PODER LEGISLATIVO

PROVINCIA DE TIERRA DEL FUEGO
ANTARTIDA E ISLAS DEL ATLANTICO SUR
REPUBLICA ARGENTINA

COMUNICACIONES OFICIALES

Nº 078 e **PERIODO LEGISLATIVO** 2008

EXTRACTO P. E. P. - NOTA Nº 122/08 adjuntando informe requerido mediante Resolución de Cámara Nº 016/08 (informe s/detalle de la cantidad de enfermos celíacos en la pcia., discriminados en niños, adolecentes y adultos y otros ítems)

Entró en la Sesión de: 10 JUN. 2008

Girado a Comisión Nº

Orden del día Nº

PODER LEGISLATIVO
PRESIDENCIA
Nº 609
15-05-08
HORA: 11:55
FIRMA:

PODER LEGISLATIVO
FOLIO
1,32

Provincia de Tierra del Fuego, Antártida
e Islas del Atlántico Sur
República Argentina

PODER LEGISLATIVO
SECRETARIA LEGISLATIVA
MESA DE ENTRADA
Nº 078 HS 10:40 FIRMA

NOTA Nº 122
GOB

USHUAIA, 14 MAYO 2008

SEÑOR PRESIDENTE:

Tengo el agrado de dirigirme a Ud. en mi carácter de Gobernador de la Provincia de Tierra del Fuego, Antártida e Islas del Atlántico Sur, con el objeto de remitirle en contestación a la Resolución Nº 16/08 de la Legislatura Provincial, Nota Nº 1191/08 Letra: M.S., emitida por el Ministerio de Salud, con la correspondiente documental indicada en la misma, Nota de la Asociación Celíaca Argentina - Filial Río Grande de fecha 26/04/08, copia simple de la Resolución Nº 1560/2007 del Ministerio de Salud de la Nación e Informe S.L.y T. Nº 742/08.

Sin otro particular, saludo al señor Presidente con atenta y distinguida consideración.

AGREGADO: Soporte Informático.-

MARIA FABIANA RIOS
GOBERNADORA

AL SR. PRESIDENTE DE LA
LEGISLATURA PROVINCIAL
Dr. Carlos D. BASSANETTI
S / D.-

Remítase a la Soc. Legislativa.
Presidencia, 15/05/08

Carlos D. BASSANETTI
Presidente
Poder Legislativo

Provincia de Tierra del Fuego, Antártida
e Islas del Atlántico Sur
República Argentina

SECRETARÍA LEGAL Y TÉCNICA

PODER LEGISLATIVO
FOLIO
2
Secretaría Legislativa

USHUAIA, 12 MAY 2008

SEÑORA GOBERNADORA
S / D.-

Remito documentación que fuera recepcionada en esta Secretaría Legal y Técnica, dando respuesta a lo solicitado mediante Resolución Nº 16/08 de la Cámara Legislativa de la Provincia, dada en sesión Ordinaria del día 03 de Abril de 2008, consistente en: Nota Nº 1191/08 Letra: M.S., emitida por el Ministerio de Salud, con su correspondiente documental indicada en la misma, Nota de la Asociación Celíaca Argentina, Filial Río Grande de fecha 26/04/08, y copia simple de la Resolución Nº 1560/2007 del Ministerio de Salud de la Nación.

Asimismo, y de conformidad con lo dispuesto en la Ley Pcial. Nº 650, se acompaña soporte magnético conteniendo la información suministrada.

En consecuencia, correspondería remitir dicha información a la Legislatura de la Provincia.

INFORME S.L. y T. N° 142 /08.

Dr. Eduardo Raúl Olivero
Secretario Legal y Técnico

Provincia de Tierra del Fuego, Antártida e Islas del Atlántico Sur
República Argentina

MINISTERIO DE SALUD

PODER LEGISLATIVO FOLIO Secretaría Técnica

NOTA Nº 1191 /08
LETRA: M.S.

USHUAIA, 07 de mayo de 2008

Ref.: Resolución Nº 16/08 Legislatura Provincial

SR. SECRETARIO LEGAL Y TECNICO:

En respuesta a la Nota D.G.A.J.P. Nº 56/08, se remite adjunto a la presente información aportada por la Dirección de Epidemiología e Información de la Salud mediante Informe M.S.-D.E.I.S.Nº 21/08, en relación a los puntos 1., 4. y 5. de los requerimientos efectuados por la Legislatura Provincial.

Asimismo y en relación a los puntos 2. y 3., se comunica que no obran en este Ministerio antecedentes en los últimos años de la conformación del Consejo Administrativo a que refiere la Ley 366.

Dra. María Haydée GRIECO
Ministro de Salud

13:50

SECRETARIA LEGAL Y TECNICA | L | F
ENTRADA:
08 MAYO 2008
SALIDA:

DGAJL 08.05.08 14:00

Provincia de Tierra del Fuego, Atlantico e Islas
del Atlántico Sur
República Argentina

MINISTERIO DE SALUD
SUBSECRETARIA DE POLITICAS DE SALUD
DIRECCIÓN DE EPIDEMIOLOGIA E
INFORMACION DE LA SALUD

PODER LEGISLATIVO FOLIO 4 Secretaría Legislativa

Cde. Nota 056/08-D.G.A.J.P.
Ref: Solic. Resolución 016/08
Legislatura Provincial
INFORME N° 021/08
LETRA: M.S.-D.E.I.S.

USHUAIA, 25 de abril de 2008.-

SEÑORA MINISTRA DE SALUD
DRA. MARIA HAYDEE GRIECO

En virtud de dar respuesta a la solicitud de pedido de informe de la Legislatura Provincial en relación a Enfermos Celíacos, se informa que al no ser ésta una enfermedad de denuncia obligatoria, esta Dirección no dispone de un registro específico que pueda determinar la incidencia. De las consultas efectuadas al efecto, podemos informar:

1. CANTIDAD ENFERMOS CELIACOS EN TIERRA DEL FUEGO.

1.1 – Cantidad de Consultas Médicas Efectuadas por enfermos Celíacos. Hospitales Regionales. Provincia Tierra del Fuego. Año 2007.

Grupo de edad	Cantidad
< 14 años	7
15 a 19 años	3
20 y mas años	6
s/e edad	2
Total	18

Fuente: Oficina Central Estadísticas. Hospitales Regionales. Tierra del Fuego. Año 2008.-

1.2 – Cantidad de Enfermos Celíacos Registrados en la Asociación Celíaca Argentina Filial Río Grande.

De la consulta efectuada a la Lic. Patricia Crocci, Presidenta de la Asociación Celíaca Argentina Filial Río Grande, se informa que dicha Asociación registra desde 5 años a la fecha, una cantidad de 137 personas celíacas residentes en la Ciudad de Río Grande, con 0 caso registrado en la Ciudad de Tolhuin. Del 100 % de estos casos, el 45% son menores de 14 años, el 18% de 14 a 19 años , y el 37 % son mayores de 19 años (Según copia de Nota fax adjunta, de fecha 23/04/08).

Provincia de Tierra del Fuego, Atlantico e Islas
del Atlántico Sur
República Argentina

MINISTERIO DE SALUD
SUBSECRETARIA DE POLITICAS DE SALUD
DIRECCIÓN DE EPIDEMIOLOGIA E
INFORMACION DE LA SALUD

1.3 - Cantidad de Enfermos Celíacos Registrados en la F.A.CEL.FU – Fundación Ayuda al Celíaco Fueguino.

De la consulta efectuada al Sr. Sergio Lares, D.N.I. N°14.172.193, Presidente de la F.A.CEL.FU., se informa que dicha entidad registra un total de 480 personas celíacas a nivel provincial, de las cuales el 70,8 % pertenecen a la Ciudad de Ushuaia y el 29,2 % a Río Grande. Dichos datos fueron proporcionados verbalmente a través de consulta telefónica, y según lo expresado por el interlocutor, los mismos no están disponibles por grupos etareos.

4. COMEDORES ESCOLARES.

De la consulta efectuada a las referentes de los Comedores Escolares de la Provincia, Sra. Cristina Bargiela en Río Grande y Sra. Gabriela Cabezas en Ushuaia, se informa que los mismos proveen dietas generales según lo establecido en pliegos licitatorios, los que no contemplan asistencia a través de dietas alimenticias especiales.

5. HOGARES PARA LA TERCERA EDAD.

Existen 2 Hogares para la Tercera Edad en Tierra del Fuego. Según consulta efectuada a la Directora de Inclusión Social en Río Grande, la Sra. Virginia de Gregorio, dicho Hogar asiste a un total de 100 personas de las cuales no hay ningún celíaco. De igual manera se consulto en Ushuaia a la Sra. Fernanda Jaimerena, Directora de Inclusión Social, quien informó que de 52 personas asistidas no hay ninguna celíaca.

Asimismo se considera oportuno darle a conocer que en el mes de junio del año 2004, autoridades de la F.A.CEL.FU. y el Dr. Christian Boggio, presentó un Proyecto Piloto de Pesquisa (Screening) Provincial de Enfermedad Celíaca en Población Pediátrica (cuya copia se adjunta). Dicho Proyecto fue diligenciado oportunamente a través de la Subsecretaria de Planeamiento, con la intervención de la Dirección Técnica Científica, Dirección de Programas Sanitarios, Dirección de Atención Primaria de la Salud y Epidemiología.

Atte.-

Lic. AURORA TERESITA GRASSI
Directora
Dirección de Epidemiología
e Información de la Salud.
Ministerio de Salud

Asociación Celíaca Argentina
Sede Nacional: calle 24 nº 1907 entre 71 y 72, CP 1900, La Plata, Bs.As., Argentina
Filial Río Grande- Tierra del Fuego- ARGENTINA

PODER LEGISLATIVO FOLIO 6 Secretaría Legislativa

PERSONERIA JURIDICA n* 4332/84

1978 - 2008 : "30 AÑOS POR UNA MEJOR CALIDAD DE VIDA DEL CELIACO ARGENTINO"

Río Grande 23/04/08.-

Al Jefe del Departamento División Río Grande de la
Dirección de Epidemiología e Información de la Salud.
DR. ABEL PALMIERI D.
S. /

De mi consideración: En respuesta a su NOTA: 18/08 DEL 23/04/08; informo a Ud. Y por su intermedio a las Autoridades del Ministerio de Salud de la Provincia de Tierra del Fuego y a la Legislatura Provincial.

Que:
La Prevalencia de CELIAQUIA **en Argentina es de 1 cada 144** nacido vivo (Según estudio de Prevalencia del DR J. C. Gomez y equipo del Hospital San Martín de La Plata).

La ASOCIACION CELIACA ARGENTINA, FILIAL RIO GRANDE que represento registra en los 5 años de su existencia un número de **137 (ciento treinta y siete) Celíacos residentes en Río Grande. De los cuales un 37% son Adultos (mayores de 19 años); un 18% son Adolescentes (de 14 a 19 años); y un 45% son niños (menores de 14 años).**
Reservo sus identidades por Ley de Confidencialidad de Datos. (constan en el Archivo de nuestra Filial y en Sede Nacional de Asoc. Celíaca Argentina).

No tenemos registradas personas Celíacas en Tolhuin.
Los datos son obtenidos de las Siguientes fuentes:

- Dirección de FISCALIZACION SANITARIA de Río Grande (Por registro de CERTIFICADOS DE DISCAPACIDAD).
- Derivación de médicos del Centro Diagnóstico local (HOSPITAL REGIONAL RIO GRANDE).
- Derivación de otras Filiales de la Asociación Celíaca Arg. (por cambio de domicilio)
- Derivación de Servicios de Acción Social y Nutrición del HRRG
- Derivación de Médicos de Instituciones Privadas.
- Consulta espontánea de personas Celíacas.
- Derivación de DIRECCION DE MEDICINA PREVENTIVA del Departamento de Asuntos Sociales de la Municipalidad de Río Grande (por trabajo conjunto de detección, difusión y asistencia de celíacos).*

- La Filial Río Grande de ACA y la Municipalidad de Río Grande participan del Proyecto "El Hambre mas urgente" focalizado a Celíacos dependiente del Ministerio de Salud de la Nación por el que se otorgan Modulos Alimentarios a Celíacos de escasos recursos presentados por nuestra Asociación y evaluados socialmente por la Municipalidad.

Aprovecho la oportunidad para informarle que nuestra Asociación es una entidad sin fines de lucro integrada sólo por celíacos y familiares directos que basados en la solidaridad trabaja para mejorar la calidad de vida de las personas celíacas.

Nuestro trabajo consiste en contención del celíaco recién diagnosticado, difusión del concepto celiaquía,
Contribuir al equipamiento del Centro Diagnóstico, actualizar profesionales, facilitar el análisis de alimentos, contribuir al sostenimiento de la Dieta SIN TACC (Sin Trigo, Avena, Cebada y Centeno), Unico Tratamiento de la Celiaquia, Organización de Talleres de Cocina para Celíacos. (Adjunto folletería oficial).-

Saludo atte. Y quedo a su disposición para mayor información.

