Title: Vision Response to Dopamine Replacement

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The purpose of the study is to evaluate and document physiologic and functional changes in visual performance of patients diagnosed with albinism (a dopamine deficiency state) following a trial of oral Levodopa/carbidopa treatment.

Background:

One person in 17,000 in the U.S.A. has some type of albinism. Albinism affects people from all races. Albinism always affects vision. The degree of vision impairment varies with the different types of albinism. Additionally, because it is present at birth, albinism contributes to bilateral organic amblyopia in the affected individual, which will lead to additional irreversible visual handicap if not treated before 7 years of age.[1]

There is presently no treatment that can replace the lack of melanin or treat the deficiency that causes the symptoms of albinism. We can only treat the eye problems that often accompany the diagnosis. Glasses or corrective lenses and low vision aids can improve vision but usually cannot correct vision to 20/20. For reading, children with albinism may need materials with large print text, depending on the severity of their vision problems. There is no treatment for involuntary eye movements (nystagmus) or the sensory deficits associated with albinism.

Oculocutaneous albinism results from autosomal recessive inheritance. In *tyrosinase-negative albinism* --OCA1 (the most common type), melanosomes don't contain melanin because they lack tyrosinase[1-2], the enzyme that stimulates melanin production. These patients also tend to have the worst visual prognosis. The production of melanin, at the cellular level, requires the biochemical conversion of tyrosine to eumelanin or pheomelanin. The first step in this biochemical pathway is the conversion of tyrosine to dopamine by the tyrosinase enzyme.

Recently, work in several areas of dopamine deficient states (Parkinson disease, cocaine withdrawal disorder, Phenylketomuria) has shown that retinal tissue is one of the richest in the concentration of dopamine. Indeed, 15 different visual functions and 13 types of dopamine retinal pathologies have been attributed in some way to the retinal dopamine system[3]. The extent to which the absence of dopamine in the retina of patients with albinism affects their visual function is unknown.

Levodopa/carbidopa replacement therapy has been used and studied in children with amblyopia since 1992[4]. This therapy has been shown to be safe and effective in the treatment of children with amblyopia at dosages of up to 3mg/kg/day body weight[7]. Standard treatment in children with Dopa responsive dystonia (DRD) is 10mg/kg/day.[17] Levodopa/carbidopa has also been studied as a treatment in children with retinal disease[5] and shown to have a beneficial effect, however none of the patients in this report carried the diagnosis of albinism.

The use of Levodopa/Carbidopa has been approved by the FDA for

treatment of Parkinson's disease. As such, it was not specifically tested in patients less than 18 years of age. Subsequently, it has been shown to be a safe and effective treatment in multiple studies as an off-label use for the treatment of amblyopia in children under 10 years old without adverse effect[3-8]. It also has been used by pediatric neurology for treatment of children with dystonia. Parkinson's disease typically requires increasing doses of Levodopa/carbidopa over many years, and eventually side effects occur. In contrast, children with Dopa-responsive dystonia often have complete resolution of symptoms on very low doses of Levodopa/carbidopa, with no need to increase the dose over time. Exceptions to this have been reported.[16]

Study Objectives:

Prior studies in children with Levodopa/carbidopa, have proposed that the improvement in visual acuity is related to a change in the neural network of the striate cortex (amblyopia treatment)[3-8]. In this study we propose that the retina itself in albinism is deficient in dopamine, and vision improvement will occur as a result of improved retinal function in response to the deficient neurotransmitter dopamine. This study has a pretest-post-test design in order to determine if improvement in vision is in response to replacement of deficiency (dopamine). The OCT will be a critical determinant to confirm vision improvement as a result of improved retinal function, but are not primary outcome data. Additionally, patients with albinism have been shown to have impaired color vision and contrast sensitivity, it is unclear if these visual functions will be affected by treatment, therefore data will be analyzed to determine if there is a treatment effect other than on visual acuity alone.

