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EDITORIAL

Alzheimer's risk and quality of life: History of Down syndrome as a case in point

Alzheimer's disease (AD) has become one of the most pressing public health concerns facing the world, with prevalence and costs of care increasing dramatically with extended life expectancy.[1] Current investments in research target risk reduction and discovery of disease-modifying treatments, but efforts to date have had only marginal impact, if even that. Some speculation has focused on improvements in general health and quality of life (e.g., Livingston et al.[2]), but any benefits of these kinds of positive changes, while having obvious other benefits, have uncertain impacts on dementia risk per se. Evidence is needed that the substantial costs inherent in implementation of policies that would have broad impacts on quality of life, either by reducing deleterious circumstances or by expanding enriching ones, would be justified. The history of AD risk in adults with Down syndrome (DS) would seem to provide a piece of that evidence.

Increased risk for AD is an established phenotypic feature of DS (trisomy 21), and DS is now recognized as the most prevalent specific genotype linked to AD clinical progression prior to age 60.[3,4] Current estimates of cumulative incidence of dementia caused by AD in adults with DS suggest a median age of onset in their late 50s to early 60s, although a significant minority of individuals can be expected to be dementia free well into their late 60s or even early 70s.[5,6] This increased risk for AD has been linked to overexpression of the gene coding for amyloid precursor protein (APP), located on human chromosome 21 and therefore triplicated in DS.

Additional evidence supporting a central role of APP triplication is provided by two independent lines of evidence. First, case reports have described two adults with DS with micro-disomy of the region including APP.[7,8] These individuals survived to late adulthood without developing either dementia or neuropathology consistent with a *post mortem* diagnosis of AD. Second, individuals without DS but with micro-trisomy of APP (*APPdup*) also show extremely high risk for AD (e.g., Rovelet-Lecrux et al.[9]).

While AD risk associated with DS has been attracting considerable attention in recent decades, interest was limited prior to what can be considered the "modern era," most likely because very few adults with DS survived to ages of risk. Fraser and Mitchell[10] noted that, never having seen an adult with DS older than 43 (referred to therein as "Kalmuc Idiocy"—this report predated terminology acknowledging Down's[11] classic paper), cause of death was often "attributed to nothing more definite than … a sort of precipitated senility" (p. 175). Of course, medical terminology was very different in 1876 (and well before Alzheimer's [1907] classic paper—see Alzheimer et al.[12] for an English translation), so it is impossible to know if these cases of "precipitated senility" actually had AD or some other condition causing aging-related frailty. Fortunately, Jervis[13] provided far more explicit treatment of the issue, clearly describing high risk for dementia in his sample of middle-aged adults with DS together with neuropathology consistent with AD. While he only examined three cases *post mortem*, clinical descriptions of 10 cases indicated a 50% prevalence of frank dementia prior to age 50. That prevalence naturally included younger cases, suggesting an even higher cumulative incidence by age 50, assuming survival, which for this birth cohort would only have been the case for the most fortunate—and constitutionally strongest—few.

Current studies of dementia risk for adults with DS indicate that cumulative incidence prior to age 50 is no higher than 10% and only reaches 50% in the late 50s (e.g., Lai et al.[14]). This represents an enormous reduction in risk compared to "historical" cohorts of adults with DS and suggests that powerful "protective factors" have been operating over the period between roughly 1900 to 1920, when the cases reported by Jervis were born, and the 1960s to 1970s, the birth cohort of adults with DS currently over the age of 50. What then, might be the nature of these protective factors?

While expression of genes on chromosome 21 (and on other chromosomes) have been identified as possible modifiers of dementia risk for adults with DS (e.g., Lee et al.[15]), there is no reason to suggest that the genotype has changed in any significant way over the past several generations. There remains a lifetime overproduction of APP and a consistent phenotype in all other respects.

For late onset AD (LOAD) more generally, nongenetic factors have also been implicated in modifying risk. These have included a protective impact of high cognitive reserve (e.g., Stern,[16] Stern and Baruli,[17] and Cabeza et al.[18]) as well as high general intelligence (e.g., Russ[19]). Of course, these factors are invariably associated with individual differences in social and vocational risks across most of the lifespan (e.g., history of head trauma; vocational exposure to environmental toxins). However, it seems unlikely that any of these specific factors could explain such a remarkable reduction in age-specific risk for adults with

DS, given their lifelong cognitive impairments and low likelihood of exposures to environmental hazards.

Reduced AD risk for adults with DS also cannot be related to a tendency toward differential survival of the "healthiest" individuals. Whatever healthy survivor effect might be operating across birth cohorts would tend toward favoring earlier generations. Nor can it reflect an artifact of improved methods of assessment given that modern improvements in diagnostic methods would have shifted cumulative incidence toward earlier detection via increased sensitivity to the relatively subtle symptoms of early clinical progression.

What, then, seems to be a likely protective factor that has changed for people with DS since the mid to late 19th century? Advances in medical care is an obvious contributor, but we believe the evidence implicates improved quality of life more broadly. Prior to the mid-20th century, all people with cognitive or mental impairments were treated extremely harshly, even by the standards of the time. Since then, virtually all aspects of the lives of people with DS have improved, as is the case for virtually all individuals with developmental disabilities. Some of these improvements no doubt happened prior to the birth of the Jervis[13] cohort, but here again, educational and social policies devalued people with developmental and mental disabilities and individuals with DS were extremely unlikely to experience positive educational or other enriching experiences.

Contemporary policies, at least in developed countries, include access to early intervention programs, and free and appropriate education is mandated by law. Social acceptance of individuals with developmental disorders is broadly supported through additional formal policies and enlightened societal attitudes. Not unexpectedly, these factors, along with advances in medical care, have resulted in a major increase in early survival and longevity in adulthood. However, a major impact on AD risk, if it is indeed another consequence of improved quality of like, is somewhat of an unexpected benefit. With a cumulative incidence of dementia for adults with DS reaching 50% by approximately age 57 to 60,[20] current relative risk remains extremely high compared to the broader population, but it represents a dramatic decrease compared to the first half of the 20th century and earlier.

The broader implication is that comparable reductions in risk might be possible for LOAD more generally with greater access to highly nutritious diets, expanded educational opportunities, increases in healthy lifestyle decisions, and decreases in deleterious environmental exposures. The question remains whether disadvantageous circumstances increase risk or advantageous circumstances are protective, but these are really two sides of the same coin. What does seem clear is that supportive environmental circumstances can shift the overall cumulative incidence curve substantially. As Zissimopoulos et al.[21] estimated, even a 2-year delay in onset of dementia would result in a 15.6% reduction in lifetime risk and a 17% reduction in expected years of living with dementia, representing enormous benefits for individuals at risk, their families, and society. This history of AD in adults with DS suggests that parallel benefits might accrue virtually automatically for all populations at risk if our society choses to support a generally improved quality of life for all its citizens.

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Wayne Silverman[1]
Sharon Krinsky-McHale[2]

[1] *Department of Pediatrics, University of California, Irvine, Inglewood, California, USA*
[2] *Department of Psychology, New York State Institute for Basic Research in Developmental Disabilities, New York, New York, USA*

Correspondence
Wayne Silverman, Department of Pediatrics, University of California, Irvine, Department of Pediatrics, 333 City Blvd. West, Suite 800, Orange CA 92628, USA.
E-mail: wsilverm@hs.uci.edu

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