Lic. PATRICIA CROCCI
Presidente
Asociación Celíaca Argentina
FILIAL RIO GRANDE- TIERRA DEL FUEGO.-

Tel Cel. 15610906-
www.celiacofueguino@yahoo.com.ar
www.pcroci59@yahoo.com.ar

Ministerio de Salud

SALUD PUBLICA

Resolución 1560/2007

Créase el Programa Nacional de Detección y Control de la Enfermedad Celíaca, a fin de contribuir a la detección temprana de la enfermedad y al fortalecimiento del Sistema Nacional de Control de Alimentos.

Bs. As., 27/11/2007

VISTO, el expediente Nº 2002-17.796/07-0 del registro del MINISTERIO DE SALUD, y

CONSIDERANDO:

Que la celiaquía es una enfermedad con alto grado de incidencia en la población de nuestro país.

Que las características propias de la enfermedad condicionan la calidad de vida de las personas afectadas y sus familias.

Que la detección temprana y el tratamiento oportuno revisten fundamental importancia para evitar complicaciones secundarias de esta patología, para lo cual no existe terapia farmacológica.

Que una vez diagnosticada, su tratamiento consiste únicamente en una dieta estricta de alimentos libres de gluten, que deberá mantenerse de por vida.

Que, en consecuencia, la identificación de alimentos libres de gluten, resulta fundamental para favorecer la accesibilidad al tratamiento adecuado de las personas afectadas.

Que con el objeto de favorecer la accesibilidad de las personas con enfermedad celíaca al sistema sanitario resulta apropiado crear un Programa Nacional de Detección y Control de la Enfermedad Celíaca que favorezca la promoción, el diagnóstico precoz y que contribuya a fortalecer el sistema de control de alimentos.

Que asimismo es imprescindible incluir en las políticas de Salud Pública la temática de la enfermedad celíaca, incorporando el desarrollo de acciones de promoción y atención en las distintas áreas y dependencias del MINISTERIO DE SALUD DE LA NACION.

Que a fin de propender a la atención integral de la problemática, resulta ineludible coordinar acciones con el MINISTERIO DE DESARROLLO SOCIAL DE LA NACION.

Que, desde el MINISTERIO DE SALUD DE LA NACION resulta también primordial la necesidad de coordinar acciones con las jurisdicciones provinciales en la búsqueda de estrategias que optimicen la atención de las personas con enfermedad celíaca.

Que la DIRECCION GENERAL DE ASUNTOS JURIDICOS ha tomado la intervención de su competencia.

Que se actúa en virtud de lo normado por la Ley de Ministerios, t.o. por decreto Nº 438 del 12 de marzo de 1992, modificada por la ley 25.233.

Por ello,

EL MINISTRO
DE SALUD
RESUELVE:

Artículo 1º — Créase el PROGRAMA NACIONAL DE DETECCION Y CONTROL DE LA ENFERMEDAD CELIACA en el ámbito de la SECRETARIA DE POLITICAS, REGULACION e INSTITUTOS, a fin de contribuir a la detección temprana de la enfermedad celíaca y al fortalecimiento del Sistema Nacional de Control de Alimentos, especialmente en lo referente a los alimentos libres de gluten para favorecer la accesibilidad al tratamiento adecuado de las personas afectadas, de acuerdo a los alcances y modalidades que se establecen en el ANEXO I que forma parte integrante de la presente.

Art. 2º — La coordinación de las acciones que demande el cumplimiento de los objetivos del PROGRAMA NACIONAL DE DETECCION Y CONTROL DE LA DE ENFERMEDAD CELIACA estará a cargo de la SECRETARIA DE POLITICAS, REGULACION e INSTITUTOS.

Art. 3º — En el cumplimiento de las competencias que le son propias, las áreas y dependencias del MINISTERIO DE SALUD deberán articular acciones con el PROGRAMA NACIONAL DE DETECCION Y CONTROL DE LA ENFERMEDAD CELIACA a fin de contribuir al cumplimiento de los objetivos propuestos.

Art. 4º — El gasto que demande esta actividad se financiará con partidas del presupuesto de esta jurisdicción.

Art. 5º — Invítase a las Provincias y al GOBIERNO AUTONOMO DE LA CIUDAD DE BUENOS AIRES a adherir al PROGRAMA NACIONAL DE DETECCION Y CONTROL DE ENFERMEDAD CELIACA.

Art. 6º — Regístrese, comuníquese, publíquese, dése a la Dirección Nacional del Registro Oficial y archívese. — Ginés M. González García.

ANEXO I

ENFERMEDAD CELíACA

INTRODUCCION:

La enfermedad celíaca o enteropatía por gluten es una afección inflamatoria que daña la mucosa del intestino delgado debido a la intolerancia al gluten, proteína que se encuentra en el trigo, avena, cebada y centeno, cuyo principal componente es la gliadina.

En su patogenia intervienen factores ambientales, genéticos e inmunológicos.

La edad de aparición es variable, es más frecuente en la infancia pero también puede presentarse en la adultez, debiendo sospecharse frente a desnutrición, síndrome de mala absorción, anemia, abortos, diabetes, Síndrome de Down, familiares de primer grado del enfermo celíaco, etc.

Su diagnóstico se realiza a través de dosaje de anticuerpos específicos en sangre y eventualmente, biopsia intestinal.

La detección temprana y el tratamiento oportuno revisten fundamental importancia para evitar complicaciones secundarias de esta patología.

Hasta el presente no existe terapia farmacológica para tratar la enfermedad. Una vez diagnosticada, su tratamiento consiste en una dieta estricta de alimentos libres de gluten, que deberá mantenerse de por vida.

La Enfermedad Celíaca es un problema de salud pública, los últimos estudios realizados en Europa revelan alta prevalencia de la enfermedad, aproximadamente del 1% y parece estar en aumento durante la última década. Este cambio de prevalencia puede responder al incremento en la vigilancia por parte del médico en la historia natural silente de la enfermedad celíaca, lo que conduce a un mejor diagnóstico o podría estar relacionado con cambios en los factores ambientales, situación que actualmente se está estudiando.

En Europa, la enfermedad celíaca es la patología genética más común. Por ello si se considera la fuerte impronta genética y presencia inmigratoria de países europeos en Argentina, particularmente España e Italia, presupone una alta incidencia entre la población de nuestro país.

FUNDAMENTACION

La celiaquía es considerada la enfermedad intestinal crónica más frecuente. A pesar de que no hay registro de casos, estudios preliminares en nuestro país indican una prevalencia de aproximadamente 1: 200. Sin embargo actualmente se calcula que 1 de cada 100 personas es celíaca (habría aproximadamente 400.000 celíacos en Argentina). Por lo tanto 400.000 familias deben adaptarse al estilo de vida del integrante celíaco.

Los síntomas de la celiaquía suelen ser variados y pueden remitir a otras enfermedades, situación que produce dificultades para el diagnóstico precoz de la enfermedad. Otras veces la enfermedad adopta forma silente y el paciente no evidencia síntomas. En ambos casos resulta difícil arribar al diagnóstico temprano.

En tal sentido, el MINISTERIO DE SALUD DE LA NACION se propone realizar las acciones necesarias para evitar o minimizar las secuelas que la detección o intervención tardía producen en el estado de salud de las personas.

PROPOSITO:

Incluir en el Sistema de Salud acciones que favorezcan la atención y cuidado integral de las personas con enfermedad celíaca.

OBJETIVO:

Contribuir a la detección temprana de la enfermedad celíaca y al fortalecimiento del Sistema Nacional de Control de Alimentos, especialmente en lo referente a los alimentos libres de gluten.

OBJETIVOS ESPECIFICOS:

1- Promover el conocimiento y la divulgación masiva de las características de la enfermedad celíaca.

2- Apoyar a las jurisdicciones para garantizar el acceso al diagnóstico oportuno.

3- Propiciar la capacitación de los equipos de salud

4- Estimular el desarrollo de la investigación.

5- Fortalecer la capacidad técnica y analítica del Sistema Nacional de Control de Alimentos en la temática.

6- Organizar un Registro Nacional de la Enfermedad Celíaca en nuestro país

ALCANCE:

El programa está dirigido al fortalecimiento del sector de salud en articulación con el MINISTERIO DE DESARROLLO SOCIAL DE LA NACION para el desarrollo de acciones que contribuyan a mejorar la atención de las personas con enfermedad celíaca en todo el país.

ACCIONES:

1a- Desarrollar campañas de difusión y educación dirigidos a la población en general, con datos relevantes de la enfermedad para el cuidado.

1b-Elaborar y difundir Guías de diagnóstico y tratamiento.

1c-Informar, difundir, divulgar mediante la distribución de folletería, afiches, videos institucionales, etc.

2a-Conformar red de Servicios de Gastroenterología y Laboratorios equipados para realizar serologías y biopsias.

2b-Apoyar a las jurisdicciones con los insumos para la determinación diagnóstica.

3a- Coordinar con Sociedades Científicas el desarrollo de cursos o talleres de capacitación de los equipos de salud que contribuyan al mejoramiento de la atención de las personas con enfermedad celíaca.

4a- Desarrollar estudios de prevalencia en Argentina.

5a- Fortalecer la capacidad analítica de los laboratorios miembro de la Red Nacional de Laboratorios Oficiales de Análisis de Alimentos.

5b- Fortalecer la capacitación de inspectores bromatológicos de las jurisdicciones bromatológicas del país en verificación de establecimientos libres de gluten.

6a-Organizar un Registro Nacional de la enfermedad en nuestro país.

ESTRATEGIAS:

Desarrollar acciones conjuntas con la ANMAT y la ANLIS, a fin de llevar a cabo los objetivos del Programa.

Articulación de acciones con el PLAN ALIMENTARIO NACIONAL dependiente del MINISTERIO DE DESARROLLO SOCIAL DE LA NACION para la entrega y distribución de alimentos específicos, para la realización de talleres de promoción y educación para la salud dirigidos a los equipos de salud y a la comunidad en general.

Colaboración para la elaboración del Registro Nacional de Pacientes con Enfermedad Celíaca.

Determinación por consenso con las Sociedades Científicas de métodos y técnicas estandarizadas de diagnóstico.

Articular con las provincias que adhieran al Programa para el desarrollo de los objetivos del programa.

ACTIVIDADES:

1.1 Elaboración conjunta con las sociedades científicas de las guías de diagnóstico y atención con la determinación de métodos y técnicas estandarizadas para ser incluidos en los programas de atención de la salud.

1.2 Entrega directa a hospitales y Asociaciones de Padres que nuclean a población afectada de las guías de diagnóstico y tratamiento más folletos ilustrativos para la comunidad en general.

1.3 Distribución de iguales elementos en los Centros de Atención Primaria a través de los diferentes Programas Ministeriales.

1.4 Difusión de listados de alimentos aptos para el consumo de personas con enfermedad celíaca (publicación online, conformación de base de datos de interesados para novedades, folleto instructivo)

2.1 Relevar y evaluar la capacidad instalada y la oferta de Servicios públicos de las Jurisdicciones para la conformación de la Red de Atención.

2.2 Determinar las necesidades presupuestarias y mecanismos de compra y distribución para cumplir con la provisión de insumos a los efectores provinciales y del equipamiento a los laboratorios regionales.

3.1 Organizar Curso Taller de Verificación de Buenas Prácticas de Manufacturas en establecimientos elaboradores de alimentos libres de gluten.

3.2 Organizar actividades de Educación para la Salud en las diferentes provincias dirigidas a la comunidad en general.

4.1 Estudios epidemiológicos, carga de enfermedad en la población.

5.1 Formación científica y técnica de agentes de 6 laboratorios miembros de la RENALOA por parte del Instituto Nacional de Alimentos para la ejecución de la técnica analítica oficial e interpretación de los resultados

5.2 Asegurar la capacitación continua de los laboratorios miembros y de Pruebas de Proficiencia Interlaboratorios para la RENALOA

6.1 Elaborar un padrón para registro estadístico, evaluación y control del programa con los datos aportados por las diferentes jurisdicciones.

RECURSOS:

El MINISTERIO DE SALUD DE LA NACION se hará cargo de:

Provisión de kits de diagnóstico serológico de Anticuerpos.

Promover y apoyar a los laboratorios pertenecientes a la Red Nacional de Laboratorios Oficiales de Análisis de Alimentos —RENALOA— dotándolas del equipamiento e insumos necesarios para poder realizar el análisis de los alimentos libres de gluten.

