Hypothyroidism is associated with significant neurocognitive deficits that develop across the life span. This article discusses the patterns of cognitive deficits associated with congenital and adult-onset hypothyroidism. A review of the extant literature shows that the successful treatment of clinically evident thyroid gland hypofunction, resulting in a return to euthyroidism in both infants and adults, may be associated with only partial and typically inconsistent patterns of recovery of overall neurocognitive function. In addition to demonstrating different patterns of cognitive impairments, patients with congenital and acquired adult-onset hypothyroidism have variable responses to thyroid replacement therapy, which increases the risk of higher neurocognitive morbidity associated with congenital hypothyroidism. An evaluation of the commonly held view that hypothyroid dementia is an imminently reversible condition is only partially supported by the medical literature, which is fraught with methodological and conceptual shortcomings. I offer some recommendations for addressing the cognitive and behavioral management concerns of individuals with clinical hypothyroidism.

Many primary endocrine disorders have notable effects on cognition. Patients with a wide range of thyroid gland abnormalities often present with combined emotional and cognitive symptoms. Unfortunately, cognitive impairments associated with thyroid gland hypofunction are often overlooked by clinicians when patients do not overtly complain of changes in their neurocognitive status. Such errors of omission would be minimized if clinicians became more knowledgeable about the patterns of cognitive deficits that accompany hypothyroidism. The early recognition of conditions such as dementia, depression, and other neuropsychiatric abnormalities known to be associated with hypothyroidism are almost exclusively dependent on the routine and systematic assessment of cognition. Herein, I review the major neurocognitive deficits associated with hypothyroidism. Primarily, I will focus on the effects of clinical (rather than subclinical) hypothyroidism, the differential patterns of cognitive deficits in congenital and acquired hypothyroidism, and the impact of thyroid pharmacotherapy on the cognitive status of patients with hypothyroidism.

Although hypothyroidism has long been known to be associated with profound depression, this review will not address that issue because excellent reviews of hypothyroidism and depression are available elsewhere.1,2

CONGENITAL HYPOTHYROIDISM

The thyroid hormone is important to the functional development and maturation of the central nervous system; the association between the absence of thyroid hormones and congenital hypothyroidism and profound mental retardation has been recognized for more than a century. It is thought that the administration of supplementary iodine prior to conception in human mothers is effective in preventing the significant neuropsychological effects of thyroid gland dysfunction.3 Results from magnetic resonance imaging scans of cerebral morphologic features and myelination in infants diagnosed as having con-
genic hypothyroidism through neonatal screening reveal findings ranging from delayed and abnormal white matter myelination patterns to normal brain myelination and circumvolutions. The latter finding of no detectable morphological brain abnormalities has been attributed to the lingering neuroprotective effects of maternal thyroid hormones introduced to fetal transport by the placenta. However, there is evidence that very little thyroxine actually crosses the placental barrier, compelling the fetus to depend almost exclusively on its own thyroid gland, which, if underdeveloped, constitutes an imminent risk for congenital hypothyroidism. The story, however, is still not that simple: evidence from animal studies suggests a critical perinatal period during which deficiencies in thyroid gland function result in permanent morphological, histopathological, and behavioral abnormalities. While this window of opportunity has not been clearly delineated in humans, there are reports of normal intellectual function in patients with hypothyroidism who underwent thyroid replacement therapy (TRT) prior to 3 or even 7 months of age. Despite these findings, the lack of a comprehensive evaluation of a wide variety of cognitive domains other than general intelligence (eg, attention, language, learning and memory skills) necessitates restraint in inferring that early intervention with TRT results in normal neurocognitive functioning. Evoked potential studies of auditory brainstem responses in children with congenital hypothyroidism who received postnatal TRT as early as 3 weeks of age showed significant audiometric deficits well into childhood. Consistent with these audiometric deficits are findings of hearing impairment and expressive language deficits, including difficulties with naming, in young children, which together call for more a comprehensive assessment of neurocognitive functioning across a broad range of domains in children with congenital hypothyroidism. Recent retrospective Canadian data report mild binaural conduction and sensorineural hearing loss in 20% of children with congenital hypothyroidism identified at neonatal screening, with strong indications that early treatment (within 2 weeks after birth) may reduce the incidence of hearing impairment. Although the children with congenital hypothyroidism and hearing impairment scored in the normal range on most general language tests, subtle impairments in their auditory speech-sound discriminations and reading skills were evident. Psychometric evidence of average IQ scores in children with hypothyroidism is not necessarily evidence that those children have normal cognitive abilities. For example, a Belgian study found notable deficits in the attention span and cognitive information processing skills of children whose average IQ was a normal 100.1 (range, 87.6-113.8).

