Age related deviation of gait from normality in alkaptonuria

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Summary

Alkaptonuria is a rare metabolic disease leading to systemic changes including early and severe arthropathy which affects mobility. For unknown reasons, the onset of degenerative changes is delayed to around 30 years of age when both objective and subjective symptoms develop. In order to complement description of the structural changes in alkaptonuria with measures of movement function, clinical gait analysis was added to the list of assessments in 2013. The aim of this study was to describe the deviation of gait from normality as a function of age in patients with alkaptonuria. Three-dimensional movement of reflective markers attached to joints were captured during walking in 39 patients and 10 controls. Subsequent to processing the data to emphasise the shape of marker trajectories, the mean Movement Deviation Profile was generated for all participants. This single number measure gives the deviation of a patient's gait from a distributed definition of gait normality. Results showed that gait deviation roughly follows a sigmoid profile with minimal increase of gait deviations in a younger patient group and an abrupt large increase around the second half of the 4th decade of life. Larger variations of gait deviations were found in the older group than in the younger group suggesting a complex interaction of multiple factors which determine gait function after symptoms manifest. Continued gait analysis of adults with AKU, extended to younger adults and children with AKU, is expected to complete understanding of both the natural history of alkaptonuria and how interventions can affect movement function.

Take-home message

Deviation of gait from normality shows an abrupt increase in the second half of the 4th decade of life in alkaptonuria.

Compliance with Ethics Guidelines

Conflict of interests

Gabor Barton received a grant from the National Alkaptonuria Centre.

Stephanie King is employed from the same grant income.

Mark Robinson and Malcolm Hawken are named co-investigators in the same grant.

Lakshminarayan Ranganath is Director of the National Alkaptonuria Centre.

Informed Consent

All procedures followed were approved by the local NHS Ethics Committee (07/H1002/111 amendment 6, and 07/Q1505/29 amendment 9) and were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Contributions of individual authors

GJB conceived the study, performed the initial analyses and was lead author of the manuscript. SLK performed some of the data collection, parts of the data analysis and collaborated in writing the manuscript. MAR was involved in defining the test protocol and contributed to revising the manuscript. MBH was involved in the advanced analysis of results and in writing the manuscript. LRR contributed to revising the manuscript.

Introduction

Alkaptonuria (OMIM #203500) is an ultra-rare autosomal recessive metabolic disease with an estimated incidence of 1:250,000-1:1,000,000 in the US (Introne and Gahl, 2013). A defect of homogentisate 1,2-dioxygenase (EC 1.13.11.5) blocks the catabolism of phenylalanine and tyrosine resulting in elevated levels of homogentisic acid. After its oxidation, a melanin-like polymer is produced which binds to virtually all fibrous connective tissues including cartilage, leading to ochronosis (Ranganath et al. 2013). While alkaptonuria begins at conception, there is only anecdotal evidence of joint pain in younger patients followed by a rapid increase of symptoms around 30 years of age (Introne and Gahl, 2013; Ranganath and Cox, 2011). Among various degenerative changes affecting the cardiovascular and renal systems, a characteristic of the disease is early and severe arthropathy (Abimbola et al. 2011; Aquaron, 2013). Despite mounting information about structural changes in alkaptonuria, little is known about the functional effects of arthritic changes on movement. A prospective randomised clinical trial showed that nitisinone reduced homogentisic acid levels by 95%, but the total hip range of motion, spinal flexion, functional reach, timed get up and go, and 6-minute walk test did not improve (Introne et al. 2011). In order to better understand how movement degenerates in alkaptonuria, in 2013 we started performing gait analysis on adults who visit the National Alkaptonuria Centre in Liverpool.

Gait analysis is a routine non-invasive procedure which allows the collection of objective and quantitative information in order to identify abnormalities, postulate their causes and propose treatments for those with walking problems (Davis et al. 2004). Body segment motion is captured by infrared cameras which track reflective markers attached to the legs and pelvis, and ground reaction forces are recorded by force platforms embedded in a walkway over which the participant walks. Dynamic joint angles, moments and powers are calculated in all anatomical planes over several strides. Interpretation of the results by gait analysts can uncover reasons for gait changes, allowing specific anatomical structures to be targeted for interventions.