Main outcome measures will be collected at pre-treatment, 1 month, 3 months, and 4 months. Change in visual acuity as measured in logMAR by Snellen or SVEP after 3 months of treatment is the primary outcome.

Additional outcome measures will be collected at pre-treatment and 3 months, and will include color vision (Farnsworth 15 or 100 hue), contrast sensitivity, optical coherence tomography (OCT), and color photography.

Because of the issues of possible permanent vision loss due to amblyopia as mentioned above, it is important that the effect be studied in children under age 7, in whom the irreversible effect of amblyopia has not occurred. Additionally however, children under 3 years of age are generally not able to subjectively participate in some of the testing proposed in this study, therefore the lower age limit will be included to provide patients who will be able to complete the testing. Finally, older patients with albinism may still appreciate an improvement in vision function from replacement therapy, despite the fact that there may be a ceiling on the improvement in vision because of the pre-existing amblyopia. Older children and adults will be included to allow for optimum assessment of vision recovery at all ages and for ability to satisfactorily recruit the number of patients necessary. Further studies will need to be designed to study the effects in younger children, and to isolate the vision effect (if found) based on the amblyopia factor.

In use in children this medication is available in liquid form and will be

prepared and dispensed by the UW/AFCH for subjects who are unable to swallow pills or take solid medications.

Patients will undergo a 3-month treatment period followed by a 1-month follow-up period. Visit length and testing is typical for an initial evaluation/consultation in the pediatric ophthalmology clinic. All testing is performed in the pediatric ophthalmology clinics by staff experienced and trained in visual testing of the pediatric population. The PI has 15 years of clinical experience in pediatric ophthalmology alone and is fellowship trained in pediatric ophthalmology, it is well within the ability of most all patients to perform these test within one setting except where noted based on age. In some cases it is expected that tests other than the primary outcome data may not be obtainable in all patients. Patients will be removed from the study if they cannot complete the primary outcome (visual acuity) testing. Other vision testing (color testing, SVEP, Contrast, photography, and OCT) will be requested, but not required to participate in the study. Please see schedule of visits below for detail.

Research Design:

Patients with Oculocutaneous albinism will be recruited ages 3 and up, weight greater than 25 pounds. Entrance into the study is dependent upon clinical evidence of decreased or absent pigmentation in skin, hair, and eyes. No ocular only albinos will be recruited. Additionally, all patients enrolled in the study will be requested but not required to undergo genotyping (TYR and OCA2 gene) of their form of albinism, if not already known. These two types of albinism are the most common, and, for most clinical observers – indistinguishable. However, the presence or absence of TYR theoretically has a direct impact on expected visual response to dopamine replacement. The genotypic form of albinism has no known implications for other aspects of health, clinical care, overall health prognosis or insurability. Indeed, because the genotype has no influence on diagnosis or treatment, it is expected that less than one in ten patients recruited will have been previously tested. Testing will be performed by a certified national clinical lab with validated testing. No “out of pocket” expense for this test will be incurred by the family of the patient. Costs for testing will be covered by funding from the UW Department of Ophthalmology.

Exclusion criteria include children under 3 or less than 25 pounds, or ocular pathology not attributable to albinism. Additionally, patients taking nonselective monoamine oxidase (MAO) inhibitors, a self-reported history of depression, neurologic disease, a history of myocardial infarction, peptic ulcer or who are pregnant or nursing will be excluded. All females that are old enough to have had a menstrual cycle will require a negative urine pregnancy test. For minor females that are old enough to have had a menstrual cycle, the subject will be informed of the requirement for pregnancy testing, given an opportunity to discuss the study requirements with the study team privately, and given the opportunity to decline participating in the study without giving a reason.

None of the standard treatments, spectacles, surgery, and occlusion

therapy or vision aides will be withheld during this study.

Subject identification and recruitment

Initial contact about the study will be made via letter or in-person by the PI and/or Co-Investigator during a routine clinic visit. Physicians not directly involved in the study can refer patients to the PI and/or Co-Investigator for potential inclusion into the study. Additionally, potential subjects or guardians of subjects can reach out to the PI or study coordinator if they become aware of the trial through one of the recruitment sources (documents or clinicaltrials.gov).