Pediatric hypothyroidism tends to be associated with attention deficits. While children with congenital hypothyroidism have demonstrated notable neurocognitive impairments based on objective cognitive tests designed to assess attention span (rather than on the basis of observer ratings of distractibility and inattention), it appears that numerous other factors, including overall treatment efficacy, disease onset, severity, and duration, as well as levels of thyroxine and thyrotropin, contribute to the clinical manifestation of the attention deficits. A recent study of children diagnosed as having attention-deficit/hyperactivity disorder reported an unexpectedly higher incidence of hypothyroidism than hyperthyroidism, the latter indicated by resistance to thyroid hormone (RTH) disorder. Resistance to thyroid hormone is, in fact, rare in community-based samples of individuals with attention-deficit/hyperactivity disorder. Although it appears that the profile of neurocognitive deficits associated with RTH disorder is not entirely consistent with that exhibited in attention-deficit/hyperactivity disorder, we are still far from understanding exactly how the neurocognitive deficits related to RTH disorder differ from children treated for congenital hypothyroidism, especially given the fact that some individuals with RTH disorder appear to be mildly hypothyroid.

**FOLLOW-UP STUDIES IN CONGENITAL HYPOTHYROIDISM**

At least 2 study groups in North America, the Quebec Screening Program and the New England Congenital Hypothyroidism Collaborative, have reported prospective findings based on neonatal screening and TRT indicating that 10% to 15% of individuals with congenital hypothyroidism were resistant to treatment in their respective studies. These patients had IQ scores in the borderline impaired range or lower by the time they entered school (ie, at ages 5-7 years). In contrast, a 26-year follow-up study showed dramatic increases (at least 20 points) in the IQ test scores of 15% of individuals with congenital hypothyroidism who were assessed at 3 separate periods from childhood (ie, at ages 5-6 years) through adulthood. This finding was interpreted as evidence that intellectual growth in treated congenital hypothyroidism may continue beyond the traditionally expected end point, well into adulthood. Unfortunately, the authors of the study failed to concede a potential difficulty that arises when predictions and assessments of changes in scores from baseline pediatric IQ tests are made: while initial test scores may be related to the condition and severity of the disease, they are not always accurate predictors of later cognitive (ie, IQ) performance in individuals both with and without mental retardation. Evidence from 4-year longitudinal studies of language and auditory processing skills in young children with congenital hypothyroidism shows essentially no difference in the expressive language skills between 7-year-olds with and without hearing impairments, although the cohorts with hearing impairments continued to exhibit receptive language and reading deficits on serial assessment.

In a cross-cultural prospective study of nonverbal short-term memory span and pictorial serial
position memory in teenagers from Papua New Guinea (most of whom had an iodine deficiency and mothers who had received supplementary iodine during pregnancy), measured levels of total maternal thyroxine were not significantly associated with simple short-term memory span when the cohorts were 14 to 15 years old. However, on testing 2 years later, levels of total maternal thyroxine were significantly associated with more complex reverse order memory span operations and moderately associated (r = 0.30) with serial position memory. This group of teenagers was also administered a serial manual dexterity test, with results indicating consistent associations between total thyroxine levels and manual dexterity over time. Evidence of impairments in the development of motor skills in children with congenital hypothyroidism appears to be consistent with other follow-up studies. In another longitudinal follow-up study in which children with congenital hypothyroidism were assigned to groups on the basis of their skeletal maturity (an indicator of uterine hypothyroidism), it was found that beginning at ages 2 to 5 years, fine motor and visuo perceptual skills were significantly depressed in those with delayed skeletal maturity. Relative deficits in expressive and receptive language abilities emerged at ages 4 through 5 years, at which time cognitive assessments also indicated gross intellectual difficulties. Those authors concluded that while early detection and treatment of congenital hypothyroidism may be useful in preventing mental retardation, it may not be as effective in preventing other neurocognitive deficits.