The traditional interpretation of gait results has recently been complemented by the successful derivation of simplified measures of gait deviation, often represented by a single number. Notable and widely used examples are the Gait Deviation Index (GDI, Schwartz and Rozumalski, 2008) and the Gait Profile Score (GPS, Baker et al. 2009). The Movement Deviation Profile (MDP, Barton et al. 2012; Barton et al. 2015) is a single curve generated by an artificial neural network model which shows quantitatively how much a patient's gait deviates from normal gait. A summary measure of the MDP,

the MDP_{mean}, has demonstrated advantages over the GDI and GPS while showing good agreement with the GDI (Barton et al. 2012). The MDP_{mean} offers a simple and effective means of quantitatively describing disease progression in alkaptonuria. The aim of this study was to examine the development of gait deviations in a cross-sectional sample of adults with alkaptonuria with a view to employing our method of objective assessment of gait function to monitor disease progression and responses to treatment.

Participants and Methods

A group of 40 patients with alkaptonuria (AKU) and 10 unimpaired controls underwent clinical gait analysis at Liverpool John Moores University between May 2013 and October 2014. One patient refused consent for the use of their data in the following analysis. Thirty-two of the patients were receiving 2 mg/day nitisinone treatment (13 of them started treatment within 3 days of testing) which is expected to slow progression of the disease, but not to reverse the effects. Eighteen of the patients had had one or more joints replaced. Table 1 shows descriptive statistics together with duration of nitisinone treatment and any joint replacements.

Table 1: Characteristics of patients with alkaptonuria (AKU) and unimpaired controls.

	AKU	**Controls**
N	39	10
Male/female	23/16	4/6
Age* (years)	24.5 (12.7)	34.2 (13.1)
Height* (m)	1.66 (0.10)	1.66 (0.08)
Mass* (kg)	74.1 (18.2)	69.5 (11.6)
Body Mass Index* (kg/m^2)	26.8 (5.4)	24.3 (4.7)
Nitisinone use		
On nitisinone for 1 year	19	n/a
On nitisinone for 1-3 days$^+$	13	n/a
No nitisinone treatment	7	n/a
Joint Replacement		
Knee or hip	14	n/a
Knee only	9	n/a
Knee and hip	5	n/a
Other	6	n/a

*mean (standard deviation); $^+$not included in "Nitisinone" group; n/a: not applicable

The gait analysis procedure followed the guidelines of the Clinical Movement Analysis Society of UK and Ireland. Fifteen reflective markers were attached to the skin or tight fitting clothes over the feet, lower legs, thighs and the pelvis according to the Helen-Hayes model (Davis et al. 1991). Several walks were performed at self-selected speed on a 10 m long walkway while the 3D coordinates of markers were captured by a 10 camera Qualisys Oqus or 16 camera Vicon T10/T160 motion capture system. The first three clean walks (without marker dropouts or measurement artefacts) of each patient and the first two walks of each control were selected for analysis.

The MDP (together with the GDI and GPS) was validated using three-dimensional joint angles but there is no universally accepted way to describe spatial joint angles given the mathematically equivalent but effectively very different 16 Euler rotation sequences (Baker 2006; Lees et al. 2010). To circumvent the uncertainties attached to selecting one particular Euler rotation sequence over others without clear justification, we used marker positions directly to describe movement as suggested by Federolf et al. (2013). Marker coordinates attached to body segments are used to calculate joint angles and so the information contained in 3D angles is also contained in marker coordinates.

Processing of the X, Y and Z coordinates of the 15 markers involved subtraction of each marker from a calculated straight line fitted onto the progression of the centre of the pelvis during one gait cycle (means of the X, Y and Z coordinates of the two ASIS markers and the sacrum marker), followed by subtracting its mean from each of the X, Y and Z coordinates of the 15 markers and division by their respective standard deviation. The mean correction and normalisation to unit standard deviation equalised the differences between the different amplitudes of markers attached to proximal and distal segments, thereby placing the emphasis on the shape of the marker trajectories as opposed to their amplitudes.