Contar con la Red Nacional de Laboratorios Oficiales de Análisis de Alimentos —RENALOA— que conforman el Instituto Nacional de Alimentos y las Jurisdicciones Bromatológicas Provinciales, resultará una herramienta fundamental de sustento para la vigilancia alimentaria y epidemiológica.

La Provincia se hará cargo de:

Detección de los pacientes.

Inscripción en el padrón federal implementado por el MINISTERIO DE SALUD DE LA NACION.

Realización de los estudios de diagnóstico específicos de la patología.

Asegurar que las condiciones ambientales de los laboratorios no invaliden los resultados ni la

calidad requerida para la determinación de gluten en alimentos.

Recursos humanos para la atención de las personas.

Recursos humanos para el desarrollo de las acciones de vigilancia y control.

Otros materiales e insumos no provistos por el Ministerio.

MONITOREO Y EVALUACION DE RESULTADOS.

Se hará a través de indicadores de proceso y resultados de satisfacción de la demanda y adecuación de la oferta según niveles de resolución.

Los indicadores deberán reflejar la accesibilidad de la población a las acciones del Programa y a las prestaciones de los Servicios de Gastroenterología.

INDICADORES:

Número de jurisdicciones con participación en el Programa.

Número de prestaciones por tipo y por jurisdicción.

Número de personas asistidas bajo la estrategia del Programa.

Número de servicios e Instituciones jurisdiccionales incorporados al Programa.

Número de personal de los laboratorios miembro de la RENALOA capacitado en la metodología oficial.

Listado de asistentes a los cursos de capacitación en verificación de Buenas Prácticas de Manufacturas para establecimientos elaboradores de alimentos libres de gluten.

Cantidad de muestras de alimentos analizadas en todo el país

Número de establecimientos fiscalizados.

Otros a establecer en conjunto con las jurisdicciones.

Oficina Nacional de Control Comercial Agropecuario

PRODUCCION DE GRANOS Y OLEAGINOSAS

Resolución 6590/2007

Autorízase el pago de compensaciones solicitadas en el marco del mecanismo creado por la Resolución N° 9/2007 del Ministerio de Economía y Producción.

Bs. As., 29/11/2007

VISTO el Expediente N° S01:0443097/2007, del Registro del MINISTERIO DE ECONOMIA Y PRODUCCION,

CONSIDERANDO:

Que por la Resolución N° 9 de fecha 11 de enero de 2007 del MINISTERIO DE ECONOMIA Y PRODUCCION se creó un mecanismo destinado a otorgar compensaciones al consumo interno a través de los industriales y operadores que vendan en el mercado interno productos derivados del trigo, maíz, girasol y soja.

Que mediante Resolución N° 378 de fecha 17 de enero de 2007, modificada por las Resoluciones Nros. 674 de fecha 24 de enero de 2007, 11 de fecha 9 de marzo de 2007 y 339 de fecha 10 de abril de 2007, todas de la OFICINA NACIONAL DE CONTROL COMERCIAL AGROPECUARIO, se estableció el procedimiento para la determinación de la compensación para la industrialización de trigo destinado al mercado interno implementado por la citada Resolución N° 9/07.

Que la referida Resolución N° 378/07 y sus modificatorias fijaron los parámetros para la determinación y pago de las correspondientes compensaciones.

Que resultan beneficiarios los molinos harineros, usuarios de molienda de trigo y productores de trigo.

Que en tal marco se presentaron las solicitudes por los molinos harineros de trigo, cuyos Nombres o Razón Social, Expediente, Clave Unica de Identificación Tributaria (C.U.I.T.) y Clave Bancaria Uniforme (C.B.U.) se detallan en el Anexo que forma parte de la presente resolución.

Que las solicitudes presentadas que se detallan en el mencionado Anexo, fueron liquidadas de conformidad con lo establecido en la citada Resolución N° 378/07 y sus modificatorias.

Que el Area de Compensaciones de la citada Oficina Nacional evaluó las presentaciones efectuadas de acuerdo a la normativa vigente, conforme surge de los informes técnicos obrantes a fojas 2, 30, 49, 76, 91 y 104.

Que asimismo, la Coordinación del Area de Compensaciones de la OFICINA NACIONAL DE CONTROL COMERCIAL AGROPECUARIO intervino favorablemente a fojas 1, 29, 48, 75, 90 y 103 respectivamente.

Que en el caso bajo análisis y, respecto de la Resolución N° 145 de fecha 7 de septiembre de 2007 del MINISTERIO DE ECONOMIA Y PRODUCCION, corresponde manifestar que a fojas 28, 47, 74, 89, 102 y 117 lucen agregados los informes respectivos correspondientes a las firmas MOLINO NUESTRA SEÑORA DE LUJAN S.H., MOLINOS TRES ARROYOS S.A., O.S. S.A., S.A.C.I. FRANCISCO CORES LTDA. y MOLINO CHACABUCO S.A. respectivamente, dando cuenta del cumplimiento de los extremos requeridos por la norma citada precedentemente.

Que la Coordinación Jurídica de la OFICINA NACIONAL DE CONTROL COMERCIAL AGROPECUARIO no ha presentado objeciones a la continuación del trámite.

Que por ello resulta procedente aprobar las solicitudes correspondientes a las presentaciones que se detallan a fojas 118, que no han merecido observaciones o que, formuladas, fueron debidamente cumplimentadas.

Que, en consecuencia, corresponde proceder a autorizar el pago de las compensaciones solicitadas conforme los montos verificados en los informes técnicos mencionados y que se encuentran detallados en el Anexo que forma parte integrante de la presente medida.

Que la Dirección de Legales del Area de AGRICULTURA, GANADERIA, PESCA Y ALIMENTOS dependiente de la Dirección General de Asuntos Jurídicos del MINISTERIO DE ECONOMIA Y PRODUCCION, ha tomado la intervención de su competencia.

Que el suscripto es competente para dictar el presente acto administrativo en virtud de las facultades conferidas por el Decreto N° 1067 de fecha 31 de agosto de 2005 y por la Resolución N° 9 de fecha 11 de enero de 2007 del MINISTERIO DE ECONOMIA Y PRODUCCION.

Por ello,

EL VICEPRESIDENTE
DE LA OFICINA NACIONAL
DE CONTROL COMERCIAL AGROPECUARIO
EN EJERCICIO DE LA PRESIDENCIA
RESUELVE:

Artículo 1° — Apruébanse las compensaciones solicitadas por los molinos harineros de trigo que se detallan en el Anexo que forma parte integrante de la presente resolución, las que ascienden a la suma total de PESOS CINCO MILLONES DOSCIENTOS CINCUENTA MIL OCHOCIENTOS SETENTA Y NUEVE CON TREINTA Y NUEVE CENTAVOS ($ 5.250.879,39) por los motivos expuestos en los considerandos precedentes.

Art. 2° — Autorízase el pago de las compensaciones consignadas individualmente a los beneficiarios mencionados en el Anexo que forma parte integrante de la presente medida, el que asciende a la suma total de PESOS CINCO MILLONES DOSCIENTOS CINCUENTA MIL OCHOCIENTOS SETENTA Y NUEVE CON TREINTA Y NUEVE CENTAVOS ($ 5.250.879,39) por los motivos expuestos en los considerandos precedentes.

Art. 3° — Comuníquese, publíquese, dése a la Dirección Nacional del Registro Oficial y archívese. — Jorge Artundo.

ANEXO COMPENSACIONES: MOLINOS DE TRIGO

Nº	EXPTE	Razón Social	CUIT	CBU	MONTO mayo	julio	agosto	septiembre	octubre
1	[illegible]	MOLINO NTRA. SRA. DE LUJAN DE LOPEZ ADRIANA, LOPEZ MAURICIO Y GALLAVA CLEMENCIA DE LOPEZ S.H.	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]
2	[illegible]	MOLINO TRES ARROYOS S.A.	[illegible]	[illegible]			[illegible]	[illegible]	
3	[illegible]	O.S. S.A.	[illegible]	[illegible]	[illegible]			[illegible]	
4	[illegible]	S.A.C.I. FRANCISCO CORES LTDA.	[illegible]	[illegible]				[illegible]	[illegible]
5	[illegible]	MOLINO CHACABUCO S.A.	[illegible]	[illegible]				[illegible]	
		TOTAL					5.250.879,39		

DISPOSICIONES

Subdirección General de Recursos Humanos

ADMINISTRACION FEDERAL DE INGRESOS PUBLICOS

Disposición 399/2007

Finalización de funciones y designación de Jefaturas Interinas en el ámbito de la Dirección Técnica.

Bs. As., 22/11/2007

VISTO las Actuaciones SIGEA Nros. 12110-110-2007 y 12110-105-2007, y

CONSIDERANDO:

Que por las mismas, los agentes Eduardo Carlos FERREIRA y Margarita Dominga AGUILAR solicitan el relevo de las funciones que les fueran asignadas oportunamente en el carácter de Firma Responsable Interino y de Jefa de la División Técnica del Departamento Técnica de Exportación de la Dirección de Técnica, respectivamente.

Que la citada Dirección accede a lo solicitado y propone dar por finalizadas funciones y designar a diversos agentes para desempeñarse en el carácter de firmas responsables y de Jefes Interinos de diversas unidades de estructura de su jurisdicción.

Que cabe introducir las modificaciones que tal situación implica.

Que por lo expuesto y en virtud de lo establecido por el artículo 2º de la Disposición N° 147 (AFIP) del 25 de abril del año en curso, corresponde asignar a los agentes Margarita Dominga AGUILAR y Ricardo HASENBALG, la Categoría C.T.A.-02 y a la Licenciada Débora Judith SEPIURKA la Categoría C.T.A.-04, con funciones acordes a la misma, del Cuadro de Ordenamiento de Cargos previsto para el personal comprendido en el Convenio Colectivo de Trabajo N° 56/92 "E" - Laudo N° 16/92.

Que sobre el particular, destácase que el agente HASENBALG ha prestado su expresa conformidad de cumplir las funciones de menor jerarquía que se proponen, de acuerdo con lo dispuesto en el Artículo 26 del citado Convenio Laboral.

Que la asignación y la finalización de funciones de que se trata encuadra dentro de los términos previstos por los artículos 89 y 90 del Convenio Colectivo de Trabajo N° 56/92 "E" - Laudo 16/92.

Que el presente acto dispositivo se dicta en el marco de la excepción de lo dispuesto en los Decretos Nros. 491 del 12 de marzo de 2002, 601 del 11 de abril de 2002 y 577 del 7 de agosto de 2004, otorgada mediante Decreto N° 1322 de fecha 26 de octubre de 2005.

PODER LEGISLATIVO
FOLIO
10
Secretaría Legislativa

La Legislatura de la Provincia de Tierra del Fuego,
Antártida e Islas del Atlántico Sur
República Argentina

R E S U E L V E .

Artículo 1º.- Solicitar al Poder Ejecutivo Provincial que, a través de las áreas correspondientes, informe a esta Cámara Legislativa lo siguiente:

1. Detalle la cantidad de enfermos celíacos de la Provincia en la actualidad, discriminado por:
   a) Niños, adolescentes y adultos;
   b) ciudades y localidades.
2. Informe conformación del Consejo Administrativo y pormenores acerca de las acciones concretas que se llevan a cabo en virtud de los objetivos establecidos en el artículo 2° de la Ley territorial 366;
3. informe detallado sobre la partida presupuestaria del año 2007 asignada a los fines de estimular dentro de los planes de dación de alimentos, que implementa el Estado Provincial, destinados específicamente a la compra de alimentos libres de gluten, para atender las necesidades especiales de comedores escolares e instituciones afines que contengan niños celíacos;
4. informe sobre la cantidad de instituciones públicas de la Provincia (escuelas, guarderías infantiles, comedores escolares y asociaciones sin fines de lucro) que tienen, en su grupo de comensales, a personas afectadas por la mencionada patología;
5. informe sobre la cantidad de Hogares para la Tercera Edad dependientes del Estado Provincial que contienen enfermos celíacos.

Artículo 2º.- Regístrese, comuníquese y archívese.

DADA EN SESIÓN ORDINARIA DEL DÍA 3 DE ABRIL DE 2008.

ES COPIA FIEL

RESOLUCIÓN Nº **016** ***/08.-***

CARLOS G. FERNANDEZ
A/C Dirección
Información Parlamentaria
Poder Legislativo

MARTIN A. ENCHIEME
Secretario Legislativo
Poder Legislativo

CARLOS D. BASSANETTI
Vicegobernador
Presidente del Poder Legislativo

PROYECTO PILOTO DE PESQUISA (SCREENING) PROVINCIAL DE ENFERMEDAD CELÍACA EN POBLACIÓN PEDIÁTRICA

Investigador Principal
Dr. Christian Boggio Marzet

Co-Investigadores
Dr. Patricio Kenny – Dr. Néstor Litwin

Lugar de realización
Provincia de Tierra del Fuego, Antártida e Islas del Atlántico Sur

Población en estudio
Alumnos de 1° grado de escuelas públicas y privadas.