Potential subjects (those with a diagnosis of albinism in the UWHC medical record database) were mailed a letter signed by the Principal Investigator inviting them to join the study. These letters were addressed to the subjects if they were of consenting age or to the parents/guardians if the subject was a minor. The letter asked the subject (if adult) or the guardian (if a minor) to respond to the invitation. That person was asked to call the study coordinator and complete a telephone screening questionnaire, if interested. If the subject was found to be eligible for the study and was willing, a screening visit was scheduled. At the screening visit, the full consent form and assent form (if applicable) was discussed before any study procedures were initiated. If there was not a response from the potential subject or guardian within 30 days, the study coordinator tried to contact the potential subject or guardian. Two attempts were made to contact the subject or guardian. This recruitment method has been completed.

Other recruitment methods that were approved for #2012-0023 but will not be used under this replacement protocol:

- Recruitment documents for placement in the monthly School of Medicine & Public Health Brief email, in National Organization for Albinism and Hypopigmentation newsletters, and possible publication by the Associated Press.
- A video about study was recorded by Dr. Struck for use on the Department of Ophthalmology & Visual Sciences website here at the University of Wisconsin-Madison.

Recruitment methods for the replacement study include listing this study on the clinicaltrials.gov website. Potential subjects can search this website anytime for possible studies related to their condition. Potential subjects or parent/guardians of potential subjects can contact the study team to inquire about the study. Initial contact has to be made from the potential subject or subject's parent or guardian. If oral consent is given, the telephone screening questionnaire will be completed. If the subject is found to be eligible for the study and is willing, a screening visit will be scheduled. At the screening visit, the full consent form and assent form (if applicable) will be discussed before any study procedures are initiated.

Currently, this study is also listed on the Department of Ophthalmology and Visual Sciences website. A brief description of the study along with the inclusion/exclusion criteria are listed. The PI and study coordinator are listed along with the telephone number of the coordinator. The general public could look at this website and see this clinical trial listing and reach out to us as well. Initial contact has to be made from the potential subject or subject's parent or guardian. If oral consent is given, the telephone screening questionnaire will be completed. If the subject is found to be eligible for the study and is willing, a screening visit will be scheduled. At the screening visit, the full consent form and assent form (if applicable) will be discussed before any study procedures are initiated.

Information collected from the record will include patient's age, sex, race, genotype of albinism (if known) and the outcome measures listed above, results of clinical testing will be recorded in the clinic chart in addition to a study chart and research will only be recorded in the study chart. Research tests including results of genotyping will not be shared with subjects or family. For females who have had a menstrual cycle, positive results of screening pregnancy tests will be given to the subject in private, not shared with the parent.

Patients include OCA1a patients, OCA1b, OCA2, and unclassified OCA. OCA1a patients clinically are known to have the worst vision, and physiologically have the lowest (or absent) levels of tyrosinase function (Dopamine Production). All patients will be treated with Levodopa/carbidopa 4mg/kg/day in three divided doses (Dose determination outlined below). Patients and their families will be asked to submit the costs of medication to their insurance companies or cover the costs themselves, if this cost is not covered by their insurance. Per the UW Pharmacy, the pricing for 30 Carbidopa/Levodopa tablets is $27.81, the oral suspension would cost $32.32 for 100 mL. Subjects under 135 pounds would require an oral suspension provided by the UW pharmacy, in order to control the appropriate dose. This formulation has been adapted from The Hospital for Sick Children (University of Toronto). The ingredients for this formulation consist of: Carbidopa 25 mg/Levodopa 100 mg tablets (quantity = 5), Ora-Plus 50 mL, and Ora-Sweet 50 mL. Subjects over 135 pounds could obtain the drug at an outside pharmacy. Treatment will continue for 3 months followed by a six day taper reduction in dose (3 days at twice per day and 3 days at once per day), as a rapid reduction in dosage can be associated with fever, stiff muscles, confusion, abnormal thinking, fast or irregular heartbeat, and sweating. Side effects reported in adults with Parkinson's disease on Levodopa/carbidopa will be monitored (see schedule) and include nausea, headache, mood changes, insomnia, nightmares, dizziness, tiredness, leg pain, tinnitus and emesis. (These have not been reported in studies of Levodopa/Carbidopa in children)