The processed marker coordinate data (X, Y and Z of 15 markers) was resampled to 101 values over one gait cycle and then concatenated into a single column with 3x15x101=4545 rows. Repeated gait cycles of each participant (2 for controls and 3 for patients) were then added as further columns, giving two sets of numerical data, one for controls and one for patients. A model of normal gait was created by passing the data of controls to the self-organising neural network for training in the MDP freeware program (Barton et al. 2012). MDP_{mean} values for the patients were then derived by the program using the trained neural network model, and processed further in MATLAB.

To summarise, the mean deviation from normal for each patient and control was calculated by averaging the MDP_{mean} values from the three walks of patients and two walks of controls, and plotted against age. As there was considerable scatter in the data, explorative median filtering was applied in order to investigate the possibility of a transitional increase in deviation from normal gait over a small age range. Median filters, under the right circumstances, preserve transitions better than more common linear filters (Huang and Lee, 2006).

Results

Preliminary examination of the values of MDP_{mean} plotted against age (Figure 1) showed that they increase significantly with age, however, the linear association is not particularly strong ($p = 0.005$, $R^2 = 0.193$). Further examination suggested that there might be an abrupt change around ages 35-40. This pattern becomes more obvious when overlaying the series of median filtered data (with filter points ranging between 5-9) which suggests a sigmoid profile. The upper half of the relationship (above 35-40 years) showed more variability than the lower half (under 35-40 years).

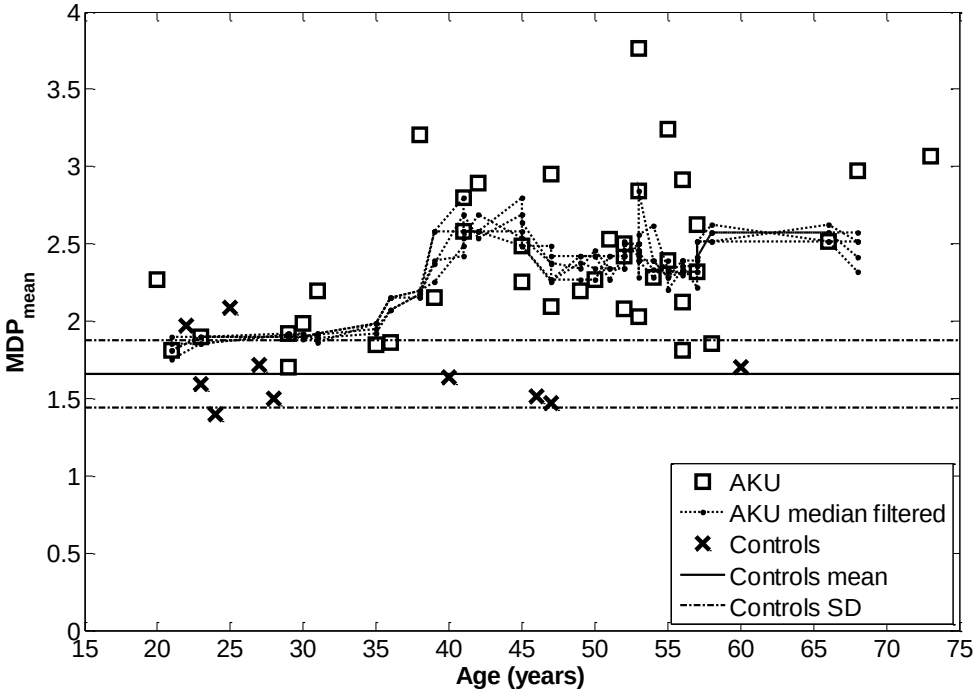

Figure 1: Deviation of gait from normality (MDPmean) as a function of age in patients with alkaptonuria (AKU) compared to unimpaired controls (individuals and their mean ± standard deviation). A series of median filtered curves of the AKU group indicates an abrupt increase around 35-40 years of age.

