

## More on Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency in a Neonate

**TO THE EDITOR:** Rice and colleagues (Oct. 25 issue)<sup>1</sup> report a severe neonatal presentation of medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency and suggest that newborn screening results should be communicated by 72 hours of age. In practice, it is unlikely that newborn screening, however timely, could prevent such events. My colleagues and I documented fatal neonatal presentations in 4 of the 81 patients with MCAD deficiency who were born in Australia between 1994 and 2004.<sup>2</sup> All died before 72 hours. Five babies in the cohort with other fatty acid-oxidation defects also died, between 22 and 65 hours of age.

Reporting all screening results by 72 hours of age appears to be virtually impossible. Samples are taken at 24 hours, leaving only 48 hours for transporting samples to the laboratory, assaying large batches, checking, reassaying, sending results, and finally, finding the baby. The risk that a baby with MCAD deficiency will die in the first 72 hours seems likely to be around 5%, or one case per 300,000 births. Maybe we need to acknowledge that these early-presenting babies cannot be saved by the screening process itself.

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1. Rice G, Brazelton T III, Maginot K, Srinivasan S, Hollman G, Wolff JA. Medium chain acyl-coenzyme A dehydrogenase deficiency in a neonate. *N Engl J Med* 2007;357:1781.

2. Wilcken B, Haas M, Joy P, et al. Outcome of neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia: a cohort study. *Lancet* 2007;369:37-42.

**THE AUTHORS AND A COLLEAGUE REPLY:** In response to Wilcken's letter, we agree that some neonates will present with severe manifestations of MCAD deficiency before it is possible to identify them by newborn screening. However, it is incumbent on screening programs to streamline the process in order to decrease the time from birth to the report of an abnormal result. By obtaining specimens at 24 to 48 hours of age (depending on the time of birth) and providing 7-days-a-week laboratory operation and overnight courier service (and educating hospitals not to batch specimens for shipping), it should be possible to provide reports within 50 to 74 hours. Thus, this response time will be within the necessary time frame to either prevent the onset of disease or favorably affect the disease course for many of the newborn presentations. Earlier identification in the child described would have probably prevented the complications. Depending on local clinical practices (e.g., the propensity to check blood glucose levels in sick newborns), expedited newborn screening is likely to provide the opportunity to avoid severe complications and death in other newborns.

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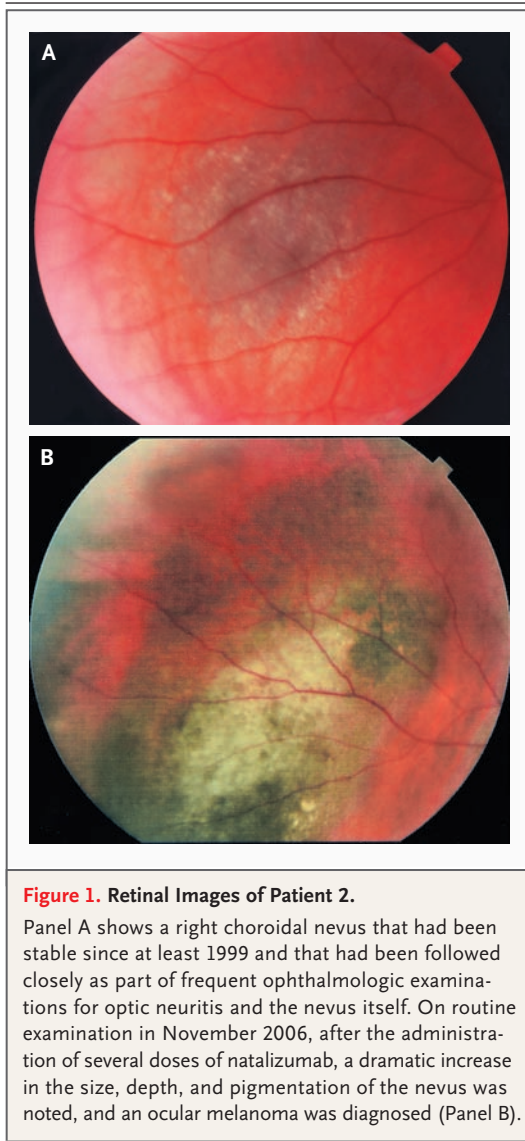
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## Melanoma Complicating Treatment with Natalizumab for Multiple Sclerosis

**TO THE EDITOR:** We report on two cases of melanoma in women with multiple sclerosis who were treated with natalizumab (Tysabri, Biogen Idec and Elan Pharmaceuticals), a humanized monoclonal antibody against  $\alpha_4$  integrins. Patient 1 was a 46-year-old woman who, shortly after receiving her first dose of natalizumab, noticed a

rapidly changing mole on her shoulder; on evaluation, it proved to be a thick, nonulcerated melanoma with metastatic disease in the regional lymph nodes. Patient 2 was a 45-year-old woman who had a long-standing ocular nevus that developed into an ocular melanoma after the administration of several doses of natalizumab (Fig. 1).



**Figure 1. Retinal Images of Patient 2.**

Panel A shows a right choroidal nevus that had been stable since at least 1999 and that had been followed closely as part of frequent ophthalmologic examinations for optic neuritis and the nevus itself. On routine examination in November 2006, after the administration of several doses of natalizumab, a dramatic increase in the size, depth, and pigmentation of the nevus was noted, and an ocular melanoma was diagnosed (Panel B).

Further treatment with natalizumab was withheld by her neurologist. The patient had no history of melanoma but did have many atypical moles. In addition, both her father and a brother had had melanoma and were alive and well.

These findings suggest that therapy with antibodies against  $\alpha_4$  integrins may lead to the development and progression of melanoma. In both patients, there were close temporal relationships between the administration of natalizumab and dramatic changes in long-standing nevi. Moreover, another case of metastatic melanoma has been reported in a patient receiving natalizumab.<sup>1</sup> In an experimental mouse model

of melanoma, expression of the  $\alpha_4\beta_1$  integrin on melanoma cells promotes homotypic intercellular adhesion and a decreased ability to invade extracellular matrix gels, thus inhibiting the metastasis of melanoma at the earliest, invasive stage of the metastatic cascade.<sup>2</sup> Bauer et al.<sup>3</sup> demonstrated that melanoma inhibitory activity protein, a small protein that is secreted by melanoma cells and that is known to promote the cells' invasive and migratory potential, binds to  $\alpha_4\beta_1$  integrin and down-regulates its activity.

In addition, the immune system plays a critical role in the control of the growth and metastasis of melanoma tumors. Antibodies to  $\alpha_4\beta_1$  integrin inhibit the migration of lymphocytes to sites of cutaneous inflammation and cytokine injection,<sup>4</sup> and anti- $\alpha_4$ -integrin antibodies induce apoptosis in activated, mature lymph-node T cells in an in vitro model.<sup>5</sup> It is thus possible that anti- $\alpha_4$ -integrin antibodies down-regulate the immune system both at the primary tumor site and in the regional nodal basin, thereby promoting the locoregional spread of melanoma.

In conclusion, we recommend that natalizumab not be administered to patients with a personal or family history of melanoma or to those with atypical moles or ocular nevi. At the very least, we recommend that alternative therapies be strongly considered in such patients.

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Dr. Vartanian reports receiving lecture fees from EMD Serono and consulting fees and grant support from Biogen Idec; and Dr. Atkins, consulting fees from Schering-Plough and grant support from SAIC-Frederick. No other potential conflict of interest relevant to this letter was reported.

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