Based on a standard deviation estimate of logMAR from a study on ocular albinism patients (Wildsoet C.F., et al: Investigative Ophthalmology and Visual Science: 2000) of 0.23, a minimum of 44 patients is the required recruitment to find a treatment effect of 0.1 logMAR visual acuity with a paired T-test between

changes due to treatment powered at 80%..Anticipated recruitment would be 50 patients total to allow for possible loss-to-follow-up and sufficient accrual.

If a patient discontinues treatment early, the treatment and the reason will be documented, and they will be asked to still report for their data collection appointments. If data is missing from the treatment phase, that patient will be unable to be used in the final analysis. Hence, we plan to recruit extra patients to ensure full data from at least 44 patients.

As previously mentioned, supportive measures are the only treatment modalities available to albinos, if a standard of care group were used it would be therefore, no treatment. The primary outcome is change from baseline, and since albinism is a chronic condition with no change in vision is the well-established natural history no standard of care group will be necessary – all patients enrolled will receive the standard supportive measures in addition to treatment.

Treatment with Carbidopa in combination with Levodopa inhibits decarboxylation of peripheral Levodopa. Carbidopa does not cross the blood-brain barrier and does not affect the metabolism of Levodopa within the central nervous system. Since its decarboxylase inhibiting activity is limited to extra cerebral tissues, administration of Carbidopa with Levodopa makes more Levodopa available for transport to the brain. Studies show Carbidopa saturates the bodies peripheral Dopa decarboxylase enzyme at approximately 70 to 100 mg (1mg/kg/day) a day. Patients receiving less than this amount of Carbidopa are more likely to experience nausea and vomiting. This is the basis for the higher dose of 4mg/kg/day of Levodopa treatment in this study, at this dose the minimum amount of Levodopa would be available to the retina (a tissue protected by the blood-brain barrier), as the Carbidopa dose of 1mg/kg/day would reach a peripheral enzyme saturation level. This is the basis for the typical starting dose for treatment of Parkinson's disease, but less than half the typical dose for treatment of DRD in children.

Drug dosing:

Levodopa dosages:

Total daily divided tid (mg)	weight lbs	weight kg
60	25-33	11-15
75	34-47	>15-21
100	48-60	>21-27
125	61-74	>27-34
150	75-89	>34-40
200	90-117	>40-53
250	118-134	>53-61
300	135-159	>61-73
4mg/kg/day	>160	>73

Confidentiality:

A physician or clinical technician trained in ophthalmology or

ophthalmologic photography will perform data collection during the clinical visit in a private setting. All procedures will be consented to.

All records, including the data collection forms, will be coded numerically to keep the data separate from any patient identification. A log that includes the subject identification and assigned code will be stored independently from the data. Data will be stored in a locked office or on an isolated hard-drive desk top computer which is password protected and can only be accessed by the PI. The hard drive of the PI is backed-up hourly. In addition, the study coordinator will have access to the paper charts used to monitor the treatment and adverse events. No study data or subject logs will be stored on portable laptop computers. Photos will not be stored with study data, only reviewed from the medical record.

Study Schedule:

I --Pretreatment

1 Informed Consent/Assent

2 Blood pressure, heart rate, weight.

Elevated blood pressure will need to be under control by the primary care provider prior to entry into the study.