Based on the effect of median filtering, individual regressions over (a) age<35 and (b) age>40 were fitted to the patient data and showed no significant variation with age. An appropriate sigmoid curve was fitted to the data ("R P", 2014) using starting and ending values from the regressions at the end of (a) and at the start of (b) respectively. The fitted curve showed a discontinuity with its 50% point around age 37, providing support for the conjecture suggested by the median filtering. Adjusting the start and end of the respective regressions to 37 years and making minor adjustments to the start and end values of the sigmoid curve from the revised regressions produced an almost identical sigmoid curve (Figure 2) which was used to model the change of gait deviation as a function of age in our AKU sample.

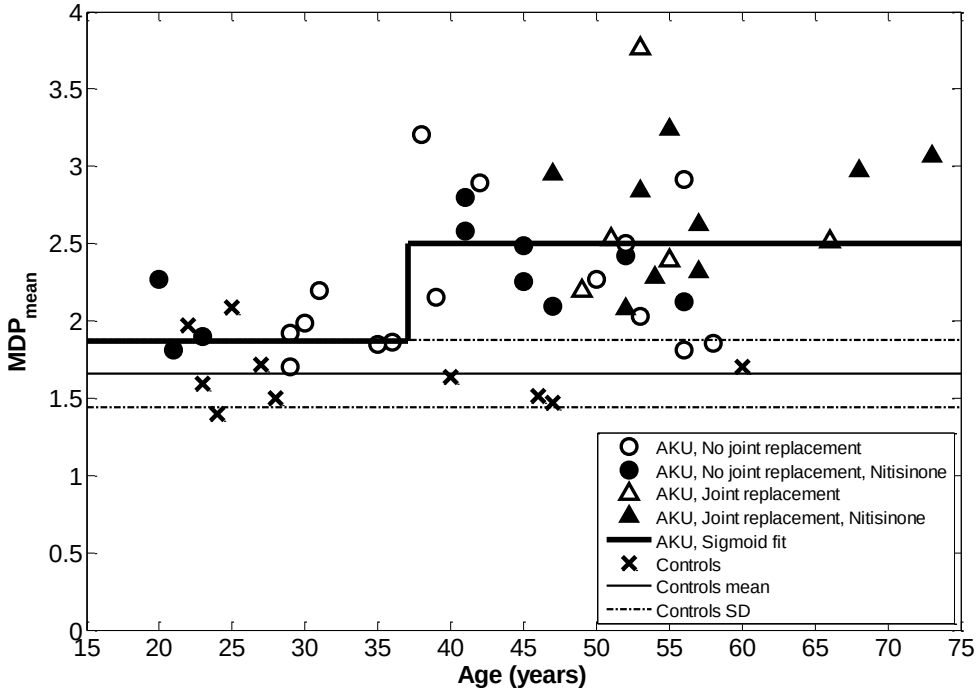

Figure 2: Subsets of AKU patients with and without joint replacement and with and without nitisinone treatment shown against controls. A sigmoid curve fitted on the AKU group confirmed the discontinuity of gait deviation around 37 years of age.

All AKU patients under 37 years show some level of gait deviation as their MDP_{mean} values are greater than the mean of controls. The majority of AKU patients over 37 years (28 out of 30) demonstrated more gait deviations than the mean+1SD of controls (1.88), but only 23 out of 30 were above the 95% confidence interval of the control group (2.159).

Only patients above 47 years had joint replacements (red empty and filled triangles in Figure 1) and their gait deviation was greater (2.70±0.47, N=14) than that of patients without joint replacements (2.24±0.4, N=25, red empty and filled circles in Figure 1). There are 8 AKU patients in the age range 37-47 years without joint replacements but considerable deviations from normal gait.