Coordinación
Ministerio de Salud del Gobierno de Tierra del Fuego

Asesoramiento
Sección Gastroenterología Pediátrica
Departamento de Bioestadística.
Hospital de Clínicas. Facultad de Medicina.
Universidad de Buenos Aires.

RACIONALIDAD DEL PROYECTO

La Enfermedad Celíaca (EC) es una enteropatía autoinmune provocada por la ingestión de gluten proveniente de cereales en individuos genéticamente susceptibles. La EC está asociada con alelos DQ2/DQ8 provenientes del sistema mayor de histocompatibilidad (HLA) y la misma se autoperpetúa en presencia del gluten en la dieta.
Para sustentar la postura de que un screening activo en búsqueda de casos de EC es una política claramente justificada, revisamos los lineamientos de la Organización Mundial de la Salud (OMS) para recomendaciones de screening masivo de enfermedades y de esta manera establecer si la EC satisface estos criterios.

Criterios de la OMS para screening masivos

1- La detección temprana de la enfermedad podría ser dificultosa sobre una base clínica.
2- La enfermedad debe ser un trastorno frecuente el cual cause una morbilidad significativa en la población general.
3- Los test de screening deben ser altamente sensibles y específicos para la enfermedad en cuestión.
4- El tratamiento para la enfermedad debe estar disponible.
5- Si no se reconoce o advierte, la enfermedad podría resultar en complicaciones severas difíciles de manejar.

Criterios de la OMS aplicables a Enfermedad Celíaca

1- **DETECCIÓN TEMPRANA**
La EC puede manifestarse en un amplio rango de presentaciones que van desde el típico sindrome de malabsorción (diarrea crónica, pérdida de peso y distensión abdominal) hasta un espectro de síntomas que pueden afectar potencialmente cualquier órgano o sistema del cuerpo. Como la EC es usualmente atípica o incluso clínicamente silente, la mayoría de los casos permanecen sin diagnóstico por muchos años y expuestos al riesgo de complicaciones a largo plazo.

2- **PREVALENCIA**
Los análisis de la codistribución mundial de los dos componentes (HLA y cereales) involucrados en la patogénesis de la EC muestran una amplia distribución de la enfermedad, tanto en regiones donde la EC es descripta como un trastorno frecuente (Europa) como en áreas donde la enfermedad ha sido históricamente considerada infrecuente (EEUU). Estudios epidemiológicos recientes demuestran que tales áreas "libres de EC" en realidad tenían un gran número de casos subdiagnosticados,

aportando de esta manera evidencia de que ***la EC es una de las enfermedades genéticas más frecuentes de la humanidad.*** Tanto los síntomas típicos como los atípicos si no son diagnosticados a tiempo pueden conducir a complicaciones irreversibles, incluyendo detención del crecimiento, osteoporosis, enfermedades autoinmunes y neoplasias intestinales.

3- **TESTS DE SCREENING**

Al demostrar que la presentación clínica de la EC es mucho más heterogénea de lo que previamente se había descripto, se han desarrollado en los últimos 15 años tests de screening específicos. El descubrimiento de la transglutaminasa tisular como el autoantígeno específico de la respuesta inmune en la EC, junto con el rol primordial de los HLA DQ2/DQ8 en la patogénesis de la EC, llevaron al desarrollo de nuevos algoritmos diagnósticos que alcanzan en la actualidad una sensibilidad y especificidad cercana al 100%.

4- **TRATAMIENTO**

La EC es la única entre las enfermedades autoinmunes en la cual está disponible el tratamiento. Como la patogénesis de la enfermedad está relacionada entre los genes (HLA y no HLA) y factores ambientales conocidos (gluten que contienen ciertas harinas) que desencadenan el proceso autoinmune, la piedra angular del tratamiento es una dieta estricta libre de gluten. El tratamiento dietoterápico está asociado con una rápida mejoría sintomática y mejoramiento de la enteropatía en el transcurso de meses, lo cual provee una confirmación diagnóstica adicional.

5- **COMPLICACIONES**

Al aportar un rol determinado al gluten como causa de autoinmunidad, la EC representa el único ejemplo de enfermedad mediada inumnológicamente en la cual el diagnóstico temprano y el tratamiento dietético pueden prevenir sus complicaciones severas e incluso mortales. Los pacientes con EC sin diagnóstico y sin tratamiento, así como aquellos diagnosticados en estadíos tardíos de la vida, tienen una morbilidad y mortalidad aumentada en relación a condiciones asociadas. Desde el momoento en que la EC es un trastorno multisistémico, estos pacientes se encuentran en riesgo de padecer una enfermedad crónica que conlleva a detención del crecimiento, infertilidad, trastornos del sistema esquelético y desarrollo de neoplasias. Estos pacientes incrementan de esta manera los costos en salud dado que requieren de la atención de múltiples especialistas y una gran cantidad de estudios de laboratorio que deben realizarse hasta que se llega a un correcto diagnóstico. El porcentaje de mortalidad es significativamente mayor a cualquier edad en pacientes celíacos no tratados.

Consideraciones

¿Cumple la EC con los criterios de la OMS para screening masivo?
Absolutamente, se cumplen los cinco criterios mayores para screening masivo.

¿Por qué hacer screening para EC?
Se sabe que, incluso sin un análisis costo-beneficio, al existir un mayor conocimiento de la enfermedad junto con un bajo umbral de testeo serológico encontraremos un gran porcentaje de la "sumergida" población del iceberg de la EC. Debido a la alta morbilidad gluten-dependiente relacionada con la EC no tratada y la demora con la cual los pacientes con EC son correctamente diagnosticados, los screenings serológicos están justificados para prevenir costos sociales y personales y para mejorar la calidad de vida de una gran cantidad de individuos afectados potencialmente por la EC.

¿Quiénes deberían ser parte del screening?
La necesidad de un screening masivo en la población general dependerá de los resultados de un análisis costo-efectivo. El mejor abordaje epidemiológico para buscar EC involucra un proceso sistemático buscando en aquellos pacientes en los cuales los síntomas y/o condiciones conocidas estén asociadas a EC.
La utilización de un momento en la vida del niño en la cual se producen cambios significativos como podría ser el comienzo de la escolaridad primaria (comienzo de 1° grado) representaría un evento importante para la detección de EC en forma rutinaria.

RESUMEN

- La EC una afectación muy común en Europa y EEUU, con una prevalencia estimada de un 1% de la población general.
- En la República Argentina, la prevalencia de la EC es de 1 caso cada 150 personas en población adulta joven.
- El diagnóstico es un desafío clínico. Existe disponibilidad de tests de screening serológicos específicos y sensibles.
- Existe un tratamiento disponible para la enfermedad (dieta libre de gluten).
- Si la EC no se trata, puede desarrollarse complicaciones irreversibles.

FACTIBILIDAD DEL PROYECTO

La detección de individuos con EC por screening resulta un método sencillo, racional, factible y económico para aplicar en grupos poblacionales. Dado que la EC en su forma de presentación simula un iceberg donde sólo el 20% de la población afectada manifiesta síntomas atribuibles a la enfermedad, este método masivo de detección permite detectar el 80% de la población asintomática que padece la enfermedad y que no consulta, generando complicaciones, como lo dicho anteriormente, que conlleva a un aumento de gastos en salud.

Según datos del INDEC existe un total de 101.079 habitantes en la Provincia de Tierra del fuego, Antártida e Islas del Atlántico Sur distribuidos de la siguiente manera:

Antártida	163 habitantes
Río Grande	55.131 habitantes
Ushuaia	45.785 habitantes

De esta población, 2.748 habitantes cursan el 1° año de Educación General Básica (EGB) siendo 1.391 varones y 1.357 mujeres. Del universo de personas que cursan 1° EGB el subgrupo de niños entre 5 y 7 años corresponde a 2.492 niños distribuidos en 1.269 varones y 1.223 mujeres. De estos individuos el 70% presenta algún tipo de cobertura social. En resumen, la población potencial en estudio sería de 2.492 niños entre 5 y 7 años.

RECURSOS- COSTOS OPERATIVOS

Se realizó la estimación de costos del estudio para las determinaciones del panel de anticuerpos (AttG IgA y dosaje de IgA sérica).

1)Costo de 2.492 determinaciones: Panel de Anticuerpos: Costo total:	25 $ ~~20~~ por determinación + EMA 1 $ ~~49.840~~ 62.660 $ 15 x d (1°
2)Honorarios del Bioestadígrafo (Manejo y procesamiento de datos):	$ 500.-
3)Honorarios Extraccionistas:	$ ~~1000.-~~ a convenir.
4) Librería (papel A4, cartuchos impresoras, etc)	$ 300.-
5)Costo del transporte 2.492 muestras a Bs As:	$ a confirmar
TOTAL	$ ~~51.640~~ 63.460

En Síntesis

¿ Por qué realizar una pesquiza de EC en Tierra del Fuego?

- Porque no existen datos de prevalencia de EC en población pediátrica en la República Argentina.
- Porque se trata de la enfermedad autoinmune más frecuente en la población que tiene un tratamiento específico.
- Porque se lograría un diagnóstico precoz evitando complicaciones de la enfermedad.
- Porque Tierra del Fuego sería el primer grupo poblacional con prevalencia demostrada de EC en población pediátrica en el país.

CURRICULUM VITAE RESUMIDO DEL INVESTIGADOR Y CO-INVESTIGADORES

Dr. Christian Boggio Marzet

- Médico Pediatra Gastroenterólogo
- Médico de Planta a Cargo de la Sección Gastroenterología y Nutrición Pediátrica del Hospital Pirovano
- Médico de Planta de la Sección Gastroenterología y Nutrición Pediátrica del Hospital de Clínicas (Universidad de Buenos Aires)
- Integrante del Grupo de Trabajo en Enfermedad Celíaca del Gobierno de la Ciudad de Buenos Aires
- Médico Asesor de la Asociación Celíaca Argentina Filial Zona Norte y Filial Metropolitana.
- Médico Itinerante a Cargo del área de Gastroenterología Pediátrica del Hospital Regional de Ushuaia y de la Clínica San Jorge.

Dr. Patricio Kenny

- Médico Pediatra Gastroenterólogo
- Jefe Sección Gastroenterología y Nutrición Pediátrica Hospital de Clínicas (Universidad de Buenos Aires)
- Director del Centro de Enfermedades Digestivas Pediátricas Hospital Británico

BIBLIOGRAFÍA

1- Fasano A, Cattasi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. Gastroenterology 2001; 120:636-51.
2- WHO mass screening recommendations: http://www.who.int/en/
3- Ferguson A, Arranz E, O´Mahony S. Clinical and pathological spectrum of coeliac disease – active, silent, latent, potential. Gut 1993;34:150-1.
4- Cattasi C. New developments in childhood celiac disease. Curr Gastroenterol Rep 2002;4:238-43.
5- Cattasi C. Celiac disease in the year 2000: exploring the iceberg. Lancet 1994;343:200-3.
6- Green P, Stavropoulos S, Panagi S et al. Characteristics of adult celiac disease in the USA: results of a national survey. Am J Gastroenterol 2001;96:126-31.
7- Not T, Horvath K, Hill ID et al. Celiac disease risk in the USA: high prevalence of antiendomysium antibodies in healthy blood donors. Scand J Gastroenterol 1998;33:494-8.
8- Hill I, Fasano A, Schwartz R et al. The prevalence of celiac disease in at-risk groups of children in the United States. J Pediatr 2000;136:86-90.
9- Cellier C, Flobert C, Comier C et al. Severe osteopenia in symptom-free adults with a childhood diagnosis of coeliac disease. Lancet 2000;355:806.
10-Corrao G, Corazza GR, Bagnardi V et al. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet 2001;358:356-61.
11-Holmes GK, Prior P, Lane MR et al. Malignancy in coeliac disease-effect of a gluten free diet. Gut 1989;30:333-8.
12-Logan RF, Rifkind EA, Turner ID et al. Mortality in celiac disease. Gastroenterology 1989;97:265-71.
13-Ventura A, Magazzu G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. Gastroenterology 1999;117:297-303.
14-Fasano A. Celiac disease: the past, the present, the future. Pediatrics 2001;107:768-70.
15-American Gastroenterological Association Medical Position Statement: Celiac sprue. Gastroenterology 2001;120:1522-5.
16-Ciclitira PJ. AGA technical review on celiac sprue. American Gastroenterological Association. Gastroenterology 2001;120:1526-40.
17-Hin H, Bird G, Fisher P et al. Coeliac disease in primary care: case finding study. BMJ 1999;318:164-7.

