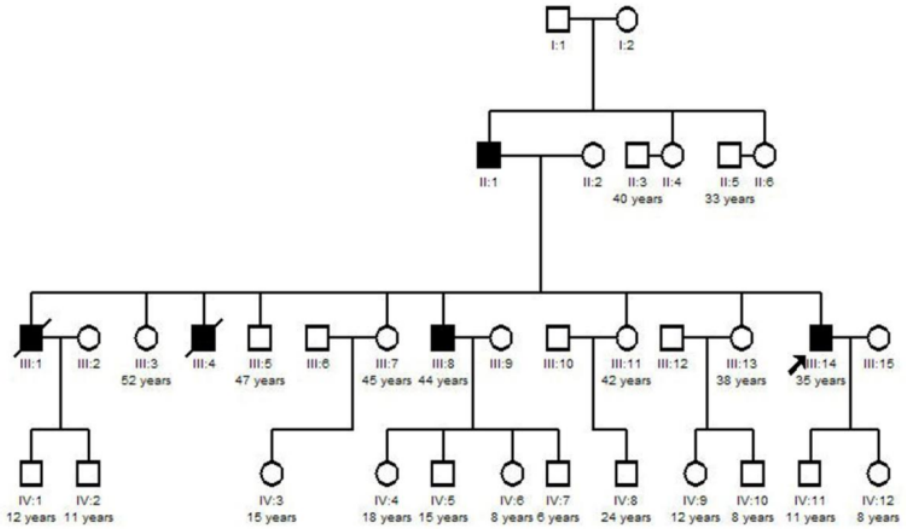

Figure 1 Pedigree of case 1. Index case (III.14, black arrow) with SCA3, where two of the older brothers have deceased and one brother [III.8] has similar condition.

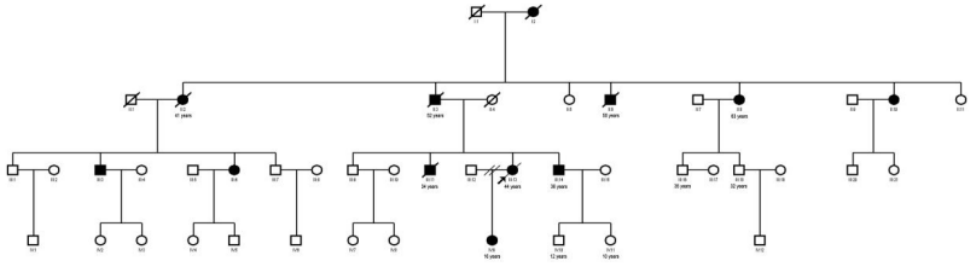

Figure 2 Pedigree of case 2. Index case (III.13, black arrow) with SCA3, with older brother already deceased and younger brother suffered from similar condition. Individuals IV.9, IV.10, and IV.11 underwent genetic testing together with index case.

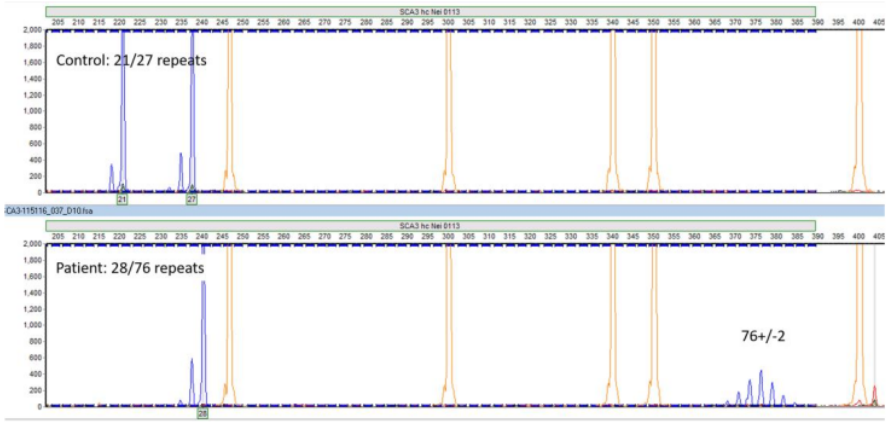

Figure 3 CAG repeat analysis of patient [III.13] of case 2 showed one expanded allele (76 repeats) and one normal allele (28 repeats) (second row), compared to control (first row).

