

# Work activity and phenylalanine levels in a population of young adults with classic PKU

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**PAROLE CHIAVE:** Fenilchetonuria; fenilalanina; malattia rara; medicina del lavoro

## SUMMARY

**Background:** Phenylketonuria (PKU) is an inborn error of metabolism characterized by increased blood concentrations of phenylalanine (Phe). **Objectives:** The aim of the present study was to assess the association between the metabolic compliance of adult patients affected by classic PKU and the characteristics of their present and past occupations. **Methods:** The study population consisted of working adults, affected by classic PKU, and following a dietary treatment. Univariate linear-mixed models and multivariate analysis were applied to assess the association between Phe blood levels and individual covariates: age, sex, time at diagnosis, educational level and work characteristics. **Results:** A linear relationship was found with age (an average annual increase of 30.56  $\mu\text{Mol/L}$  (C.I. 95%: 7.53; 53.60) in the mean Phe blood levels). Full-time work appeared to be associated with a worse metabolic compliance when compared to part-time work (mean Phe blood levels >281.11  $\mu\text{Mol/L}$ ). Shift work was related to a worse metabolic compliance, with mean Phe plasmatic levels >356.73  $\mu\text{Mol/L}$ . **Conclusions:** Our data suggests that work may influence the metabolic compliance in adults with PKU. In particular, a part-time employment could allow for a better metabolic compliance, while daily work should be preferred to shift work.

## RIASSUNTO

«Attività lavorativa e livelli di fenilalanina in una popolazione di giovani adulti affetti da PKU classica». **Introduzione:** La fenilchetonuria (PKU) è un errore congenito del metabolismo caratterizzato da elevate concentrazioni di fenilalanina (Phe) nel sangue. **Obiettivi:** Lo scopo del presente studio è valutare l'associazione tra la compliance metabolica di una popolazione di adulti affetti da PKU classica e le caratteristiche delle loro attività lavorative presenti e passate. **Metodi:** La popolazione era composta da lavoratori adulti affetti da PKU classica in trattamento dietetico. Sono state effettuate analisi univariate e multivariate per valutare l'associazione tra le concentrazioni ematiche di Phe e le covariate individuali: età, sesso, età alla diagnosi, livello di istruzione, e caratteristiche del lavoro. **Risultati:** Si è individuata una relazione lineare con l'età, con un incremento annuo medio di 30,56  $\mu\text{Mol/L}$  (I.C.95%: 7,53; 53,60) nei livelli ematici medi di Phe. L'attività a tempo pieno sembra essere associata

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*a una peggiore compliance metabolica quando confrontata con l'attività part-time (livelli ematici medi di Phe più elevati di 281,11  $\mu\text{Mol/L}$ ). Il lavoro a turni è risultato correlato a una compliance metabolica peggiore, con livelli ematici medi di Phe più alti di 356,73  $\mu\text{Mol/L}$ . **Conclusioni:** I nostri dati suggeriscono che l'attività lavorativa potrebbe essere in grado di influenzare la compliance metabolica in adulti con PKU. In particolare, un lavoro part-time potrebbe consentire una migliore compliance metabolica, mentre un lavoro a giornata dovrebbe essere preferito ad un lavoro a turni.*

**Abbreviations:** PAH: phenylalanine hydroxylase; Phe: phenylalanine; PKU: Phenylketonuria

## INTRODUCTION

Phenylketonuria (PKU) is an inborn error of metabolism due to autosomal recessive mutations in the gene coding for phenylalanine hydroxylase (PAH), an enzyme that metabolizes the amino acid phenylalanine (Phe) to tyrosine. The increased blood concentrations of Phe (hyperphenylalaninemia) have serious pathological consequences: severe mental retardation and a variety of additional symptoms, which may include motor deficits, seizures, eczematous rash, hypopigmentation of skin and hair, aberrant behaviour and psychiatric symptoms (2). Nowadays, mass screening programmes and the introduction of a Phe-restricted diet in the first weeks after birth, can prevent hyperphenylalaninemia and the consequent mental retardation, allowing the patients to live a normal life.