GASTROENTEROLOGY 2001;120:1522–1525

American Gastroenterological Association Medical Position Statement: Celiac Sprue

This document presents the official recommendations of the American Gastroenterological Association (AGA) on Celiac Sprue. It was approved by the Clinical Practice and Practice Economics Committee on September 23, 2000, and the AGA governing board on November 12, 2000.

Celiac sprue is a life-long inflammatory condition of the gastrointestinal tract that affects the small intestine in genetically susceptible individuals. The prevalence in Northern Europe is approximately 1:300, whereas in the United States it occurs less frequently. A small intestinal biopsy is mandatory to confirm the diagnosis. Treatment involves a strict gluten-free diet that excludes wheat, rye, and barley and that should be supervised by a dietician. Follow-up is important because of potential long-term complications.

Introduction

The objective is to define celiac sprue, document the prevalence, and summarize available therapy.

Celiac sprue or gluten-sensitive enteropathy is a chronic malabsorption disorder of the small intestine caused by exposure to dietary gluten in genetically predisposed individuals. The condition is characterized by villous atrophy, a lowering of the villous height to crypt depth ratio (normal, 3–5:1), an increase in intraepithelial lymphocytes (normal, 10–30 per 100 epithelial cells), and extensive surface cell damage and infiltration of the lamina propria with inflammatory cells. There are a wide range of presentations from asymptomatic through fatigue, and vague abdominal symptoms, weight loss, and diarrhea to frank malabsorption with steatorrhea. Both the symptoms and abnormal small intestinal mucosal morphology resolve on removal of gluten from the diet.

Epidemiology

The age of presentation and prevalence of celiac sprue have altered over the last 30–40 years. The condition was previously thought to be a disease of childhood. However, adult presentation is increasingly common and celiac sprue can occur at any age.

The prevalence in different countries ranges widely. Several European studies have recently revealed values between 1:152 to 1:300 in countries that include Ireland, the United Kingdom, Italy, and Sweden. Previous figures from the United States suggested that the condition affected 1:6000, however, a recent study involving serologic screening of blood donors suggested that this figure is more likely to be 1:250.

In 1997, Maki and Collin suggested the concept of the "celiac iceberg," the majority of cases going clinically undetected with either "silent" or "latent" disease. Silent celiac sprue refers to those with celiac sprue but without any symptoms, and latent celiac sprue to individuals with a normal small intestine on a normal diet but who either in the past or in the future will develop morphologic changes responsive to gluten withdrawal.

Gluten Dicke reported that the alcohol soluble fraction of wheat gluten termed gliadin is the toxic fraction contained within wheat. It was subsequently shown that the equivalent fractions of rye (secalins), barley (hordeins), and possibly oats (avenins) exacerbated celiac sprue. Several recent studies have indicated that a moderate amount of oats is not harmful in individuals with either celiac sprue or dermatitis herpetiformis. Care should be exercised because the majority of commercially available oat flour is contaminated with wheat gluten. It is therefore current practice usually to advise against the use of oats in the diet of gluten-sensitive subjects.

Genetic Predisposition

Celiac sprue is an HLA-associated condition, the primary association being with major histocompatibility complex class II alleles DQA1*0501 and DQB1*0201. This may be in *cis* in DR3-positive individuals with the DQA and DQB alleles on the same chromosome. Alternatively, they may be in trans in DR5, DR7 heterozygotes, in which the DQA and DQB alleles are on different chromosomes. In Southern Europe, there is a smaller group of individuals with susceptibility who are DR4, DQ8 heterozygotes.

Pathogenesis

Current evidence suggests that small intestinal gluten–sensitive T cells recognize gluten-derived peptide epitopes when presented in association with DQ2. The activation by the gluten of the T cells produce the observed damage to the small intestinal villous architecture that occurs in celiac sprue.

Clinical Features

Adult presentation usually involves weight loss, diarrhea, lassitude, and anemia. Children frequently present with failure to thrive, vomiting, diarrhea, muscle wasting, signs of hypoproteinemia including possible ascites, and general irritability and unhappiness.

Patients may present at any hospital department with associated conditions. One important example is insulin-dependent diabetes mellitus, in which 6%–8% of sufferers have concomitant celiac sprue. Other conditions include cerebral calcification, Sjögren syndrome, and thyroid disease. The diagnosis should be considered with unexplained folic acid, iron or B_{12} deficiency, reduced serum albumin, osteoporosis, and osteomalacia. Other presentations may include failure to grow in children, infertility, or recurrent miscarriage.

Dermatitis herpetiformis deserves special mention because it can be considered an extraintestinal manifestation of gluten-sensitive enteropathy. This manifests with a pruritic, blistering rash. The diagnosis depends on the demonstration of granular immunoglobulin (Ig) A in uninvolved skin. Treatment involves dapsone and a gluten-free diet, which, if strictly adhered to, frequently allows, after a period of 6 months, for dapsone to be withdrawn.

Serologic Markers

The main role of these tests is to screen patients who have nonspecific symptoms or an associated condition such as insulin-dependent diabetes mellitus. IgA antiendomysial antibodies are currently the best serologic test for celiac sprue with a sensitivity of 97%–100% and specificity of 98%–99%. Because 2%–3% of individuals with celiac sprue have selective IgA deficiency, IgA levels should be measured. Alternatively quantifying antigliadin antibody may be the best approach. Recently, the enzyme tissue transglutaminase has been found to be the antigen for antiendomysial antibody. This has allowed the development of a tissue transglutaminase enzyme-linked immunosorbent assay, which is reported to have a sensitivity of 95% and specificity of 94%. The sensitivity of these assays in certain commercial laboratories may not be as high as published from research centers.

Disorders of Bone Metabolism

Osteomalacia is well recognized and responds to calcium and vitamin D supplementation. Bone pain, pseudofractures, or deformity may occur, and the finding of a raised serum alkaline phosphate with normal calcium and phosphate levels may be present.

Osteopenia and osteoporosis are common features. Bone mineral density is almost always reduced. Osteoporosis carries a significant fracture risk, and thus dual energy x-ray absorptiometry (DEXA) screening of celiac sprue patients is important and now recommended. DEXA scans suggest osteoporosis if the T values obtained are less than 2.0 standard deviations below the mean values for comparable age-matched controls. If osteoporosis is found, strict adherence to a gluten-free diet should be confirmed. This may provide an indication for consideration of a repeat small intestinal biopsy in those already treated because it suggests possible poor dietary compliance. Treatment may comprise hormone replacement therapy in postmenopausal women, biphosphonates, or calcitonin. Dietary calcium supplementation up to 1500 mg/day has been recommended. Smoking should be discouraged and exercise advised. Monitoring by repeat DEXA scanning after a year allow an estimate of the rate of change of bone mineral density.

Splenic Atrophy

This occurs in celiac sprue. It has been suggested that pneumococcal immunization be administered, although whether this should be advocated for all celiac sprue patients is unknown.

Diagnosis

The mainstay of diagnosis of celiac sprue is a small intestinal biopsy specimen, which is usually taken at endoscopy. At least 3 biopsy specimens preferably should be taken with "jumbo" forceps from the distal duodenum. Some individuals, especially pediatricians, use a dedicated Watson or Crosby capsule. The characteristic changes involve damage to the normal villous morphology with decreased villous height to crypt depth, decreased epithelial surface cell height, and increased lymphocytic infiltration of the mucosa.

The generally accepted diagnostic criteria are that there should be an abnormal small intestinal mucosa while individuals continue to take a gluten-containing diet. There should then be unequivocal improvement in villous architecture on a repeat small intestinal biopsy procedure after some months on a gluten-free diet with symptomatic improvement. A repeat biopsy should usually be taken 4–6 months after induction of treatment and if there has been no improvement in the small intestinal mucosal morphology, the original diagnosis should be questioned. However, many gastroenterologists do not take a follow-up biopsy specimen and the cost-effectiveness of this approach has not be demonstrated. Most clinicians do not undertake formal gluten

Decreasing incidence of coeliac disease. Arch Dis Child 1987; 62:465–468.
61. Greco L, Maki M, DiDonato F, Visakorpi JK. Epidemiology of coeliac disease in Europe and the Mediterranean area. Dyn Nutr Res 1992;2:25–44.
62. Catassi C, Ratsch IM, Fabiani E, Rossini M, Bordicchia F, Candela F, Coppa GU, Giorci PL. Coeliac disease in the year 2000: exploring the iceberg. Lancet 1994;343:200–203.
63. Catassi C, Ratsch IM, Fabiani E, Ricci S, Bordicchia F, Pierdomenico R, Giorgi PL. High prevalence of undiagnosed coeliac disease in 5280 Italian students screened by antigliadin antibodies. Acta Paediatr 1995;84:572–576.
64. Mazzetti di Pietralata M, Giorgetti GM, Gregori M, De Simone M, Leonardi C, Barcetta PA, Ricciardi MM, Sandri G. Sub-clinical coeliac disease. Ital J Gastroenterol 1992;24:352–354.
65. Grodzinsky E, Franzen L, Hed J, Strom M. High prevalence of celiac disease in healthy adults revealed by antigliadin antibodies. Ann Allergy 1992;69:66–70.
66. Ascher H, Krantz I, Kristiansson B. Increasing incidence of celiac disease in Sweden. Arch Dis Child 1991;66:608–611.
67. Kolho KL, Farkkila MA, Savilahti E. Undiagnosed celiac disease is common in Finnish adults. Scand J Gastroenterol 1998;33: 1280–1283.
68. Catassi C, Fabiani E, Ratsch IM, Coppa GV, Giorgi PL, Pierdomenico R, Alessandrini S, Iwanejko G, Domenici R, Mei E, Miano A, Maran M, Bottaro G, Spina M, Dotti M. Montanelli A, Barbato M, Viola F, Lazzari R, Vallini M, Guariso G, Plebani M, Cataldo F, Traverso G, Ventura A, De Simone M, Leonardi C, Barcetta PA, Ricciardi MM, Sandri G. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subsets. Acta Paediatr Suppl 1996;412:29–35.
69. Weile B, Krasilnifoff PA. Extremely low incidence rate of celiac disease in the Danish population of children. J Clin Epidemiol 1993;46:661–664.
70. Ascher H, Krantz I, Kristiansson B. Increasing incidence of coeliac disease in Sweden. Arch Dis Child 1991;66:608–611.
71. Maki M, Holm K, Ascher H, Greco L. Factors affecting clinical presentation of coeliac disease: role of type and amount of gluten-containing cereals in the diet. Dyn Nutr Res 1992;2:76–82.
72. Ascher H, Kristiansson B. Childhood coeliac disease in Sweden. Lancet 1994;44:340–341.
73. Fasano A. Where have all American celiacs gone? Arch Dis Child 1996;412:20–24.
74. Rossi TM, Sibini CH, Kumar V. Incidence of celiac disease identified by the presence of serum endomysial antibodies in children with chronic diarrhea, short stature, or insulin-dependent diabetes mellitus. J Pediatr 1993;123:262–264.
75. Talley NJ, Valdovinos M, Petterson TM, Carpenter HA, Melton L Jr. Epidemiology of celiac sprue: a community-based study. Am J Gastroenterol 1994;89:843–846.
76. Hill ID, Horvath K, Fasano A. Epidemiology of celiac disease. Am J Gastroenterol 1995;90:163–164.
77. Hill I, Fasano A, Schwartz R, Counts D, Glock M, Horvath K. Prevalence of celiac disease in at risk groups of children in United States. Pediatr Res 2000;136:86–90.
78. Berti I, Horvath K, Green PHR, Not T, Fasano A. Prevalence of celiac disease among first and second degree relatives in the U.S.A. (abstr). Gastroenterology 1999;116:A861.
79. Berti I, Horvath K, Green PHR, Sblattero D, Not T, Fasano A. Prevalence of celiac disease among risk groups and the general population in U.S.A. (abstr). J Invest Med 2000;48:220A.
80. Not T, Horvath K, Hill ID, Partanen J, Hammed A, Magazzu G, Fasano A. Celiac disease risk in the USA: high prevalence of antiendomysium antibodies in healthy blood donors. Scand J Gastroenterol 1998;33:494–498.
81. Gerarduzzi T, Berti I, De Gregorio E, Horvath K, Green PHR, Sblattero D, Not T, Pietzak M, Hill I, Murray J, Fasano A. Celiac disease in U.S.A. among risk groups and the general population in USA (abstr). J Pediatr Gastroenterol Nutr 2000; 31:S29.
82. Gandolfi L, Pratesi R, Cordoba JCM, Tavil PL, Gasparin M, Catassi C. Prevalence of celiac disease among blood donors in Brazil. Am J Gastroenterol 2000;95:689–692.
83. Catassi C, Ratsh IM, Gandolfi L, Pratesi R, Fabiani E, El Asmar R, Frijia M, Bearzi I, Vizzoni L. Why is coeliac disease endemic in the people of the Sahara? Lancet 1999;354:647–648.
84. Yachha SK, Mohindra S, Srivastava A, Krishnani N, Saxena A. Effects of gluten-free diet on growth and small bowel histology in children with celiac disease in India. J Pediatr Gastroenterol Nutr 2000(suppl);31:S23.
85. Shahbazkhani B, Maghari M, Nasseri Moghaddam S, Kamalian N, Sotoudeh M, Minapour M, Malekzadeh R. Prevalence of celiac disease among Iranian patients with chronic diarrhea. J Pediatr Gastroenterol Nutr 2000(suppl);31:S4.
86. Logan RFA. Problems and pitfalls in epidemiological studies of coeliac disease. Dyn Nutr Res 1992;2:14–24.
87. Picarelli A, Maiuri L, Mazzilli MC, Coletta S, Ferrante P, Di Giovanbattista F, Greco M, Torsoli A, Auricchio S. Gluten-sensitive disease with mild enteropathy. Gastroenterology 1996; 111:608–616.
88. Holmes GKT, Catassi C. Coeliac disease. Oxford, England: Health Press—Fast Facts, 2000.
89. Ivarsson A, Persson LA, Nyström L, Ascher H, Cavell B, Danielsson L, Dannaeus A, Lindberg T, Lindquist B, Stenhammar L, Hernell O. Epidemic of coeliac disease in Swedish children. Acta Paediatr 2000;89:165–171.
90. Meeuwisse GW. Diagnostic criteria in coeliac disease. Acta Paediatr Scand 1970;59:461–463.
91. Burgin-Wolff A, Berger R, Gaze H, Huber H, Lentze MJ, Nussle D. IgA and IgG gliadin antibody determinations as screening test for untreated coeliac disease in children, a multicentre study. Eur J Pediatr 1989;148:496–502.
92. Murray JA, Herlein J, Goeken J. Multicenter comparison of serologic tests for celiac disease in the USA: results of phase 1 serological comparison (abstr). Gastroenterology 1997;112:A389.
93. Sulkanen S, Halttunen T, Laurila K, Kolho KL, Korponay-Szabo IR, Sarnesto A, Savilathi E, Colun P, Maki M. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. Gastroenterology 1998;115:1322–1328.
94. Troncone R, Maurano F, Rossi M, Micillo M, Greco L, Auricchio R, Salerno G, Salvatore F, Sacchetti L. IgA antibodies to tissue transglutaminase: an effective diagnostic test for celiac disease. J Pediatr 1999;134:166–171.
95. Fasano A. Tissue transglutaminase: the holy grail for the diagnosis of celiac disease, at last? J Pediatr 1999;13:134–135.
96. Sblattero D, Berti I, Trevisiol C, Marzari R, Tommasini A, Bradbury A, Fasano A, Ventura A, Not T. Human tissue transglutaminase ELISA: a powerful mass screening diagnostic assay for celiac disease. Am J Gastroenterol 2000:98:1253–1257.
97. Baldas V, Tommasini A, Trevisiol C, Berti I, Fasano A, Sblattero D, Bradbury A, Marzari R, Ventura A, Not T. The development of a novel rapid non-invasive screening test for celiac disease. Gut 2000;47:628–631.
98. Walker-Smith JA, Guandalini S, Schmitz J, Shmerling DH, Visakorpi JK. Revised criteria for diagnosis of coeliac disease. Arch Dis Child 1990;65:909–911.
99. Scott BB, Losowsky MS. Patchiness and duodenal-jejunal variation of the mucosal abnormality in coeliac disease and dermatitis herpetiformis. Gut 1976;17:984–992.
100. Hummel M, Bonifacio E, Stern M, Dittler J, Schimmel A, Ziegler AG. Development of celiac disease-associated antibodies in

