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Putting Evidence into Practice

Cerebrospinal Fluid Biomarkers for Detection of Alzheimer Disease in Patients with Mild Cognitive Impairment

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Clinical Question

Are cerebrospinal fluid (CSF) tau and ß-amyloid biomarkers accurate and practical tests for predicting which patients with mild cognitive impairment (MCI) will develop Alzheimer disease or other forms of dementia?

Evidence-Based Answer

There is insufficient evidence to support the routine use of CSF biomarkers for the detection of progressive dementias in patients with MCI. These tests carry the risk of overdiagnosis of dementia and, therefore, overtreatment. They have better sensitivity than specificity and may be more helpful at ruling out than ruling in progression to Alzheimer disease in patients with MCI.[1] (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

The initial symptoms in patients ultimately diagnosed with Alzheimer disease are often problems with planning, judgment, and memory, but they typically have preserved functionality in daily life. If formal testing confirms objective evidence of cognitive impairment, they are considered to have MCI. There are four potential outcomes for those with MCI: progression to Alzheimer disease, progression to another dementia, stable MCI, and recovery. Studies indicate that 6% to 15% of persons with MCI progress to Alzheimer disease each year.[2] Currently, there is no clinical method to determine which patients with MCI will progress to Alzheimer disease or other forms of dementia.

These are summaries of reviews from the Cochrane Library.

This series is coordinated by Corey D. Fogleman, MD, Assistant Medical Editor.

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Growing evidence shows that measurable changes occur in the CSF of patients with MCI who are at risk of progression to Alzheimer disease or other variant dementias, which may allow for earlier intervention to delay the onset of dementia.[3]

The authors of this Cochrane review evaluated the diagnostic accuracy of CSF t-tau, CSF p-tau, the CSF t-tau:ß-amyloid ratio, and the CSF p-tau:ß-amyloid ratio index tests for detecting which patients with MCI at baseline would develop Alzheimer disease or other forms of dementia.[1] The diagnosis of Alzheimer disease was made using various accepted definitions, including criteria from the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders*.[4] The review included 15 longitudinal cohort studies and 1,282 participants with MCI; 430 participants progressed to Alzheimer disease, and 130 participants progressed to other forms of dementia. Participants were 45 to 76 years of age, and follow-up ranged from one to four years. Because of the variation in index test thresholds, estimates of sensitivity and likelihood ratios were made at the fixed median value of specificity among the included studies.

The CSF p-tau:ß-amyloid ratio was the best test at ruling out conversion to Alzheimer disease, and the CSF t-tau:ß-amyloid ratio was the best test at ruling in conversion to Alzheimer disease, although there were only two studies. For example, consider 100 patients with MCI who undergo lumbar puncture and have these biomarkers assayed. Using a prevalence of 37%, a positive CSF t-tau result would correctly predict that 28 patients would develop Alzheimer disease, whereas nine patients who would develop Alzheimer disease would be missed (i.e., false negative). Eighteen would be misdiagnosed (i.e., false positive). In the same group, a positive CSF p-tau result would correctly predict that 30 patients would develop Alzheimer disease; there would be seven false-negative results and 33 false-positive results. A positive CSF p-tau:ß-amyloid ratio would correctly predict that 30 patients would develop Alzheimer disease, whereas there would be seven false-negative results and 22 false-positive results. Lastly, a positive CSF t-tau:ß-amyloid ratio would correctly predict that 34 to 36 patients would develop Alzheimer disease, and there would be one to three false-negative results and 31 or 32 false-positive results[1] *(Table 1)*.

A meta-analysis was not conducted on the studies evaluating CSF p-tau:ß-amyloid ratio or CSF t-tau:ß-amyloid ratio because of the limited number of participants and heterogeneity. Overall, study quality was limited by poor reporting about how the clinical diagnosis of dementia

TABLE 1

Longitudinal Cohort Studies of CSF Markers for the Detection of Conversion from MCI to Alzheimer Disease*

Marker	Number of studies (participants)	Sensitivity % (95% CI at median specificity)	Median specificity % (range)	LR+ (range)	LR– (range)	PPV (%)	NPV (%)
CSF t-tau	7 (N = 709)	77 (67 to 85)	72 (48 to 88)	2.7 (2.4 to 3.0)	0.32 (0.22 to 0.47)	62	84
CSF p-tau	6 (N = 492)	81 (64 to 91)	48 (22 to 86)	1.5 (1.3 to 1.8)	0.39 (0.19 to 0.82)	48	81
CSF p-tau: ß-amyloid ratio	5 (N = 433)	81 (80 to 96)	65 (33 to 95)	2.31 (1.2 to 19.2)	0.29 (0.04 to 0.61)	57.6	85.3
CSF t-tau: ß-amyloid ratio	2 (n = 37) (n = 214)	50 51	91 96	1.8 1.96	0.18 0.08	52 54	91 97

CI = confidence interval; CSF = cerebrospinal fluid; LR+ = positive likelihood ratio; LR– = negative likelihood ratio; MCI = mild cognitive impairment; NPV = negative predictive value; PPV = positive predictive value.