Although early detection and treatment are essential to improve the psychosocial outcome of the patients, early- and well-treated patients may also show some neurological and psychiatric symptoms (3, 4). These patients may also experience what are commonly referred to as “hidden disabilities”, including mild impairment of executive functions, reduced processing speed, social difficulties, and emotional problems that may remain unnoticed for years (6). Several studies have associated these manifestations of PKU in adult patients to their Phe blood levels (6, 9), addressing the importance of the maintenance of a good metabolic control throughout life. The nutritional management of PKU is complex, costly and highly time-consuming, requiring knowledge of food composition, and continuous food measurement (3, 5, 9). Given its complexity,

different social aspects – including work – may influence the adherence to the dietary treatment and metabolic compliance (1). In the present study, we aimed at correlating the Phe level in a population of adult patients affected by classic PKU with their present and past occupations.

## METHODS

### Study design and patient enrolment

We enrolled PKU patients attending a specialist outpatient clinic. The inclusion criteria were adult age (18 years old or older), diagnosis of classic PKU (blood Phe:  $>1200 \mu\text{Mol/L}$ ), and availability of monthly data – in the period from 2006 to 2014 – regarding their blood Phe levels, dietary treatment, and occupational status. We selected only those patients who had worked for at least one month during the follow-up period. Subjects might have changed their occupational status during this time.

In detail, we considered age, sex, time at diagnosis (neonatal or  $>4$  weeks after birth), educational level (primary, lower secondary school, upper secondary school, and higher education), employment status (employment and unemployment), type of contract (regular and irregular) and work characteristics (full-time employment, part-time employment, daily work, shift work). The last three covariates were evaluated monthly during the follow-up period.

### Statistical analysis

Results were reported as frequency for discrete variables, and as mean values ( $\pm$  standard deviation) for continuous variables. Differences between proportions were tested with Fisher's exact test. We applied univariate linear-mixed models to assess the

association between concentrations of Phe in the blood and individual covariates. With a multivariate analysis, we evaluated the combined effects of the covariates that resulted significantly associated with a variation of Phe blood levels in the univariate analysis. For all statistical tests, a pre-specified two-sided  $\alpha$  of 0.05 was regarded as statistically significant. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

## RESULTS

The study population consisted in 20 adult subjects affected by classic PKU. At baseline, the mean age of the study population was 32.55 ( $\pm 7.37$ ) years; 35.0% were men and most of the patients had primary (50.0%) and lower secondary school (40.0%)

educational level. Half of the patients worked for at least 87.32 (62.15-89.16) months during the follow-up period. Thirteen subjects (65.0%) had an early diagnosis because of new-born screening programmes. The median number of Phe measurements was 46 (36-76), and the mean Phe levels in the population was 582.61 ( $\pm 251.96$ )  $\mu\text{Mol/L}$  (table 1).

In the univariate model (table 2), no significant difference in Phe blood levels was observed in relation to sex, educational levels and time at diagnosis. A linear relation was found with age, with an average annual increase of 30.56  $\mu\text{Mol/L}$  (95% confidence interval (CI): 7.53; 53.60) in the mean Phe blood levels. Full-time employment appeared to be associated with a worse metabolic compliance when compared to part-time employment, with mean Phe blood levels  $>281.11$   $\mu\text{Mol/L}$  (95% CI: 159.63; 402.59). Table 2 shows a significant difference for

**Table 1.** Main characteristics of study population

Patients, n	20
<b>Baseline - Demographic characteristics</b>	
Sex, n (%)	
Men	7 (35.0)
Women	13 (65.0)
Age, years	
Mean (SD)	32.55 (7.37)
Median (IQR)	31.50 (37.00-38.50)
Time at diagnosis, n (%)	
Neonatal screening	13 (65.00)
After 4 week from born	7 (35.00)
Educational level, n (%)	
Primary school	10 (50.00)
Lower secondary school	8 (40.00)
Upper secondary school	2 (10.00)
Higher education	0 (0.00)
<b>Follow-up - Clinical characteristics</b>	
Follow-up period, months	
Median (IQR)	88.31 (84.85-89.34)
Period of employment during follow-up, months	
Median (IQR)	87.32 (62.15-89.16)
Number of Phe measurements for each patients during follow-up	
Median (IQR)	46 (36-76)
Phe ( $\mu\text{Mol/L}$ ) average value	
Mean (SD)	582.61 (251.96)