offspring of parents with type I diabetes. Diabetologia 2000; 43:1005–1011.
101. Iltanen S, Collin P, Korpela M, Holm K, Partanen J, Polvi A, Mäki M. Celiac disease and markers of celiac disease latency in patients with primary Sjögren's syndrome. Am J Gastroenterol 1999;94:1042–1046.
102. Cataldo F, Marino V, Ventura A, Bottaro GR, SIGEP, Club del Tenue Working Groups on Coeliac Disease. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study. Gut 1998;42:362–365.
103. Viscardi M, Barera G, Bonfanti R, Menni L, Zappa L, Leone BE, Bianchi C, Chiumello G. Occurrence of coeliac disease after the onset of insulin-dependent diabetes mellitus: a six years follow-up (abstr). J Pediatr Gastroenterol Nutr 2000;31:S216.
104. Leonard JN, Tucker WFG, Fry JS, Coulter CA, Boylston AW, McMinn RM, Haffenden GP, Swain AF, Fry L. Increased incidence of malignancy in dermatitis herpetiformis. BMJ 1983; 286:16–18.
105. Catassi C, Corrao G, Barbato M, De Renzo A, Carroccio A, D'Altilia MR, Guariso G, Baldassarre M, Caramaschi P, Bertolani P, Bellentani S, Corazza GR. The risk of non-Hodgkin lymphoma (NHL) in patients with coeliac disease (CD): preliminary results of the Italian multicentre case-control study (abstr). Gastroenterology 1999;116:G3770.
106. Colletti RB. The effect of prevalence on the value of serological tests for celiac disease. J Pediatr Gastroenterol Nutr 2000; 31(suppl 3):S11.
107. Gerarduzzi T, Horvath K, Rabsztyn A, Berti I, Kryszak D, Fasano A. Should risk group patients be retested for celiac disease? (abstr). J Pediatr Gastroenterol Nutr 2000;31:S29.
108. Fabiani E, Taccari LM, Rätsch IM, Di Giuseppe S, Coppa GV, Catassi C. Compliance with gluten-free diet in adolescents with screening-detected celiac disease: a 5-year follow-up study. J Pediatr 2000;136:841–843.
109. Hallert C, Granno C, Grant C, Hulten S, Midhagen G, Strom M, Svensson H, Valdimarsson T, Wickstrom T. Quality of life of adult coeliac patients treated for 10 years. Scand J Gastroenterol 1998;33:933–938.
110. Hin H, Bird G, Fisher P, Mahy N, Jewell D. Coeliac disease in primary care: case finding study. BMJ 1999;318:164–167.
111. Hardman CM, Garioch JJ, Leonard JN, Thomas HJ, Walker MM, Lortan JE, Lister A, Fry L. Absence of toxicity of oats in patients with dermatitis herpetiformis. N Engl J Med 1997;337:1884–1887.
112. Forssell F, Wieser H. Spelt wheat and celiac disease. Z Lebensmittel Untersuch Forsch 1995;201:35–39.
113. Ellis HJ, Doyle AP, Day P, Wieser H, Ciclitira PJ. Demonstration of the presence of coeliac-activating gliadin-like epitopes in malted barley. Int Arch Allergy Immunol 1994;104:308–310.
114. Horvath K, Fasano A. Celiac disease in children. Curr Opt Gastroenterol (in press).
115. Cellier C, Delabesse E, Helmer C, Patey N, Matuchansky C, Jabri B, Macintyre E, Cerf-Bensussan N, Brousse N, French Coeliac Disease Study Group. Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. Lancet 2000;356:203–208.
116. Stuart BM, Gent AE. Atrophy of the coeliac mucosa. Eur J Gastroenterol Hepatol 1998;10:523–525.
117. Mitchison HC, Al Mardini H, Gillespie S, Laker M, Zaitoun A, Record CO. A pilot study of fluticasone propionate in untreated coeliac disease. Gut 1991;32:260–265.
118. Vaidya A, Bolanos J, Berkelhammer C. Azathioprine in refractory sprue. Am J Gastroenterol 1999;94:1967–1969.
119. Rolny P, Sigurjonsdottir HA, Remotti H, Nilsson LA, Ascher H, Tlaskalova-Hogenova H, Tuckoua L. Role of immunosuppressive therapy in refractory sprue-like disease. Am J Gastroenterol 1999;94:219–225.
120. O'Mahony S, Howdle PD, Losowsky SM. Review article: management of patients with non-responsive coeliac disease. Alim Pharmacol Ther 1996;10:671–680.
121. Patey N, Scoazec JY, Cuenod-Jabri B, Canioni D, Kedinger M, Goulet O, Brousse N. Distribution of cell adhesion molecules in infants with intestinal epithelial dysplasia (Tufting enteropathy). Gastroenterology 1997;113:833–843.
122. Ryan BM, Kelleher D. Refractory celiac disease. Gastroenterology 2000;119:243–251.
123. 9th International Symposium on Celiac Disease. J Pediatr Gastroenterol Nutr 2000;31(suppl 3):S1–S35.
124. World Congress of Pediatric Gastroenterology, Hepatology and Nutrition Proceedings: working group report on celiac disease.
125. Catassi C, Fabiani E, Ratsch IM, Coppa GV, Giorgi PL, Pierdomenico R. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. Acta Paediatr Suppl 1996;412:29–35.
126. Johnston SD, Watson RG, McMillan SA, Sloan J, Love AH. Prevalence of coeliac disease in Northern Ireland. Lancet 1997; 350:1370.
127. Ascher H, Krantz I, Kristiansson B. Increasing incidence of coeliac disease in Sweden. Arch Dis Child 1991;66:608–611.
128. Csizmadia CG, Mearin ML, von Blomberg BM, Brand R, Vanloove-Vanhorick SP. An iceberg of childhood coeliac disease in The Netherlands. Lancet 1999;353:813–814.
129. Hovdenak N, Hovlid E, Aksnes L, Fluge G, Erichsen MM, Eide J. High prevalence of asymptomatic coeliac disease in Norway: a study of blood donors. Eur J Gastroenterol Hepatol 1999;11: 185–187.
130. Kolho KL, Farkkila MA, Savilahti E. Undiagnosed coeliac disease is common in Finnish adults. Scand J Gastroenterol 1998; 33:1280–1283.
131. Rostami K, Mulder CJ, Werre JM, van Beukelen FR, Kerckhaert J, Crusius JB, Pena AS, Willekens FL, Meijer JU. High prevalence of celiac disease in apparently healthy blood donors suggests a high prevalence of undiagnosed Celiac disease in the Dutch population. Scand J Gastroenterol 1999;34:276–279.
132. Gandolfi L, Bocca AL, Pratesi R. Screening of celiac disease in children attending the outpatient clinic of a university hospital (abstr). J Pediatr Gastroenterol Nutr 2000;31:S212.
133. Lindquist BL, Rogozinski T, Moi H, Danielsson D, Olcén P. Endomysium and gliadin IgA antibodies in children with coeliac disease. Scand J Gastroenterol 1994;29:452–456.
134. Grodzinsky E, Jansson G, Skogh T, Stenhammar L, Fälth-Magnusson K. Anti-endomysium and anti-gliadin antibodies as serological markers for coeliac disease in childhood: a clinical study to develop a practical routine. Acta Paediatr 1995;84: 294–298.
135. Cataldo F, Ventura A, Lazzari R, Balli F, Nassimbeni G, Marino V. Antiendomysium antibodies and coeliac disease: solved and unsolved questions. An Italian multicentre study. Acta Paediatr 1995;84:1125–1131.
136. Russo PA, Chartrand LJ, Seidman E. Comparative analysis of serologic screening tests for the initial diagnosis of celiac disease. Pediatrics 1999;104:75–78.
137. Valdimarsson T, Franzen L, Grodzinsky E, Skogh T, Strõm M. Is small bowel biopsy necessary in adults with suspected celiac disease and IgA anti-endomysium antibodies? Dig Dis Sci 1996;41:83–87.
138. Troncone R, Ferguson A. Anti-gliadin antibodies. J Pediatr Gastroenterol Nutr 1991;12:150–158.

Received September 6, 2000. Accepted November 29, 2000.

Address requests for reprints to: Alessio Fasano, M.D., Center for Celiac Research, University of Maryland School of Medicine, 685 West Baltimore Street HSF Building, Room 465, Baltimore, Maryland 21201. e-mail: afasano@umaryland.edu; fax: (410) 328-1072.