In an attempt to clarify the association of gait deviations with nitisinone treatment and joint replacements, the MDP_{mean} of sub-groups of AKU patients were plotted in Figure 3. While clear cause-effect mechanisms cannot be established without longitudinal data of individual patients, nevertheless the comparisons of sub-groups revealed some interesting findings. The 19 patients under nitisinone treatment showed higher deviations of gait from normality than the 20 patients without nitisinone treatment. Similarly, the gait of 14 patients with knee or hip joint replacements is further away from normality than those 25 without any joint replacements. Comparing the effects of knee and/or hip replacement on gait normality showed negligible differences. Nine AKU patients had a single knee replacement and an additional five had hip and knee replacements.

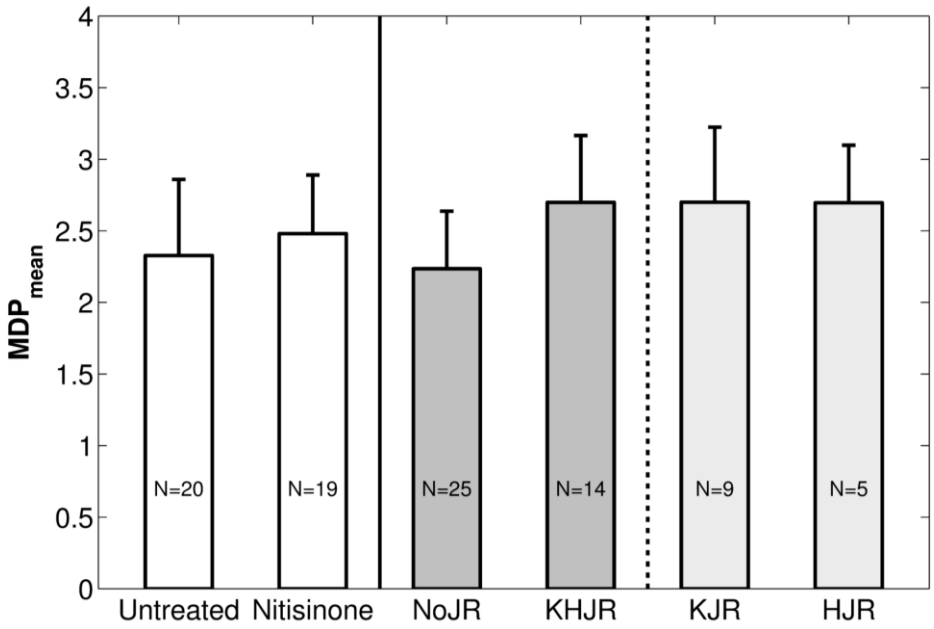

Figure 3: A comparison of subsets of AKU patients (group means and SD with the size of group indicated on each bar). ***Untreated*** *(no nitisinone, no joint replacement),* ***Nitisinone*** *(on nitisinone with or without joint replacement),* ***NoJR*** *(no joint replacement, with or without nitisinone),* ***KHJR*** *(knee or hip joint replacement, with or without nitisinone),* ***KJR*** *(knee joint replacement only, with or without nitisinone) and* ***HJR*** *(hip joint replacement, all 5 with knee replacement, with and without nitisinone).*

Discussion

An objective measure of gait function, the MDP_{mean}, showed a pattern of deterioration in alkaptonuria similar to other indices of disease severity (Ranganath and Cox, 2011). Our data suggests a non-linear deterioration of gait function in the second half of the 4th decade which differs somewhat from the findings of Ranganath and Cox (2011) who described a gradual change in the 3rd decade followed by an accelerated progression of the disease in the 5th and 6th decades of life using clinical measures and patient questionnaires. Considering that AKU is an ultra-rare disease, gait related measures of 39 patients can be regarded as a large pool of data but certainly this particular sample of patients might have influenced the fit therefore caution is advisable with setting a firm age threshold. Although the regression line in the AKU group over 37 years has a low slope (0.0026 units of MDP_{mean}/year) indicating minimal change as a function of age, there are considerable inter-individual differences in their gait deviations. An interaction of several factors which may influence gait function (causing gait variability) justifies individualised clinical assessment for patients in this group in order to identify their specific problems which can then be targeted with appropriate treatment.

