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EBV-requisitioning physicians' guess on fatigue state 6 months after acute EBV infection

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ABSTRACT

We assessed referring medical practitioner's ability to predict chronic fatigue development in adolescents presenting with acute infectious mononucleosis. Compared with *'not fatigued'* being predicted as *'unsurely fatigued'* and *'likely fatigued'* were both strongly associated with developing fatigue 6 months later (OR 2.5, 95% CI 1.16% to 5.47% and 3.2, 95% CI 1.19% to 8.61%, respectively, P=0.012). The positive and negative predictive values were 66% and 62%, respectively. Disentangling the physician's intuition may be of interest in further investigations of risk factors and prophylactic factors for fatigue development.

INTRODUCTION

Infectious mononucleosis (IM), normally caused by Epstein-Barr virus (EBV), is a common infection in adolescence and a well-known trigger of chronic fatigue (CF) and chronic fatigue syndrome (CFS); 11–13,5% of IM-patients are diagnosed with CFS 6 months after acute EBV-infection.[1–3] The present study is part of the CEBA-project (CF following acute EBV-infection in adolescents, post-results), and in this research letter we aimed at assessing the referring medical practitioners' ability to predict fatigue development based on their initial encounter with EBV-infected adolescents.

METHOD

The CEBA-project (ClinicalTrial ID: NCT02335437) has been approved by the Norwegian Committee for Ethics in Medical research. Participation was based on written informed consent.

Patient and Public Involvement (PPI)

Patients were not directly involved in the design of the CEBA-project.

Individuals with a serological pattern indicating acute EBV-infection, age between 12 and 20 years and living in South-East Norway were eligible for participation in CEBA; exclusion criteria were more than 6 weeks since debut of symptoms, medication due to chronic disease and pregnancy. Patients enrolled in the study were extensively investigated during the acute infection episode (baseline) and 6 months later; details of the investigational programme are provided elsewhere.[3] Fatigue (predefined primary endpoint) was assessed by the Chalder Fatigue Questionnaire (CFQ); bimodal scoring (0-0-1-1) was applied, and in line with earlier studies, a total score of four or higher was considered a case of CF.[4]

At baseline, a short questionnaire was administered to the physicians who requisitioned the primary EBV analyses (online supplementary file), asking them to guess whether the particular teenager would develop CF 6 months later or not; possible answers were 'Yes', 'No' and 'Don't know'. The questionnaire also charted initial symptoms and signs during the consultation, as well as simple demographic information.

SPSS statistical software (IBM SPSS Statistic 24 Inc., Chicago, IL, USA) was used for statistical analyses. Primarily we performed binary logistic regression analysis with CF at 6 months as dependent variable (CFQ total score ≥4 or <4) and the prediction (Yes/No/ Don't know) given by the referring physician at baseline as independent variable. Secondarily, sex, C reactive protein (CRP) measured by the referring units and the physician's work experience (time in years) were included in the model. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 200 patients with acute EBV infection were included in the CEBA-project; five were lost to follow-up 6 months later. A total of 165 physicians returned the questionnaire, yielding a complete dataset for 161 patients that were subjected to further analyses. A comparison of patients from physicians that returned and did not return the questionnaire showed no significant difference (table 1).

Table 1 Comparison of patients with referring medical practitioner not responding versus referring medical practitioner responding to questionnaire administered per mail

	Not responding (n=35)	Responding (n=165)	Diff.	95% CI of diff.
Gender—no. (%)				
Male	14 (40)	57 (34.5)	n.a.	n.a.
Female	21 (60)	108 (65.5)		
Age—years, mean (SD)	16.9 (1.3)	16.9 (1.6)	−0.01	−0.52% to 0.49%
BMI—kg/m^2, mean (SD)	21.1 (2.4)	21.4 (2.6)	−0.23	−1.2% to 0.67%
Steps per day—number, mean (SD)	7559 (2860)	7506 (3131)	56	−1146% to 1253%
Chalder Fatigue Questionnaire—total score, mean (SD)	7.5 (2.9)	6.8 (2.7)	0.64	0.55% to −0.44%
Function Disability Inventory—total score, mean (SD)	18.6 (12.8)	16.1 (11.6)	2.5	−2.1% to 6.8%

BMI, body mass index.

Table 2 Predicted and observed fatigue 6 months after acute Epstein-Barr virus-infection

	Observed		
	Fatigued (CFQ≥4)	Not fatigued (CFQ<4)	CFQ-score (95% CI)
Prediction			
Likely fatigued* (%)	14 (66.7)	7 (33.3)	5.6 (3.9 to 7.3)
Unsurely fatigued* (%)	22 (61.1)	14 (38.9)	4.8 (3.7 to 5.8)
Not fatigued* (%)	40 (38.5)	64 (61.5)	3.2 (2.7 to 3.8)
	Sensitivity†=18.4%	Specificity†=75.3%	

*Referring medical practitioner's guess; no=not fatigued, don't know=unsurely fatigued, yes=likely fatigued.
†Sensitivity and specificity are calculated after an intention-to-diagnose principle[5]; when calculating sensitivity, unsurely fatigued is included in the false negatives, while in calculation of specificity those predicted unsurely fatigued is included in false positives.
CQF, Chalder Fatigue Questionnaire.

Compared with *'not fatigued',* being predicted as *'unsurely fatigued'* and *'likely fatigued'* were both strongly associated with being fatigued 6 months later (OR 2.5, 95% CI 1.16% to 5.47% and 3.2, 95% CI 1.19% to 8.61%, respectively, P=0.012). Neither gender, CRP nor the doctors work experience had significant impact on the OR estimate when included in the model. The positive and negative predictive values were 66% and 62%, respectively. Of the observed patients, 75% of the non-fatigued were predicted correctly, while only 18% of the fatigued got a correct prediction (table 2).

DISCUSSION
Low sensitivity and specificity reject the physicians' intuition as a suitable screening tool for fatigue development following an acute EBV-infection, still the present report shows that the physician's prediction of fatigue development significantly relates to actual fatigue status 6 months later. Disentangling the physician's intuition may be of interest in further investigations of risk factors and prophylactic factors for fatigue development.

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