In summary, untreated congenital hypothyroidism causes profound mental retardation characterized by severe cognitive deficits. Although early identification and treatment of congenital hypothyroidism has been known to improve scores on formal tests of intelligence, there is still evidence of neurocognitive deficits in attention, visuospatial processing, motor dexterity, and language comprehension skills that may persist through late childhood and in some cases adolescence. In addition, with the exception of studies that found a consistent association between total thyroxine levels and motor dexterity over time, improvements in neurocognitive abilities do not generally appear to follow a predictable course, even with continued return to euthyroidism.

**NEUROCognitive DYSFUNCTION IN ADULTS WITH HYPOTHYROIDISM**

The onset of primary clinical hypothyroidism in adults has a variety of adverse effects on adaptive neurocognitive functioning. The **Table** shows some of the major patterns of cognitive deficits that have been documented in association with hypothyroidism.

Unfortunately, most of the published reports on neuropsychological functioning in adults with hypothyroidism are based on the assessment of only limited aspects of cognitive domains. For instance, there is a paucity of extant research on sustained and selective visual attention, speed of visual information processing, abstract concept formation and complex problem-solving abilities, academic achievement skills, tactile perception, and praxis/motor functions in patients with thyroid gland hypofunction. Of the cognitive domains that have been studied (Table), one may conclude that hypothyroidism is associated with deficits in memory, psychomotor slowing, and visuo perceptual and

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**Neurocognitive Deficits in Hypothyroid Adults**

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Source, y</th>
<th>Impaired</th>
<th>Treatment Outcome</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>General intelligence</td>
<td>Crown, 1949</td>
<td>Yes</td>
<td>Improvement after 3 mo</td>
<td>RPM, MMV, SVT</td>
</tr>
<tr>
<td>Complex attention and concentration</td>
<td>Mennemeier et al, 1993</td>
<td>Yes</td>
<td>Not generally affected</td>
<td>WAIS-R</td>
</tr>
<tr>
<td>Memory</td>
<td>Haggerty et al, 2010</td>
<td>Yes</td>
<td>No change after 10.5 mo</td>
<td>TMT (Parts A and B)</td>
</tr>
<tr>
<td>Perceptual and visuospatial function</td>
<td>Osterweil et al, 1992</td>
<td>Yes</td>
<td>Improvement</td>
<td>Inglis Paired Associates Learning Test</td>
</tr>
<tr>
<td>Language (expressive)</td>
<td>Osterweil et al, 1992</td>
<td>Yes</td>
<td>No improvement</td>
<td>Cube Copying</td>
</tr>
<tr>
<td>Language (receptive)</td>
<td>Osterweil et al, 1992</td>
<td>No</td>
<td>No improvement</td>
<td>Word Fluency Test (Animals)</td>
</tr>
<tr>
<td>Executive frontal system functions</td>
<td>Osterweil et al, 1992</td>
<td>No</td>
<td>No change</td>
<td>Word Discrimination, Oral Reading</td>
</tr>
<tr>
<td>General screening</td>
<td>Osterweil et al, 1992</td>
<td>No</td>
<td>No movement</td>
<td>Modified Mini-Mental State Examination</td>
</tr>
<tr>
<td>Motor function</td>
<td>Mennemeier et al, 1993</td>
<td>No</td>
<td>Progressive decline</td>
<td>Mini-Mental State Examination</td>
</tr>
</tbody>
</table>