In case 1, presymptomatic testing for both children showed negative results. There was no further implication following the posttest counseling, due to the gene-negative results. The negative results decreased parents' uncertainty and anxiety about the future of their children. This is one of the arguments beside others, such

as positive effect on the family, ability on planning for the future, and promoting the individual autonomy, supporting presymptomatic testing for late-onset diseases in children.[8] Other documented benefits were described, such as reduced worry and situational distress after negative results, and being able to plan for future education and employment.[10]

In case 2, an allele with 77 CAG repeats showed that the daughter will be affected with the same condition at later age. This daughter, who was below 18 years old, has no information about the purpose of testing, and subsequently has not given any consent nor assent regarding genetic testing. When the results were received, the uncle III.14 was guardian of the daughter and he will withhold the information until she will reach adulthood.

In our families, the decision to have presymptomatic testing in minors was made due to anxiety and curiosity of affected parents and other family members who wanted to know their children's condition before they died. Consequently, parent's psychological aspects outweighed the interests of their children. From the cultural point of view, Indonesia has a large power distance, where children are obedient towards parents' decisions, and low individualism dimensions, implying the parents' significant role in decision making for their children.[11]

In most countries, decision making in relation with ethical issues can be discussed in a clinical ethic committee. In Indonesia however, although a committee on medical ethics (Honorary Board of Medical Ethics/*Majelis Kehormatan Etika Kedokteran*) exists, there is no recommendation adapted from international guidelines regarding presymptomatic genetic testing. In general, informed consent and approval of medical procedures, including preventive, diagnostic and therapeutic intervention are regulated in The Ministry of Health Regulation No. 290 Year 2008. On article 12, informed consent should be made by a competent patient or the guardian. A competent patient is described as adult, aged 21 years and above or have been married. On article 14, there is further explanation regarding parents or guardians who have rights to give informed consent on a medical procedure for their child, for their best interest.[12] Thus, it is implied that the parents are the main decision maker on the children's behalf for approving medical procedure.

Disclosing the genetic test results is one of the most important issues to be addressed in these families. Although children's rights to obtain and search for information are guaranteed by Indonesian government through Law No. 23 Year 2002 on the Child Protection,[13] parents are generally allowed to make a medical judgement for their children, except parents who have lost their custody, and therefore they have the right to decide to have their children below the age of 18 years being tested for a condition.[9] Testing children may interfere with the child's autonomy for making an informed decision as an adult in the future.[14] Thus, parents and family members should also consider that children do not want to know the genetic test results, and if so respect their decision. Adolescents have unique perceptions on dealing with genetic testing; most of them experience more burden of knowing that they would develop a genetic condition and would rather remain uncertain. However, another study showed that adolescents with affected family members who pursued predictive testing sensed more relief upon receiving results, compared to experiences before testing, possibly due to previous participation in dealing with relatives with adult-onset disorders.[15] These findings need to be taken into account when preparing to share information on future genetic counseling.

It is also important to consider psychosocial aspects that play a role in disclosing genetic information. Going through the presymptomatic testing procedure and obtaining positive results may have negative consequences for children, and may increase the risk of mental health problems, such as depression, anxiety, or even thoughts of suicide, including discrimination in the society, disturbed interpersonal relationship, difficulties in finding a marriage partner, changing family planning perspectives, or being ineligible for insurance.[16] In Indonesia, genetic diseases are not covered by the National Health Insurance (*Jaminan Kesehatan Nasional*/JKN) plan. Furthermore, majority of private insurances are unable to fully cover individuals with chronic, debilitating disease.

In Indonesia, living with a rare disease like SCA, unknown to most people, one might encounter mistaken beliefs that such a rare disease is a curse. In most cases in the Indonesian setting, fatalistic beliefs help affected individuals and the family to accept their condition by considering their disease as a fate (*'takdir'*) given by God. Through all this, family members may support affected individuals to facilitate disease acceptance and cope with it.