Table 5. Research Priorities Identified at the 9th International Symposium on CD

Area of research
Searching for the CD genes
Developing a vaccine against CD
Who, when, and how to screen for CD
Engineering gluten-free grains
Gaining more insight on CD pathogenesis
Developing noninvasive, fast, and reliable tests for the diagnosis and follow-up of CD
Web information
http://www.celiaccenter.org
http://www.nowheat.com/grfx/nowheat/index.htm
http://www.niddk.nih.gov/health/digest/pubs/celiac/index.htm
http://www.fastlane.net/homepages/thodge/archive.shtml

lymphoma, refractory sprue, and ulcerative jejunitis. Patients with CD in whom the lack of compliance to a GFD has been ruled out belong to the refractory sprue category. An aberrant clonal intraepithelial T-cell population can be found in up to 75% of patients with refractory sprue, a condition that is currently classified as cryptic enteropathy-associated T-cell lymphoma.[115] These patients typically undergo pharmacologic therapies, including treatment with steroids[116,117] or immunosuppressants, such as azathioprine[118] and cyclosporine.[119] If patients do not respond to these treatments, the ultimate treatment is total parenteral nutrition. None of these therapies have been subjected to rigorous controlled studies.[120]

In young children with villus atrophy whose symptoms do not respond to a gluten-free diet, diseases that must be considered include tufting enteropathy and other congenital ultrastructural abnormalities of the enterocyte,[121] unrecognized chronic giardiasis, and autoimmune enteropathy.

For a more comprehensive overview on refractory sprue, the reader is referred to a recently published review.[122]

Future Directions

A multidisciplinary research effort to understand the pathogenesis of CD is currently taking place worldwide. This effort is fueled by the appreciation that CD represents a unique example of an autoimmune disease in which the environmental factor(s) that induce the immune response has been identified. Therefore, scientists view CD as a model to tackle key questions on the pathogenic mechanisms involved in other autoimmune diseases (i.e., multiple sclerosis, diabetes mellitus, rheumatoid arthritis, etc.) whose environmental triggers are still unknown. Future directions in CD research (Table 5) have been clearly identified and were recently discussed both at the 9th International Symposium on CD that was held on August 10–13 in Baltimore and at the first World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition in Boston.[124] Although some of these goals are in an advanced state of development (i.e., engineering gluten-free grains), others (i.e., the search for the CD genes) are extremely challenging and will require an international task force to generate meaningful data. Nevertheless, the appreciation that CD is not a disease confined in Europe but a global problem affecting continents such as North and South America, Africa, and Asia, where it was historically considered an extremely rare condition, is catalyzing the scientific attention of new generations of investigators who will surely help achieve these challenging targets.

References

1. Sollid L, Thorsby E. HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. Gastroenterology 1993;105:910–922.
2. Shuppan D. Current concepts of celiac disease pathogenesis. Gastroenterology 2000;119:234–242.
3. Madara JL, Trier JS. Structural abnormalities of jejunal epithelial cell membranes in celiac sprue. Lab Invest 1980;43:254–261.
4. Schulzke JD, Bentzel CJ, Schulzke I, Riecken EO, Fromm M. Epithelial tight junction structure in the jejunum of children with acute and treated celiac sprue. Pediatr Res 1998;43:435–441.
5. Wang W, Uzzau S, Goldblum SE, Fasano A. Human zonulin, a potential modulator of intestinal tight junctions. J Cell Sci 2000; 113:4435–4440.
6. Fasano A, Not T, Wang W, Uzzau S, Berti I, Tommasini A, Goldblum SE. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. Lancet 2000;358:1518–1519.
7. Ventura A, Magazzu G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in celiac patients. Gastroenterology 1999;117:303–310.
8. Bjorkman PJ, Saper MA, Samraoui B, Bennet WS, Strominger JL, Wiley DC. The foreign antigen binding site and T-cell recognition regions of class I immunohistocompatibility antigens. Nature 1987;329:512–518.
9. Cuvelier C, Barbatis C, Mielants H, De Vos H, Roels H, Veys E. Histopathology of intestinal inflammation related to reactive arthritis. Gut 1987;28:394–401.
10. Molberg O, McAdam SN, Sollid LM. Role of tissue transglutaminase in celiac disease. J Pediatr Gastroenterol Nutr 2000;30: 232–240.
11. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken E, Schuppan D. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med 1997;3:797–801.
12. Mäki M, Kallonen K, Lahdehao ML, Visakorpi JK. Changing pattern of childhood coeliac disease in Finland. Acta Paediatr Scand 1988;77:408.
13. Logan RF, Tucker G, Rifkind E, Heading RC, Ferguson A. Changes in clinical features of coeliac disease in adults in Edinburgh and the Lothians 1960-79. BMJ 1983;286:95–97.
14. Swinson CM, Levi AJ. Is coeliac disease underdiagnosed? BMJ 1980;281:1258–1260.
15. Pare P, Douville P, Caron D, Lagace R. Adult coeliac sprue: changes in the pattern of clinical recognition. Gastroenterology 1988;10:395.
16. Berti I, Horvath K, Green PHR, Sblattero D, Not T, Fasano A.

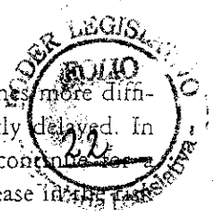
Differences of celiac disease's clinical presentation among pediatric and adults relatives of CD patients in U.S.A. J Invest Med 2000;48:215A.
17. Fry L. Dermatitis herpetiformis. Baillières Clin Gastroenterol 1995;9:371–393.
18. Reunala T, Collin P. Diseases associated with dermatitis herpetiformis. Br J Dermatol 1997;136:315–318.
19. Carroccio A, Iannitto E, Cavataio F, Montalto G, Tumminello M, Campagna P, Lipari MG, Notarbartolo A, Iacono G. Sideropenic anemia and celiac disease: one study, two points of view. Dig Dis Sci 1998;43:673–678.
20. Groll A, Candy DC, Preece MA, Tanner JM, Harries JT. Short stature as the primary manifestation of coeliac disease. Lancet 1980;2:1097.
21. Cacciari E, Salardi S, Lazzari R, Cicognani A, Collina A, Pirazzoli P, Tassoni P, Biasco G, Corazza GR, Cassio A. Short stature and coeliac disease: a relationship to consider even in patients with no gastrointestinal symptoms. J Pediatr 1983;103:708.
22. Stenhammar C, Fallstrom SP, Jansson G, Lindberg T. Celiac disease in children of short stature without gastrointestinal symptoms. Eur J Pediatr 1986;145:185.
23. Verkasalo M, Kuitenen P, Leisti S, Perheentupa J. Growth failure from symptomless coeliac disease. Helv Paediatr Acta 1978; 47:489–495.
24. Prader A, Tanner JM, Von Harnack GA. Catch-up growth in coeliac disease. Acta Paediatr Scand 1969;58:311–316.
25. Smith DMH, Miller J. Gastroenterology, coeliac disease and enamel hypoplasia. Br Dent J 1979;147:91–95.
26. Aine L. Dental enamel defects and dental maturity in children and adolescents with coeliac disease. Proc Finn Dent Soc 1986;82:222–229.
27. George EK, Hertzberger-ten Cate R, Van Suijlekom-Smit LW, Von Blomberg BM, Stapel SO, Van Elburg R M, Mearin ML. Juvenile chronic authritis and coeliac disease in the Netherlands. Clin Exp Rheumatol 1996;14:571–575.
28. Lepore L, Martelossi S, Pennesi M, Falcini F, Ermini ML, Ferrari R, Perticarari S, Presani G, Lucchesi A, Lapini M, Ventura A. Prevalence of celiac disease in patients with juvenile chronic arthritis. J Pediatr 1996:129:311–313.
29. O'Farrelly C, Marten D, Melcher D, McDougall B, Price R, Goldstein AJ, Sherwood R, Fernandes L. Association between villous atrophy in rheumatoid arthritis and a rheumatoid factor and gliadin-specific IgG. Lancet 1988;2:819–822.
30. Mäki M, Hallstrom O, Verronen P, et al. Reticulin antibody arthritis and coeliac disease in children. Lancet 1988;1:479–480.
31. Maggiore G, De Giacomo C, Scotta MS, Sessa F. Coeliac disease presenting as chronic hepatitis in a girl. J Pediatr Gastroenterol Nutr 1986;5:501–503.
32. Leonardi S, Bottaro G, Patane' R, Musumeci S. Hypertransaminasemia as the first symptom in infant coeliac disease. J Pediatr Gastroenterol Nutr 1990;11:404–406.
33. Vajro P, Fontanella A, Greco L. Hepatite chronique cryptogenetique revelant une maladie coeliaque. Proceedings of Groupe Francophone de Gastroenterologie et Nutrition Pediatrique. Lyon, France, July 2–3, 1990.
34. Fontanella A, Vajro P, Ardia E, Greco L. Danno epatico in corso di malattia celiaca. Studio retrospettivo in 123 bambini. Riv Ital Pediatr 1987;5:80–85.
35. Valdimarsson T, Lofman O, Toss G, Strom M. Reversal of osteopenia with diet in adult coeliac disease. Gut 1996;38:322–327.
36. Mora S, Barera G, Beccio S, Proverbio MC, Weber G, Bianchi C, Chiumello G. Bone density and bone metabolism are normal after long-term gluten-free diet in young celiac patients. Am J Gastroenterol 1999;94:398–403.
37. Sategna-Guidetti C, Grosso SB, Grosso S, Mengozzi G, Aimo G, Zaccaria T, Di Stefano M, Isaia CC. The effects of 1-year gluten withdrawal on bone mass, bone metabolism and nutritional status in newly-diagnosed adult coeliac disease patients. Aliment Pharmacol Ther 2000;14:35–43.
38. Hadjivassiliou M, Gibson A, Davies-Jones GA, Lobo AJ, Stephenson TJ, Milford-Ward A. Does cryptic gluten sensitivity play a part in neurological illness? Lancet 1996;347:369–371.
39. Pellecchia MT, Scala R, Filla A, De Michele G, Ciacci C, Barone P. Idiopathic cerebellar ataxia associated with celiac disease: lack of distinctive neurological features. J Neurol Neurosurg Psychiatry 1999;66:32–35.
40. Farthing MJ, Rees LH, Edwards CR, Dawson AM. Male gonadal function in coeliac disease. 2. Sex hormones. Gut 1983;24: 127–136.
41. Auricchio S, Greco L, Troncone R. Gluten-sensitive enteropathy in childhood. Pediatr Clin North Am 1988;35:157–187.
42. Infertilities and CD (editorial). Lancet 1983;1:453.
43. Gasbarrini A, Sanz Torre E, Trivellini C, De Carolis S, Caruso A, Gasbarrini G. Recurrent spontaneous abortion and intrauterine fetal growth retardation as symptoms of coeliac disease. Lancet 2000;256:399–400.
44. Ciacci C, Cirillo M, Auriemma G, Di Dato G, Sabbatini F, Mazzacca G. Celiac disease and pregnancy outcome. Am J Gastroenterol 1996;91:718–722.
45. Auricchio S, Mazzacca G, Tosi R, Deritis G. Coeliac disease as a familial condition: identification of asymptomatic coeliac patients within family groups. Gastroenterol Int 1988;1:25.
46. Hed J, Leiden G, Ottosson E, Strom M, Walan A, Groth O, Sjogren F, Franzen L. IgA anti-gliadin antibodies and jejunal mucosal lesions in healthy blood donors (letter). Lancet 1986; 2:215.
47. Ferguson A, Arranz E, O'Mahony S. Clinical and pathological spectrum of coeliac disease—active, silent, latent, potential. Gut 1993;34:150–151.
48. Maki M, Kallonen K, Lahdeaho ML, Visakorpi JK. Changing pattern of childhood coeliac disease in Finland. Acta Paediatr Scand 1988;77:408–412.
49. Mustalahti K, Collin P, Sievanen H, Salmi J, Mäki M. Osteopenia in patients with clinically silent coeliac disease warrants screening. Lancet 1999;354:744–745.
50. Fabiani E, Catassi C, Villari A, Gismondi P, Pierdomenico R, Rätsch IM, Coppa GV, Giorgi PL. Dietary compliance in screening-detected coeliac disease adolescents. Acta Paediatr Suppl 1996;412:65–67.
51. Swinson CM, Slavin G, Coles EC, Booth CC. Coeliac disease and malignancy. Lancet 1983;1:111–115.
52. Logan RFA, Rifkind EA, Turner ID, Ferguson A. Mortality in coeliac disease. Gastroenterology 1989;97:265–271.
53. Davidson LSP, Fountain JR. Incidence of sprue syndrome with some observation on the natural history. BMJ 1950;1:1157–1161.
54. Meeuwisse GW. Diagnostic criteria in coeliac disease. Acta Paediatr Scand 1970;59:461–463.
55. Mylotte M, Egan-Mitchell B, McCarthy CF, McNicholl B. Incidence of coeliac disease in the west of Ireland. BMJ 1973;1: 703–705.
56. Logan RFA, Rifking EA, Busuttil A, Gilmous HM, Ferguson A. Prevalence and 'incidence' of celiac disease in Edinburgh and the Lothian region of Scotland. Gastroenterology 1986;90:334–342.
57. Van Stirum J, Baerlocher K, Fanconi A, Gugler E, Shmerling DH. The incidence of coeliac disease in children in Switzerland. Helv Paediatr Acta 1982;37:421–430.
58. Littlewood JM, Crollick AJ, Richards IDG. Childhood coeliac disease is disappearing. Lancet 1980;2:1359.
59. Dossetor JFB, Gibson AAM, McNeish AS. Childhood coeliac disease is disappearing. Lancet 1981;1:322–323.
60. Stevens FM, Egan-Mitchell B, Cryan E, McCarthy CF, McNicholl B.