*Data pertain only to studies that focused on outcome following treatment. RPM indicates Raven Progressive Matrices Test; MMV, Mill Hill Vocabulary Scale; SVT, Shipley Vocabulary Test; WAIS, Wechsler Adult Intelligence Scale; DSR, Dementia Rating Scale (Mattis); WAIS-R, Wechsler Adult Intelligence Scale—Revised; PASAT, Paced Auditory Serial Addition Task; TMT, Trail-Making Test; SDMT, Symbol Digit Modalities Test; NA, not applicable; CVMT, Continuous Visual Memory Test; FMT, Milner Facial Memory Test; RCFT, Rey-Osterrieth Complex Figure Test; SRT, Selective Reminding Test (Buschke); WMS, Wechsler Memory Scale.\(^*\)
Any discussion about health care ated pharmacological management. slowed with prompt and appropri-roidism cannot be averted or at least patients with untreated hypothy-
ocognitive decline usually seen in evidence for complete reversibility.

However, a recent review of the lit-
terature that must be considered is the lack of adequate classification criteria by which different degrees of thyroid gland hypofunction may be associated with their respective neurocognitive sequelae. As a consequence, for example, there is no clear indication of how the cognitive profiles of patients with mild hypothyroidism may differ from those with more severe cases.

HYPOTHYROIDISM AND DEMENTIA

Myxedema traditionally has been classified as one of the reversible causes of dementia in the elderly. However, a recent review of the literature on hypothyroidism as a cause of dementia has found no strong evidence for complete reversibility. This, however, does not imply that the progressive and relentless neurocognitive decline usually seen in patients with untreated hypothyroidism cannot be averted or at least slowed with prompt and appropriate pharmacological management. Any discussion about health care management concerns with elderly patients necessitates addressing the following issues related to cognitive status and assessment: the prevalence of sensory defects such as reduced visual and auditory acuity, multiple drug treatments for the typically chronic physical illnesses that many older adults experience, the higher susceptibility among geriatric populations to the serious adverse effects of altering medications, and the increased likelihood of a latent coexisting dementia caused by something other than hypothyroidism. Older patients are particularly susceptible to developing primary hypothyroidism, a disease that becomes more common with age. Only a few empirical investigations of the neurocognitive effects of hypothyroidism in older populations have addressed these issues. Further studies will be necessary to assess intellectual decline in patients with late-onset hypothyroidism.

REVERSIBILITY OF HYPOTHYROID DEMENTIA

A number of researchers have reported that between 10% and 30% of patients diagnosed as having syndromes that cause dementia have reversible or potentially treatable dementia. However, when these claims are subjected to critical scrutiny, one is led to believe that the actual incidence of reversible dementia may be much lower, probably in the order of 8% partial and 3% full-reversal over relatively brief periods. There is evidence from prospective follow-up data indicating that reversal to normal premorbid levels is the exception rather than the norm, and that many of the patients who show improvements in cognitive functioning after treatment may not have had dementia in the first place. Currently, to meet diagnostic criteria for dementia, an individual must have multiple cognitive deficits that include memory dysfunction severe enough to impair adaptive social or occupational functioning. Also, and perhaps more importantly, these cognitive impairments must have declined significantly from a higher level of functioning. Studies of neurocognitive aspects of hypothyroid dementia may need to demonstrate objective or estimated declines from premorbid levels using one of the many innovative assessment techniques now available. Without such evidence, reports of dementia in the medical literature may be less defensible, particularly when the data presented indicate a complete reversal of the underlying degenerative process. Nevertheless, the fact that current pharmacotherapies may not be able to fully reverse the clinical complexes of patients with hypothyroidism does not mean that the progressive decline of their neurocognitive abilities cannot be slowed or stopped. Early reports regarding the reversibility of dementia have had to contend with spurious artifacts such as the practice effects that may accrue from serial testing over brief periods, thereby unduly overestimating actual cognitive abilities at retest. In addition, it has often been questioned whether reversals of dementia would be sustained if the patients were observed for extended follow-up periods, thus raising concerns about the duration of treatment effects.

