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The development of a clinical screening instrument for tumour predisposition syndromes in childhood cancer patients

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Abstract ***Background:*** Identification of tumour predisposition syndromes in patients who have cancer in childhood is paramount for optimal care. A screening instrument that can help to identify such patients will facilitate physicians caring for children with cancer. The complete screening instrument should consist of a standardised series of pictures and a screening form for manifestations not visible in the pictures. Here we describe the development of such a

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syndromes
Delphi process
Questionnaires

screening form based on an international two-stage Delphi process and an initial validation of the complete instrument.

Patients and methods: We identified manifestations that may contribute to the diagnosis of a tumour predisposition syndrome through the Winter–Baraitser Dysmorphology Database and the textbook "Gorlin's Syndromes of the Head and Neck". In a two-round Delphi process, eight international content-experts scored the contribution of each of these manifestations. We performed a clinical validation of the instrument in a selected cohort of 10 paediatric cancer patients from another centre.

Results: In total, 49 manifestations were found to contribute to the diagnosis of a tumour predisposition syndrome and were included in the screening form. The pilot validation study showed that patients suspected of having a tumour predisposition syndrome were recognised. Excellent correlation for indications of patient's referral between the screening instrument and the reference standard (personal evaluation by an experienced clinical geneticist) was found.

Conclusions: The Delphi process performed by international specialists with a function as opinion leaders in their field of expertise, has led to a screening instrument for childhood cancer patients. Patients who may have a tumour predisposition syndrome and thus have an indication to be referred for further genetic analysis, can be identified using the screening instrument.

1. Introduction

The diagnosis of a specific tumour predisposition syndrome in patients with childhood cancer is important and clinically relevant because it can affect management. Some syndrome-associated malignancies require specific treatment strategies and some require screening for subsequent malignancies. Also, it may guide care for non-malignancy manifestations; it facilitates recurrence risk assessments and can facilitate pre-symptomatic identification of other relatives at risk for malignancies.

In previous studies, we found a substantial incidence of morphological abnormalities and recognisable clinical genetic syndromes in patients with childhood cancer. Half of these syndromes had not been recognised by the routine caregivers involved, despite expert paediatric care.[1–3] We and others recommended that all children diagnosed with a malignancy should be assessed by a clinical geneticist or a paediatrician skilled in clinical morphology.[2,4,5] However, in many countries there is limited access to such consultations and genetic consultations can be a low priority in acutely ill patients. A screening instrument could be a reliable aid in assuring that all childhood cancer patients at risk of having a tumour predisposition syndrome can be recognised and referred.

We argue that an easy-to-use screening form together with a standard series of 2D and 3D pictures could serve as a screening instrument. The form should easily be completed by a genetic nurse or physician involved in treatment of paediatric cancer patients. This would allow for a quick, efficient screen of completed forms accompanied by corresponding sets of pictures by a clinical geneticist who can then select those suspected to have a syndrome for a full genetic consultation. Such a screening form should be based on manifestations of known tumour predisposition syndromes, as these manifestations have already shown to indicate the cancer susceptibility. The number of tumour predisposition syndromes is large, which would result in a significant number of individual manifestations making a "non-focused' form unfeasible. Therefore, it is important to extract the most significant manifestations.

Part of the manifestations in tumour predisposition syndromes will be visible on a standard set of two-dimensional (2D, overview; face in two directions; hands; feet) and three-dimensional (3D) pictures (face). The goal of this study was to identify the most sensitive manifestations of known tumour predisposition syndromes, not visible on these pictures, to include these in a screening form.

2. Patients and methods

2.1. General strategy

Two important sources for the manifestations of tumour predisposition syndromes were used; a database (Winter–Baraitser Dysmorphology Database [WBDD])[6] and a textbook (Gorlin's Syndromes of the Head and Neck).[7] The recently published set of standardised terms to describe human morphology was used in the definite screening form.[8–14]

2.2. Expert-based opinion/Delphi process

We used a two-phase Delphi process[15,16] in which eight international specialists in this field participated. The Delphi technique is a widely accepted method for achieving convergence of opinion from experts. It is used as a method for consensus-building using a series of questionnaires in multiple consultation rounds to collect data from a panel of experts, where evidence from literature is lacking.[15] In the present study we interrogated the expert-panel regarding manifestations that