3 Ophthalmic Exam – complete with cyclopentolate 1% dilation (standard dilation drops used in the pediatric clinic in children over 20 pounds)

a. Snellen visual acuity or HOTV

b. Color vision Farnsworth 15 or 100 hue, patients old enough to participate (estimated 6 years old and up)

c. Sweep visual evoked potential (VEP) (standard test in clinical setting -10 min test patients “watch a computer monitor” while recordings are made of vision response)

d. Contrast Sensitivity (5 min test on contrast board)

e. Color photography (Only performed If not current within the last 3 yrs) (all photos and Optical Coherence Tomography (OCT) take about 10mins)

predilation iris and full face
postdilation fundus
postdilation OCT

4 Optional Blood draw for genetic subtype analysis – if unknown (5ml purple tube).

5 Females who are pregnant, lactating, or intending to become pregnant within the next 12 weeks. A negative urine pregnancy test will be required for all females who have had a menstrual cycle.

II – 1 day, 1 week and 1-month treatment – phone call check compliance, and adverse events.

III -- 3 months treatment—prior to wash-out/weaning

Drug count/compliance, adverse event monitoring.

1 Ophthalmic Exam – complete with dilation
a. Snellen visual acuity or HOTV
b. Color vision Farnsworth 100 hue
c. Sweep VEP
d. Contrast Sensitivity
e. Color photography
postdilation fundus
postdilation OCT

2 Blood pressure, heart rate

3. Taper of medications over 6 days as outlined (3 days of twice daily dosing, then 3 days of once daily dosing).

IV – 4-month 1 month post treatment

1 Ophthalmic exam – nondilation
a. Snellen acuity
b. Color vision 15 Hue
c. Sweep VEP
d. Contrast Sensitivity

Pharmacology:
Carbidopa/Levodopa oral commercially available

Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Protect from light.
Dosage: 4mg/kg/day Levodopa orally, 1mg/kg/day Carbidopa, in three equally divided doses.

Disallowed medications:

- Clorgyline
- Iproniazid
- Pargyline
- Phenelzine
- Procarbazine
- Selegiline
- Toloxatone
- Tranylcypromine
- Apomorphine
- Bitolterol
- Desipramine
- Dobutamine
- Dopamine
- Epinephrine
- Isocarboxazid
- Isoetharine
- Isoniazid
- Isoproterenol
- Linezolid
- Methyldopa
- Moclobemide
- Nialamide
- Norepinephrine
- Venlafaxine
- Bromperidol
- Bupropion
- Droperidol
- Ferric Ammonium Citrate
- Fosphenytoin
- Indinavir
- Iron
- Kava

- Metoclopramide
- Phenylalanine
- Phenytoin
- Spiramycin
- Phenothiazines
- Risperidine
- Tyrosine

Rescue medication/overdose: Management of acute over dosage with Carbidopa Levodopa is the same as management of acute over dosage with Levodopa. Pyridoxine is not effective.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given.

Clinical lab: none

Data/Safety monitoring:

Adverse events will be monitored by the study coordinator, who will record the events on AE collection forms, and report events upon discovery to the PI and co-investigators. Adverse events will be monitored at each visit, and during the phone interview on days 1, 7, and 30 after first dose of medication (see attached AE form) and patients/parents will be given the AE form and phone number of the study coordinator to report these events. The PI and co-investigators will review each adverse event and confirm if it is related, serious, or expected. Adverse event reports will be reviewed for possible trends, the PI and/or co-investigator would consider modifying or stopping the study in the event of an emerging pattern of events. The study team will report such events to the IRB in accordance with the posted guidance. If a patient is withdrawn from the study (either by themselves, a guardian, or the study staff) prematurely or the study is stopped, they will be contacted by phone to assure that the medication is tapered correctly (3 days at twice per day and 3 days at once per day) and asked to return for a post-treatment visit.

Risks:

Risks of entering this study arise from three potential areas. These potential areas are:

- Medication risks
- Clinical testing risks, and
- Confidentiality risks

As stated above, while this medication has not been tested by the FDA in children, however its use in children dates as early as 1993. In general, the side effect profile in patients without Parkinson's disease (the primary FDA indication) is considerably less. Adverse events recording will include the 16 possible side effects reported in the literature. Subjects will be withdrawn from the study and

instructed on tapering of medication if the AE is of significant severity that the subject, their guardian, or the PI feel continuation is not justified. Please see AE reporting form.