*—Overall prevalence of 37%.

was established, selection bias, inadequate blinding, variability in length of follow-up, and lack of a widely accepted threshold of the CSF diagnostic tests in patients with MCI.

The Biomarkers for Alzheimer's disease and Parkinson's disease European working group recommends the use of CSF Alzheimer disease biomarkers for the prediction of clinical progression or conversion to Alzheimer disease in patients with MCI with appropriate pre- and postbiomarker counseling.[5] In the primary care setting, the utility of these invasive and expensive tests remains unclear because of the risk of overdiagnosis and lack of disease-modifying interventions that make early diagnosis beneficial.

The practice recommendations in this activity are available at http://www.cochrane.org/CD010803.

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Atypical Antipsychotics for Disruptive Behavior Disorders in Children and Adolescents

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Clinical Question

Does the atypical antipsychotic risperidone (Risperdal) safely and effectively treat disruptive behavior disorders in children and adolescents?

Evidence-Based Answer

Risperidone reduces measures of aggression and improves conduct in children with disruptive behavior disorders; however, only short-term use is recommended. Weight gain of 2 to 2.5 kg (4.4 to 5.5 lb) is common. There is insufficient evidence to evaluate the benefits of other antipsychotics.[1] (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Disruptive behavior disorders in children and adolescents include conduct disorder and oppositional defiant disorder. These disorders are common, affecting 5.7% of children.[2] The authors of this Cochrane review sought to demonstrate whether atypical antipsychotics safely and effectively reduce aggression and improve conduct in children and adolescents with these disorders.[1]

TABLE 1

Comparison of Risperidone and Placebo for Disruptive Behavior Disorder in Children and Adolescents

Significant outcomes	Difference between risperidone (Risperdal) and placebo groups	Studies	Participants	Quality of evidence
Aggression (Aberrant Behavior Checklist–Irritability subscale; reference range = 0 to 45)	MD = 6.49 points lower with risperidone	3	238	Low
Aggression (Modified Overt Aggression Scale combined with Antisocial Behavior Scale–Reactive subscale)	Standardized MD = 1.30 (favoring risperidone)	2	190	Moderate
Conduct (Nisonger Child Behavior Rating Form–Conduct Problem subscale; reference range = 0 to 48)	MD = 8.61 points lower with risperidone	2	225	Moderate
Weight gain (antipsychotic alone)	MD = 2.37 kg (5.22 lb) more with risperidone	2	138	Moderate
Weight gain (stimulant plus antipsychotic)	MD = 2.14 kg (4.72 lb) more with risperidone	3	305	Low

MD = mean difference.

The review included 10 trials and 896 patients five to 18 years of age. Follow-up ranged from four to 10 weeks. Risperidone was evaluated in eight of the 10 trials[1] *(Table 1)*.

Three trials using risperidone measured aggression with the Aberrant Behavior Checklist–Irritability subscale (reference range: 0 to 45). Patients taking risperidone scored, on average, 6.49 points lower than those taking placebo (95% confidence interval [CI], –8.79 to –4.19). One risperidone trial used the Modified Overt Aggression Scale, whereas another used the two-part Antisocial Behavior Scale. Both parts of the Antisocial Behavior Scale were analyzed separately with the trial that used the Modified Overt Aggression Scale. When the Antisocial Behavior Scale–Reactive subscale was combined with the Modified Overt Aggression Scale, the analysis showed significant improvement after risperidone therapy. This change, a standardized mean difference of –1.30 (95% CI, –2.21 to –0.40), is considered clinically significant.

Conduct was measured via the Nisonger Child Behavior Rating Form–Conduct Problem subscale (reference range: 0 to 48). In a meta-analysis of two trials, patients treated with risperidone scored on average 8.61 points lower than those in the placebo group (95% CI, –11.49 to –5.74). This result is also considered clinically significant.

The most commonly reported adverse effect was weight gain. Patients taking risperidone alone gained an average of 2.37 kg (5.22 lb) more than patients taking placebo (95% CI, 0.26 to 4.49), whereas patients taking both a stimulant and risperidone gained an average of 2.14 kg (4.72 lb) more than those taking placebo (95% CI, 1.04 to 3.23). Metabolic laboratory changes were reported in one trial that involved 168 children.[3] It showed a significant incidence of hyperprolactinemia in the risperidone group (68% vs. 5% with placebo); however, only one patient taking risperidone had a clinically significant prolactin elevation.

Guidelines from the National Institute for Health and Care Excellence recommend against the routine use of psychotropic medications for disruptive behavior disorders in children and adolescents, but recommend considering short-term risperidone use for explosive anger and severe emotional dysregulation that has been unresponsive to psychosocial interventions.[4] Canadian guidelines give a conditional recommendation in favor of risperidone use for disruptive behavior disorders.[5]

The practice recommendations in this activity are available at http://www.cochrane.org/CD008559.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. government.

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