Thus, disclosing information to an affected individual should be handled carefully. It is common that initially the affected child shows various reactions of denial. However, we should provide psychological support to child and the family to foster the child's acceptance of its SCA. It is important to help families with communication problems related to a genetic disease in the family so that the family can play its role as the supportive environment for the affected child.

Role of genetic testing and counseling in complex disorder settings

Genetic counselors play significant roles in encouraging communication about genetic disorders between parents and offspring. Genetic counseling and consultation in Indonesia have become available for almost two decades, provided by general practitioners and specialists.[17] However, the number of genetic counselors in Indonesia is still very small, and many clinicians are not aware of the availability and capacity of genetic counselors, making it underutilized. It is important to employ genetic counselors as a platform for transferring information from clinicians to families, thereby serving everyone's best interests. In fact, children, parents, and family members may have different concepts of what entails best interest. Therefore, genetic counselors as part of healthcare providers have a responsibility to communicate, mediate, and serve children's best interests.[18]

In case 2, the adolescent daughter was not involved in pretest counseling as requested by the affected mother, nor did she consent or assent to be tested. She was found to have a CAG repeat expansion of the *MJD* gene. Consequently, she was denied to execute her right to know or not to know her genetic status. However, since she has started inquiring the results of her test, genetic counseling should be provided as soon as she reaches the age of 18 years in the presence of her guardian and maybe other relatives. In order to give her the opportunity to still execute her right to know or not to know this genetic counseling should have the content of a pretest counseling. Preferably nothing will be decided during this session and she will be allowed some time to come to a decision. When she decides to know the result, this will be disclosed to her in a real posttest counseling. A follow-up by a psychologist and/or social worker will be initiated. In case she decides not or not yet to know the test result, that decision will of course be respected by both the counselors and her guardian and other relatives. A follow-up genetic counseling after some time will be offered to her. Whether a pre-marriage or preconception genetic counseling should be offered more actively, is a matter of debate. Careful consideration should be made, based on the child's maturity, to involve her in the counseling session together with its parents/guardians.

CONCLUSION

We presented two families with multiple affected cases of SCA type 3 along with dilemmas on diagnosis and presymptomatic testing in children. We have faced dilemmas in carrying out genetic testing of patients with late onset genetic diseases due to unavailability of local and national ethical recommendations, less awareness of health care providers, lack of laboratory facilities and underutilized genetic counselors in a developing country. Collaboration between healthcare professionals is important for achieving patient's and family members' best interests. Various cultural and psychosocial aspects should be considered when dealing with similar complicated cases in the future. Additionally, ethical recommendation regarding genetic testing is warranted.

ACKNOWLEDGEMENTS

We would like to thank Nurin Aisyiyah Listyasari, MD for her involvement in the patients' examination, and the families for their participation. We thank Prof. em. Ben CJ Hamel, MD, for his valuable input on the manuscript.

