formation of paraproteins has been shown to correlate with high lipemic indices in clear samples (2). Formation of these precipitates can interfere with the measurement of other analytes, especially those that rely on spectrophotometric detection. This patient had Waldenstrom macroglobulinemia (IgM kappa, 1280 mg/dL).

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References


News & Views

Predictive Testing and Alzheimer Disease
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Alzheimer disease (AD),2 the most common form of dementia, is a progressive degenerative neurological disorder characterized by the accumulation of β-amyloid plaques and τ protein neurofibrillary tangles in brain gray matter. There are currently no therapies to halt or reverse AD progression and no laboratory tests to make a definitive diagnosis. To date, the bulk of AD research has focused on amyloid-β deposition. In response to the largely disappointing results of β-amyloid–targeting therapies in clinical trials, it appears that interest may now be shifting toward apolipoprotein E (ApoE) as described in the recent Nature article, “The Forgetting Gene,” by Laura Spinney (1). With a projected 13.8 million Americans over the age of 65 living with AD by 2050, renewed focus on ApoE as both a therapeutic target and predictive test could have major impacts in delaying symptoms and slowing disease progression (2).

ApoE is not a newcomer to the AD research scene, yet the time and money dedicated to researching its role have been largely overshadowed by β-amyloid. Research from 2004 showed an association between the presence of the APOE (apolipoprotein E)3 allele ε4 (ApoE4) and an earlier onset of AD and the extent of AD-related brain pathology (3). Although the exact role of ApoE4 is not known, it is hypothesized that production of ApoE4 by stressed neurons may generate mitochondrial-toxic breakdown products and/or promote β-amyloid deposition. Possible therapies include the development of “corrector” molecules to revert ApoE4 to the less harmful ApoE3 form, and molecular targeting of DNA coregulatory elements of both ApoE and the mitochondrial support protein, Tom40

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2 Nonstandard abbreviations: AD, Alzheimer disease; ApoE, apolipoprotein E; TOMM40, translocase of outer mitochondrial membrane 40 homolog (yeast).

3 Human genes: APOE, apolipoprotein E; TOMM40, translocase of outer mitochondrial membrane 40 homolog (yeast); BRCA, early-onset breast cancer.
In terms of clinical diagnostics, the value of ApoE genotyping as a predictor of AD risk has yet to be fully delineated. Such efforts are complicated by the notion that AD does not conform to the 1 gene–1 disease hypothesis. While the majority of Americans possess the ApoE3 allele, which is not associated with accelerated AD onset, additional risk factors such as age, sex, and familial history can play an important role (3). A phase III clinical trial (TOMMORROW) of a predictive risk-assessment algorithm examining age and APOE and TOMM40 genotype, expected to run over the next 6 years, could provide the insight to fill this knowledge gap.

An additional issue with ApoE genotyping is that AD falls into the same category as polycystic kidney disease and Huntington disease—diseases for which there are currently no effective preventative treatments or therapeutic interventions. As such, ApoE genotyping differs from other gene-associated risk assessment strategies. In BRCA (early-onset breast cancer) mutation analysis, for example, identification of a deleterious mutation can mitigate breast and ovarian cancer development through interventions such as prophylactic medications or elective surgery (4). Still, it is estimated that even delaying AD onset by 2 years could result in 2 million fewer cases of AD over the next 50 years (5). In 2009, researchers noted delayed symptom progression in type 2 diabetic patients with mild AD taking the drug pioglitazone (6). The TOMMORROW clinical trial will also explore the utility of pioglitazone in individuals deemed high risk by the age and genotype algorithm.

AD-related brain pathology precedes the onset of symptoms; a diagnosis during life is currently made through a combination of psychological and cognitive clinical criteria. As the incidence of AD is expected to grow in the coming years, identifying those at greatest risk through genotype analysis, in combination with other risk factors, will be essential for delaying symptom onset and slowing disease progression while additional therapies continue to be evaluated.

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References