Abbreviation: SD: Standard Deviation; IQR: Interquartile Range

**Table 2.** Linear-mixed models to assess the association between Phe values and covariates

	Beta	95% CI	p-value	N
<b>Univariate model</b>				
Age	30.56	7.53 ; 53.60	0.0093*	1,230
Sex (reference category: Man)				1,230
Woman	127.76	-109.79 ; 365.31	0.2918	
Time at diagnosis (reference category: Neonatal screening)				1,230
After 4 weeks	-75.64	-307.95 ; 156.67	0.5234	
Education (reference category: Upper Secondary School)				1,230
Primary School	81.41	-97.07 ; 259.89	0.3713	
Lower Secondary School	24.81	-158.52 ; 208.14	0.7908	
Employment Status (reference category: Employed)				807
Unemployed	-61.96	-225.56 ; 101.65	0.4579	
Type of contract (reference category: Regular)				803
Irregular	227.87	8.81 ; 446.93	0.0415*	
NA	-35.58	-234.65 ; 163.48	0.7261	
Work Characteristics (reference category: Full-time employment)				803
Shift work	356.73	242.58 ; 470.87	<.0001*	
Part-time employment	-281.11	-402.59 ; 159.63	<.0001*	
NA	-87.17	-279.78 ; 105.45	0.3751	
<b>Multivariate model</b>				
Age	23.34	2.13 ; 44.55	0.0310*	803
Work Characteristics (reference category: Full-time employment)				
Shift work	450.12	338.41 ; 561.82	<.0001*	
Part-time employment	-208.69	-334.67 ; -82.70	0.0012*	
NA	-96.54	-267.21 ; 74.13	0.2676	

Abbreviations: CI: confidence interval; N: number of observations used in the linear-mixed models; NA: not applicable (periods when patients did not work)

\*Statistically significant at the level 0.05

irregular vs. regular type of contract. In addition, shift work was related to a worse metabolic compliance, with mean Phe blood levels  $>356.73 \mu\text{Mol/L}$  (95% CI: 242.58; 470.87).

Finally, we associated the covariates age and work characteristics (full-time employment, part-time employment, shift work) to the Phe blood levels in the multivariate analysis (table 2). Adjusting for the other variables in the model, age still showed a linear relationship with Phe blood levels, with an average annual increase of  $23.34 \mu\text{Mol/L}$  (95% CI: 2.13; 44.55). Shift work and part-time employment seemed to be related respectively to an increase and a decrease of the average Phe blood levels.

## CONCLUSIONS

To the best of our knowledge, this is the first study to investigate the potential effects of work activity on Phe levels in PKU, one of the most common amino acid metabolism disorders. PKU is a rare disease and, as a consequence, the number of subjects enrolled in this study was low, but the high number of Phe measurements available for each subject and the long follow-up period allowed us to investigate the relationship between Phe levels and work activity.

We did not find any difference in Phe blood levels when the subjects were unemployed as op-

posed to when they were employed. In particular, the influence of employment status on Phe blood levels may not be satisfactorily investigated in our study because of the short periods of inactivity of each subject. Some characteristics of work seem to influence the Phe blood levels of workers with classic PKU. A part-time employment seems to be related to a better compliance as opposed to a full-time employment. In relation to the work schedule, a worse compliance seems to be found in shift work. A possible explanation of our findings lies in the increased difficulties that certain aspects of the work schedule may put in following an already complex strict dietary scheme. It is not always feasible for workers, for example, to have a lunch break at home or to prepare their meals in advance and to consume them at the workplace. Nor it is recommended, in order to maintain constantly low Phe blood concentrations throughout the day, to have a free daily meal and compensate for it with a more Phe restricted diet in the remaining meals of the day. The amino acidic component of the diet importantly affects the stability of Phe blood levels, and should be spread evenly in three to four doses throughout the day (7). Due to the aforementioned “hidden disabilities”, such as a reduced processing speed, a poor metabolic compliance may have an influence on working performance, increasing the likelihood of operative errors and work-related injuries – that may also involve third parties. For this reason, employers should guarantee these workers to follow adequately their dietary treatment during working time for a better metabolic control. In this regard, the possibility to have a personalised menu in agreed restaurants near the workplace or at the company’s canteen could be of extreme help. Furthermore, at least one break apart from lunch break should be allowed, to consume protein substitutes that can help in achieving stable Phe concentrations.

Finally, the findings in the present study – that should be confirmed on a larger population of PKU workers and be implemented on the aspects con-

cerning the effects of PKU on work activity – could also be of help for occupational health physicians in evaluating the occupational clearance of PKU workers: a part-time employment could allow for a better metabolic compliance. Daily work should be generally preferred to a shift work.

NO POTENTIAL CONFLICT OF INTEREST RELEVANT TO THIS ARTICLE WAS REPORTED

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