REFERENCES

1. Rossi M, Perez-Lloret S, Doldan L, Cerquetti D, Balej J, Millar Vernetti P, et al. Autosomal dominant cerebellar ataxias: A systematic review of clinical features. Eur J Neurol. 2014;21(4):607–15.
2. Kim JS, Cho JW. Hereditary Cerebellar Ataxias: A Korean Perspective. J Mov Disord [Internet]. 2015;8(2):67–75. Available from: http://e-jmd.org/journal/view.php?doi=10.14802/jmd.15006
3. Jayadev S, Bird TD. Hereditary ataxias: overview. Genet Med [Internet]. 2013;15(9):673–83. Available from: http://www.nature.com/doifinder/10.1038/gim.2013.28
4. Paulson HL. The Spinocerebellar Ataxias. J Neuroophthalmol. 2009;29(3):227–37.
5. Paulson H. Machado-Joseph Disease/Spinocerebellar Ataxia Type 3. Handb Clin Neurol. 2012;103:437–49.
6. Orozco-Gutierrez MH, Cervantes-Aragon I, Garcia-Cruz D. Ethical considerations in presymptomatic diagnosis of autosomal dominant spinocerebellar ataxias. Neurologia [Internet]. 2015; Available from: http://dx.doi.org/10.1016/j.nrleng.2015.06.018
7. Sequeiros J, Martindale J, Seneca S. EMQN Best Practice Guidelines for molecular genetic testing of SCAs. Eur J Hum Genet. 2010;18(11):1173–6.
8. Mand C, Gillam L, Delatycki MB, Duncan RE. Predictive genetic testing in minors for late-onset conditions: A chronological and analytical review of the ethical arguments. J Med Ethics. 2012;38(9):519–24.
9. The Indonesian Ministry of Law and Human Rights. Law of The Republic of Indonesia Number 1 of 1974 on Marriage. 1974. p. 16.
10. Wakefield CE, Hanlon L V., Tucker KM, Patenaude AF, Signorelli C, McLoone JK, et al. The psychological impact of genetic information on children: A systematic review [Internet]. Vol. 18, Genetics in Medicine. Nature Publishing Group; 2016 [cited 2020 Sep 17]. p. 755–62. Available from: https://www.nature.com/articles/gim2015181
11. Hofstede G, Hofstede GJ, Minkov M. Cultures and Organizations: Software of The Mind Intercultural Cooperation and its Importance for Survival. Third edit. The McGraw-Hill Companies; 2010. 103–107 p.
12. Ministry of Health Republic Indonesia. Ministry of Health of Indonesia Regulation Number 290 Year 2008 on Medical Consent. 2008.
13. The Indonesian Ministry of Law and Human Rights. Law of The Republic of Indonesia Number 23 of 2002 on Protection of Children. 2002.
14. Borry P, Shabani M, Howard HC. Is There a Right Time to Know? The Right Not to Know and Genetic Testing in Children. J Law, Med Ethics. 2014;42(1):19–27.
15. Mand C, Gillam L, Duncan RE, Delatycki MB. "It was the missing piece": Adolescent experiences of predictive genetic testing for adult-onset conditions. Genet Med. 2013;15(8):643–9.
16. Lim Q, McGill BC, Quinn VF, Tucker KM, Mizrahi D, Farkas Patenaude A, et al. Parents' Attitudes toward Genetic Testing of Children for Health Conditions: A Systematic Review. Clin Genet. 2017
17. Laurino MY, Leppig KA, Abad PJ, Cham B, Chu YWY, Kejriwal S, et al. A Report on Ten Asia Pacific Countries on Current Status and Future Directions of the Genetic Counseling Profession: The Establishment of the Professional Society of Genetic Counselors in Asia. J Genet Couns. 2018;27(1):21–32.

18. Borry P, Stultiens L, Nys H, Cassiman JJ, Dierickx K. Presymptomatic and predictive genetic testing in minors: A systematic review of guidelines and position papers. Clin Genet. 2006;70(5):374–81.

Dilemma of Presymptomatic Testing in Children with History of Late Onset Neurodegenerative Spinocerebellar Ataxia in Indonesia

ORIGINALITY REPORT

5%	4%	4%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	onlinelibrary.wiley.com Internet Source	1%
2	Submitted to Universiti Teknologi Malaysia Student Paper	1%
3	"Inherited Neurological Disorders", Springer Science and Business Media LLC, 2017 Publication	1%
4	Achmad Zulfa Juniarto, Mahayu Dewi Ariani, Stefani Harumsari, Nurin Aisyiyah Listyasari et al. "The use of high-resolution melting techniques for mutation screening of diseases caused by trinucleotide repeats expansion, with emphasis on the *AR* gene", Medical Journal of Indonesia, 2019 Publication	1%
5	Henry Paulson. "Machado–Joseph disease/spinocerebellar ataxia type 3", 'Elsevier BV', 2011 Internet Source	1%

6	kepakaran.apps.undip.ac.id Internet Source	1%
7	www.indianjcancer.com Internet Source	1%

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		

Dilemma of Presymptomatic Testing in Children with History of Late Onset Neurodegenerative Spinocerebellar Ataxia in Indonesia

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6