Risks from testing: Patients will undergo a complete ophthalmic exam twice in three months. Children under 7 have this every 6 months and over 7 yearly. Standard, but more invasive testing procedures include: VEP, photography, and OCT. Visual Evoked Potential (VEP) testing is an electrophysiologic recording of brain wave activity similar to EEG recording that takes 10 minutes while subjects watch a computer screen. This test is performed routinely (30 times/wk) on preverbal patient in the clinic and is very well tolerated. Photography and OCT (a form of photography) requires subjects look into the camera while image is captured -- each image is recorded in less than 5 seconds.

Finally, every safety measure will be put into place to limit breaches of confidentiality. Patient confidentiality has been discussed in several areas of this protocol and include, but are not limited to: genotyping results, pregnancy testing of minors, and clinical documentation of visual performance including photographic information.

Statistical:

The primary analysis will be to look at the paired differences of the changes in logMAR due to 3-month treatment for each subject when compared to baseline. Sample size calculations based on finding a 0.1 logMAR difference in visual acuity at 95% confidence, with a standard deviation of .23, shows a minimum sample size of 44 patients needed to find a significant effect with 80% power. Other investigators have used the .2 logMAR vision improvement as marker of utility of vision improvement.[6]

This study will have an intent to treat goal. Anyone that fits the inclusion criteria for the study regardless of baseline logMAR vision or OCA type will be entered in the study. The goal will be to have 50 patients to ensure at least 44 patients in treatment, after any possible dropouts. Stopping criteria for enrollment will be a total recruitment of 50 patients, additionally after 22 patients (half) complete the course of treatment, the data will be analyzed for potential benefit. If significant results are found, the trial will be concluded.

Data from 19 completed subjects was analyzed. The standard deviation of differences of logMAR (from baseline to on-treatment) has been estimated to be 0.085. Using a more conservative estimate of 0.1, a one-sample t-test with a significance level of 0.05 and power of 80% would be able to detect a difference of 0.053 when 30 subjects are included in the trial. Hence, 30 subjects will enable us to achieve enough power to confidentially test for changes of 0.1 logMAR.

Data collection:

A physician or clinical technician trained in ophthalmology or

ophthalmologic photography will perform clinical data collection during the clinical visit in a private setting. All procedures will be consented to. Results of research testing (genotyping and pregnancy testing) will be kept in a study chart; results of clinical test will be recorded in the UW clinical chart and study chart. Additionally, all the data collection forms will be coded numerically to keep the data separate from any patient identification.

Genotyping (5cc purple top tube)

All tubes will be labeled with a study patient ID number, drawn at the University Station lab. Upon receipt at the central laboratory (Casey Oregon) the lab coordinator will remove the blood from the tubes and transfer it to the centrifuge for DNA extraction. All DNA samples will be held for only 6 months after completion of the study, in the event the testing would need to be validated, and labeled only with study ID number, a number that cannot be identified with a particular individual by anyone outside of the study clinical center at the UW. Casey eye institute will not be using DNA for any additional purposes.

Urine pregnancy testing will be performed anonymously by the UW lab and resulted to the study coordinator within one hour.

Labeling Procedures

Specimen labels will be provided to the clinic by the Study Coordinating Center. Each set of labels will have a unique *5-digit random specimen identification number* that will be pre-printed on the labels. The date the sample was drawn will be completed by the clinical center at the time the specimen is obtained. No other markings will be placed on the specimen or its container that contain personally identifying information.

All study patient records and data with study patient ID numbers and name codes are stored independent from the data, in a locked office at 2880 University Ave. Madison. The clinic coordinator and PI have access to records.

No study data or subject logs will be stored on portable laptop computers. Photos and electrophysiologic raw data will not be stored with study data, only reviewed from the medical record. Identifiers and study data will be kept for five years after the conclusion of the study.

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