In sum, the current empirical studies that claim that hypothyroidism is a fully reversible dementia are constrained by significant conceptual and methodological difficulties, and in many cases do not report consistent improvements to normal or premorbid levels of cognitive functioning following treatment. Unfortunately, one cannot always be sure that these neuropsychological findings are exclusively due to the effects of hypothyroidism, because the likelihood of co-morbidity with neurodegenerative disorders or other factors influencing cognitive status may be quite high. It has often been argued that more emphasis should be placed on the appropriate social management of patients with cognitive decline related to hypothyroidism, and that classification of reversible and irreversible forms of dementia be avoided. Clearly, more data are needed to determine the extent to which hypothyroid dementia can be treated and the level of disease severity for which pharmacological intervention would be most effective.

CONGENITAL VS ACQUIRED HYPOTHYROIDISM

At first glance, congenital and adult-onset hypothyroidism may appear to be associated with similar patterns
of neurocognitive deficits, especially with regard to short-term memory, visuospatial perception, and general intelligence. However, there are a number of factors that militate against making such an inference. One has to do with the extent and ability of the brain to recover lost function. In general, neuroplasticity varies directly with age, favoring infants over older individuals. Thus, although certain sensorineural deficits such as hearing loss may occur in both congenital and adult hypothyroidism, the developmentally based neurocognitive expression of such deficits, including treatment responses, may differ remarkably in these populations. This variability in treatment response and partial recovery may have more severe delayed neurobehavioral consequences in congenital hypothyroidism on TRT than may be expected in adult-onset hypothyroidism. Hence, the age at which hearing loss may have occurred in association with hypothyroidism is bound to have a differential impact on the nature and severity of subsequent language disorders exhibited on neurocognitive assessment in various age groups. In terms of motor deficits, the lack of comprehensive empirical data on manipulative dexterity and other pure motor functions in adults does not permit clear comparisons between congenital and acquired hypothyroidism.

While there is conflicting evidence in the literature on adult and congenital hypothyroidism regarding the extent and duration of recovery of cognitive functions following treatment with TRT, such recovery may not always be complete and does not seem to follow a consistent pattern in all cases. What is patently clear in both age groups, however, is the inexorable global decline in cognition when TRT is either delayed or absent.

CONCLUSIONS

Although the current empirical literature on the neurocognitive effects of clinical hypothyroidism is quite rudimentary, it is obvious that every individual diagnosed as having this disorder should be referred for comprehensive neuropsychological evaluation in view of the strong risk for cognitive morbidity. A number of methodological and conceptual issues need to be addressed to advance our understanding of the neurocognitive correlates of hypothyroidism. For instance, because the sole reliance of physicians on cognitive screening instruments such as the Mini-Mental State Examination tends to yield high misclassification rates, more comprehensive neurocognitive evaluations are essential to better determine the patterns of cognitive strengths and weaknesses associated with hypothyroidism. Also, issues pertaining to the confounding influence of test-retest constraints (including practice effects, statistical regression to the mean, etc) need to be seriously considered if serial evaluations are used to document changes in cognitive functioning following treatment. Recent innovative and promising techniques used to determine the reliability of data indicating neurocognitive change following intervention are currently being explored in clinical neuropsychological research and may be useful in assessing the reversibility of hypothyroid dementia. In concert with these and other methods, end points other than total reversal of cognitive decline related to hypothyroidism may have to be considered as viable clinical targets (eg, reduction in the negative slope of decline in treated patients compared with untreated cohorts) should future empirical research consensus indicate intractability of the hypothyroid dementia complex. Children diagnosed as having hypothyroidism have a greater likelihood of experiencing educational difficulties similar to what adults might experience in their vocational or occupational pursuits. Comprehensive neuropsychological evaluations can provide useful suggestions regarding the extent to which any difficulties with learning and memory, fine-motor skills (which influence writing abilities), phonetic, or other linguistic skills can be circumvented in the academic setting. Early assessment of cognition in adults can provide objective evidence for changes in their neuropsychological status over time, with ramifications for the establishment of long-term care planning and management. Whether an adult patient with hypothyroidism would need a restrictive level of management and care or be able to live independently in a supervised setting usually depends on the patient’s cognitive and behavioral strengths and weaknesses, which are best determined by a comprehensive neurocognitive evaluation.

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