Adults with AKU under 37 years of age show some movement deviations although their MDP_{mean} is only one standard deviation away from normality. Our youngest patient was 20 years of age and so we have no information about the gait function of even younger patients and children with AKU. Early detection of movement problems may trigger focused management in order to prevent cumulative deterioration. Especially in case of children, treatment with nitisinone may have to be delayed to prevent any potential side effects (Bendadi et al. 2014). Evidence of gait deviations in the young would support earlier intervention (either nitisinone or alternatives e.g. physiotherapy), and conversely a lack of movement problems would support delaying nitisinone treatment to a later time when the chance of side effects is minimal.

Adults older than 37 years of age with AKU show more deviation from normal gait than the younger group. Nevertheless if our method based on the MDP_{mean} was used to decide if a patient moved away from normality, then the sensitivity/specificity would likely be low with false positives given that 23% of AKU patients fall within the 95% confidence interval of the control group. Further evaluation of the MDP_{mean} as a method to separate a patient with AKU from controls is necessary using a larger sample.

Patients with AKU and joint replacements were all above 47 years and their gait deviations were higher than those of the group without joint replacements. The higher age of this group likely reflects clinical

decisions of when a joint replacement is indicated. Gait does not easily return to normality; in osteoarthritis, gait was shown not to return to normal until about 11 months after total hip arthroplasty (Beaulieu et al. 2010). Potential mechanisms underlying slow recovery are: unnecessary but continued pain avoidance strategies and persistent muscle weakness due to disuse, both of which may hinder not only the affected but the contralateral side too. Persisting gait abnormality following joint replacement in AKU is likely to be due to the systemic nature of the disease which affects anatomical structures beyond the joint itself. AKU potentially affects all joints including their related ligaments, tendons and muscles and this might explain why repairing a single joint may not lead to a rapid recovery.

Deviation of controls from normality, as measured by the MDP_{mean}, shows minimal increase as a function of age. This might be explained by the self-organising neural network's method of operation underlying the MDP method. Subsequent to defining an internal model of gait normality based on the gait of controls, the deviation from the closest matching variant of normal gait is calculated (Barton et al. 2012). As the control group included older individuals (40, 46, 47 and 60 years of age) the MDP_{mean} of AKU patients could reflect the deviation from this subgroup of controls with altered gait due to their age. In order to determine if the gait of the older control sub-group affected the calculation of the MDP_{mean}, a separate neural network model was generated by training with the younger group of controls and then calculating the MDP_{mean} of the older control group. The similar MDP for the older control group (MDP_{mean} = 1.82) compared to younger controls (22-28 years, MDP_{mean} = 1.67) indicates that only minimal gait deviations occur as a result of ageing. As such the increased MDP_{mean} of the older individuals with AKU is referenced to a rather coherent definition of gait normality regardless of age. Increased gait deviations therefore were due to genuine deterioration of gait related to AKU together with other factors like joint replacements and nitisinone treatment. More in-depth sub-group analyses will be required to differentiate between these factors.

A limitation of our method is that on its own the single number MDP_{mean} can only be used to flag an increased deviation of gait from normality. This should then be followed up by establishing the specific gait problems which eventually is expected to lead to improved clinical decision making and treatment. Movement of body-attached markers was used to quantify deviation of gait but this approach can be complemented by including the forces acting on the body at each joint. Such an extension of the method may offer further advantages due to its focus on joint loading which is the ultimate cause of pain in alkaptonuria. An inevitable limitation of our study was the low number of participants and the cross-sectional nature of gait data.

Conclusions

This was the first attempt to evaluate gait function in patients with alkaptonuria using a summary measure of gait deviation (the MDP). Patients with AKU showed minimally increased gait deviations between 20-37 years, followed by an accelerated increase around the second half of the 4th decade of life. The older group of patients was characterised by elevated and varied levels of gait deviation. Together with continued gait analysis of adults with AKU, evaluation of gait deviations in younger adults and children with AKU is necessary to complete and refine our understanding of disease progression moderated by the influence of interventions including joint replacements and nitisinone treatment.

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