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Anti-müllerian hormone deficiency in females with inherited bone marrow failure syndromes

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Fanconi anemia (FA), dyskeratosiscongenita (DC), and Diamond-Blackfan anemia (DBA) are rare inherited bone marrow failure syndromes (IBMFS) characterized by birth defects, bone marrow failure, and increased frequency of malignancy. Females with FA are known to have a high incidence of infertility which may be associated with primary ovarian insufficiency (POI), while infertility in DC and DBA has not been reported. Anti-Müllerian hormone (AMH) is a marker of ovarian reserve and the decline of AMH is correlated with the loss of fertility as AMH decreases to undetectable levels five to ten years prior to menopause. In this study, we examined whether serum levels of AMH could serve as a menstrual cycle-independent marker for the diagnosis of POI in patients with IBMFS. Serum AMH levels were measured in female participants in the National Cancer Institute's IBMFS cohort in 22 FA patients (median age 15 years, range 7-37), 20 unaffected FA relatives (age 33.5, range 3-40), 15 patients with DC (age 17, range 4-32), 18 unaffected DC relatives (age 22.5, range 2-40), 12 patients with DBA (age 15.5, range 1-30), 13 unaffected DBA relatives (age 11, range 1-34), and 21 unrelated healthy females (age 27, range 12-40). FA females had very low or undetectable AMH levels (median 0.05 ng/ml, range 0-2.32ng/ml) compared with both unaffected FA relatives (2.10 ng/ml, range 0.04-4.73ng/ml, $p<0.0001$) and unrelated healthy females (1.92ng/ml, range 0.31-6.64 ng/ml, $p<0.0001$). All five females with FA over the age of 25 had undetectable AMH levels and were diagnosed with POI. Six of seven FA patients over the age of 20 developed cancer (median age 27; three prevalent, three incident) while all unaffected female relatives and unrelated controls were cancer-free. Females with DC had AMH levels that were significantly lower (0.55 ng/ml, range 0.01-4.82 ng/ml) than their unaffected relatives (2.33 ng/ml,range0.44-10.03 ng/ml, $p=0.001$) and unrelated healthy controls ($p=0.001$) while AMH levels of females with DBA (0.90 ng/ml, range 0-10.20) did not significantly differ from their unaffected relatives (1.71 ng/ml, range: 0.56-5.10 ng/ml, $p=0.21$) or unrelated healthy controls ($p=0.14$). One patient with DC reported fertility issues, two patients with DBA were diagnosed with POI, and all three had AMH levels under 1ng/ml. Only one patient with DC had prevalent cancer while DBA patients and all relatives of patients with IBMFS were cancer-free. This study is the first to demonstrate AMH deficiency in females with IBMFS and to suggest that measurement of AMH is useful for the early diagnosis of POI in IBMFS. Our data suggest that AMH may be lower in FA than in DC and DBA. Prior studies indicate that the rates of cancer are highest in FA, followed by DC, and lowest in DBA. Further research is warranted to determine whether there is an association between AMH deficiency and increased cancer risk in IBMFS or within the general (unaffected) population.

Biography

Martha Sklavos earned her undergraduate degree from Johns Hopkins University andher PhD in Immunology from the University Of Pittsburgh School Of Medicine. Currently, Martha is a post-doctoral fellow at the HPV Immunology Laboratory at the Frederick National Laboratory for Cancer Research where she was awarded a grant from the National Cancer Institute to investigate a novel biomarker for cervical cancer risk. She is now leading several studies to define the role of this novel biomarker in additional cancer types. Martha enjoys conceptualizing ideas and driving projects forward and hopes to fill a similar role in the pharmaceutical industry upon completion of her post-doctoral training.

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