example, the relative risk of developing a lymphoma complication was reported to be as high as 30–100,[53,104] whereas an ongoing case-control multicenter Italian study investigating the prevalence of CD in patients with lymphoma seems to indicate only a slight increase in the risk of this malignancy (odds ratio ~2) in comparison with the general population.[105] Despite the high sensitivity of the serologic CD markers, the positive predictive value of these investigations decreases when they are used in the general population rather than in at-risk groups.[106] The appropriate age to screen for CD also remains to be established, as well as whether periodic repetition of the screening would be required to rule out a "late onset" gluten sensitization.[107] Because of the ethical implications of mass screening, the difficulties of treating patients with apparently silent CD should not be overlooked. A recent 5-year follow-up study revealed a 30% decrease in adherence to the GFD in patients with screening-detected CD compared with age-matched, pital-detected CD cases.[108] Wherever products containing wheat flour represent the staple food, treatment with a GFD is likely to interfere with quality of life, especially in adults, and it has been shown that adults with CD undergoing long-term treatment fail to attain the same degree of subjective health as the general population.[109]

Finally, mass screening for CD will depend on the results of comprehensive, well-performed cost-effectiveness analyses. Currently, the "best buy" approach to the submerged portion of the iceberg of undiagnosed CD seems to be a systemic process of case finding, as suggested by a recent study developed in a primary care setting in central England.[110] By simply investigating at-risk subjects, e.g., those with anemia, fatigue, thyroid disease, diabetes, or a family history of CD, Hin et al. observed a 4-fold increase in the number of CD diagnoses ing a 1-year period.[110] Increased awareness of the extraintestinal manifestations of CD, coupled with a low threshold for serologic testing, uncovers a large portion of the submerged iceberg.[110]

Why Early Diagnosis Is Important

Our better understanding on the pathogenesis of CD[2] and the observation that CD patients' risk of developing autoimmune diseases[11] and intestinal lymphomas[51,52] is proportional to the time of exposure to gluten suggest that prompt diagnosis is crucial to minimize if not prevent serious complications. Based on epidemiologic data, it might be hypothesized that if CD develops early with typical gastrointestinal symptoms, prompt diagnosis and thus timely prescription of a GFD are more likely. If, on the other hand, symptoms are atypical or completely absent, diagnosis of CD becomes more difficult and the diet treatment is significantly delayed. In these subjects, exposure to gluten will continue for a prolonged period, with a subsequent increase in the risk of complications.



The Treatment

Total lifelong avoidance of gluten ingestion remains the cornerstone treatment for the disease. The diet requires ongoing education of patients and their families by both doctors and dieticians. Regional CD support groups are instrumental sources of information and support. One of the major controversies in the treatment of CD relates to the amount of gluten allowed in the diet of CD patients. The National Food Authority has recently redefined the term "gluten-free." Previously, <0.02% gluten was considered gluten-free, but gluten-free now means no gluten, and <0.02% is currently labeled "low gluten." However, the stringency of gluten restriction (zero tolerance versus low gluten ingestion) is an issue that is far from being resolved because opinions differ among scientists and CD support groups worldwide. These controversies are attributable to a lack of solid scientific evidence for a threshold of gluten consumption below which no harm occurs. The gliadin fraction of wheat gluten and similar alcohol-soluble proteins (prolamins) in other grains are the environmental factors responsible for the development of intestinal damage. Prolamins are found in a variety of widely used grains (Table 4). Therefore, products labeled "wheat-free" are not necessarily gluten-free. They may contain gluten as well as other grains that are not allowed. Wheat, rye, and barley are the predominant grains containing toxic peptides. Both in vivo challenges and in vitro immunologic studies support the possibility that oats (once considered toxic for CD patients) can be ingested safely.[111] However, because of uncontrolled harvesting and milling procedures, cross-contamination of oats with gluten is a concern. Triticale (a combination of wheat and rye), kamut, and spelt[112] (sometimes called farro) are also toxic. Other forms of wheat are semolina (durum wheat), farina, einkorn, bulgur, couscous, and any form that includes wheat in the name, such as wheat germ, wheat bran, whole wheat, and cracked wheat. Foods made from rye and barley are toxic. Malt is also toxic because it is a partial hydrolysate of barley prolamins. It may contain 100–200 mg of barley prolamins /100 g of malt.[113] In general, an ingredient with malt in its name (barley malt, malt syrup, malt extract, malt flavorings) is made from barley.

Table 4. General Guidelines for the CD Diet

Not allowed		Allowed
Wheats (*Triticum* family)		Rice, wild rice
All forms, including	Einkorn wheat (*Triticum monococcum*)	Corn (maize)
Wheat flour		
Wheat germ		
Wheat bran		
Cracked wheat		
	Emmer wheat (*Triticum dicoccon*)	Sorghum
	Couscous (endosperm of durum wheat)	Millet
	Kamut (*Triticum polonicum*)	Buckwheat (kasha)
	Spelt (farro, drinkle)	Beans, peas, and bean flours
	Semolina (durum wheat)	Quinoa
Rye (*Secale cereale*)		Potato
Triticale (wheat-rye hybrid)		Soybean
Barley (*Hordeum vulgare*) and malt		Tapioca
		Amaranth
		Teff
		Nuts
		Fruits
		Milk (cheeses[a])
		Plain meat
		Fish
		Egg
		Oat (*Avena sativa*)[b]

[a]The coat of some cheeses may contain gluten.
[b]Awaiting definitive scientific confirmation and regulation to avoid cross-contamination.

Gluten in Medications

Medications and vitamin and mineral supplements may also contain gluten as an inactive ingredient. The inactive ingredients of these products can be changed by the manufacturers without warning because there are no regulations on the formulation of inactive drug components. Nebulous (questionable) ingredients, such as vegetable gum and modified food starch, can contain gluten. All medications should be checked for nebulous ingredients, especially if they must be taken for a long period. It is imperative to know the lot number of nonprescription medications when contacting the manufacturer for clarification of the inactive ingredients.

Prescription medications purchased through a pharmacy come with an ingredient list on the package insert. However, different batches of medications may contain different ingredients.

The limited expertise of health care professionals regarding celiac diet and the absence of federal regulations for accurate food and drug labeling both represent significant challenges for patients with newly diagnosed CD. Despite the efforts of celiac support groups, there are still no laws regulating gluten-free labeling in the United States. The American Dietetic Association's National Center for Nutrition and Dietetics Consumer Nutrition Hotline at 1-800-366-1655 is a valuable source of updated information on the treatment of CD. One of the functions of the Consumer Nutrition Hotline is to refer consumers and health care professionals to registered dietitians who have expertise in special diseases. The Consumer Nutrition Hotline can also provide phone numbers and addresses of companies within the food industry to help clarify the ingredients of a given food product and how it has been processed.

Problems in Practical Dietary Management

Possible gluten contamination of products that are presumed to be gluten-free is a recurrent problem. This cross-contamination can happen in farms where the grains are grown and harvested, in mills where grains are processed into flours, or on food processing lines where one line produces a food that includes gluten and the line next to it produces a gluten-free product. Contamination might also occur in stores where grains are available from open bins, in restaurants, at salad bars, or any place where a variety of different meals are produced or different ingredients come together.[114]

Refractory Sprue

In a minority of adult patients, CD does not respond to treatment with a gluten-free diet. The most likely cause of nonresponsiveness is continued gluten ingestion, which can be voluntary or inadvertent. Other causes of nonresponsiveness that must be considered include other food intolerance diseases (e.g., milk, soya), pancreatic insufficiency, enteropathy-associated T-cell

diagnostic test that could be used at the general practitioner's site would represent a great advance. The recent report of a human tTG dot blot test based on the detection of anti-tTG antibodies in serum or in 1 drop of whole blood[97] opened new horizons for the diagnosis of CD. These preliminary results show that the test seems to be extremely sensitive (100%) and reasonably specific (96%). If these data are confirmed, this test holds great potential because it is quick (30 minutes) and inexpensive, requires minimal handling, and in view of its high sensitivity and specificity could easily be introduced into the general practitioner's armory for ambulatory screening of CD.

Current guidelines for serologic diagnosis and follow-up of CD. Because the guinea pig–based tTG ELISA has been only recently commercialized and the human-based tTG ELISA is still experimental, serologic diagnosis of CD still relies on the combined use of AGA and AEA assays. Interpretation of these assays should take into account the fact that AEA can have false-negative results in both IgA-deficient subjects and children younger than 2 years of age, whereas AGA (particularly the IgG subclass) can yield false-positive results in gastrointestinal conditions other than CD, including cow's milk protein intolerance and parasite infections. Once a definitive diagnosis is established (see below), use of these serologic tests is recommended to verify compliance with the GFD, which should be evaluated on a yearly basis or every time patients experience symptoms possibly related to gluten exposure. If the preliminary data so far reported on the sensitivity and specificity of the tTG ELISA (Table 3) are confirmed on a large scale, it is likely that this test will make the AGA and possibly the AEA assays obsolete.

Algorithm for the definitive diagnosis of CD. Given the high sensitivity and specificity reported for some of the screening tools currently available (Table 3), the ESPGHAN has recently proposed a revised CD diagnostic protocol[98] (Figure 4). Based on these revised criteria, if the symptoms (either typical or atypical) and screening results are suggestive, a single intestinal biopsy followed by a favorable response to the GFD is sufficient to definitely confirm the diagnosis (Figure 4). However, total villous atrophy, once considered the only histologic finding compatible with a diagnosis of CD, is now considered only the extreme of a continuous spectrum of tissue damage that can be detected during the acute phase of the disease (Figure 5). Furthermore, the possible patchy characteristics of intestinal damage[99] and the importance of correct orientation of the biopsy for appropriate evaluation of the intestinal damage both add further challenge to a conclusive histologic diagnosis of CD.

Table 3. Sensitivity, Specificity, and Positive and Negative Predictive Values of Serologic Screening Tests Reported in the Literature for the Diagnosis of CD

Test	Sensitivity	Specificity	PPV	NPD
AGA IgG	57–100	42–98	20–95	41–88
AGA IgA	53–100	65–100	28–100	65–100
AEA IgA[a]	75–98	96–100	98–100	80–95
Guinea pig tTG[b]	90.2	95		
Human tTG[b]	98.5	98		

PPV, positive predictive value; NPD, negative predictive value.
[a]Patients older than 2 years.
[b]IgG + IgA antibodies.
Data from references 132–138.

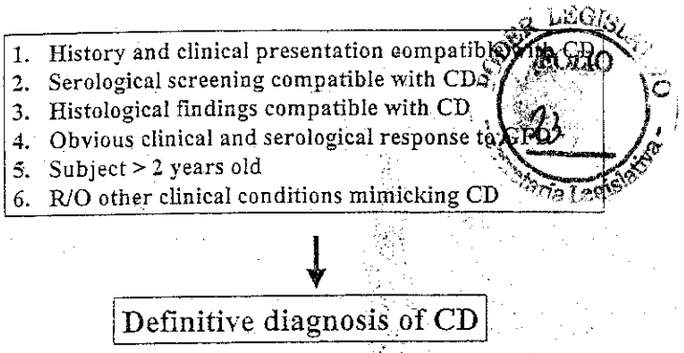


Figure 4. Revised criteria for the diagnosis of CD proposed by the ESPGHAN.

Who Should Be Tested?

At-risk groups. Serologic testing is indicated for subjects with symptoms suggestive of CD, as well as for those with CD-associated diseases (Table 1). However, small intestinal biopsies should always be performed if the clinical suspicion is strong, regardless of the serology results. Some at-risk groups showing a particularly high prevalence of associated CD (Figure 6) deserve a special mention: (1) first- and second-degree relatives of patients with CD: younger siblings can be checked at age 2 years or earlier if CD is clinically suspected; (2) patients and relatives of patients with type I diabetes[100] and patients with immune thyroid or liver disorders; (3) patients with Sjögren syndrome and other connective tissue diseases: in a recent Finnish series, 5 (15%) of 34 patients with Sjögren syndrome were found to have CD,[101] although ongoing inflammation was often present in the small intestinal mucosa of patients without CD[101]; (4) subjects with either Down or Turner syndrome; and (5) subjects with selective IgA deficiency, who show a 10-fold increased risk of associated CD.[102] In these cases, the screening test should be an IgG class antibody, e.g., AGA IgG or anti-tTG IgG.[86]

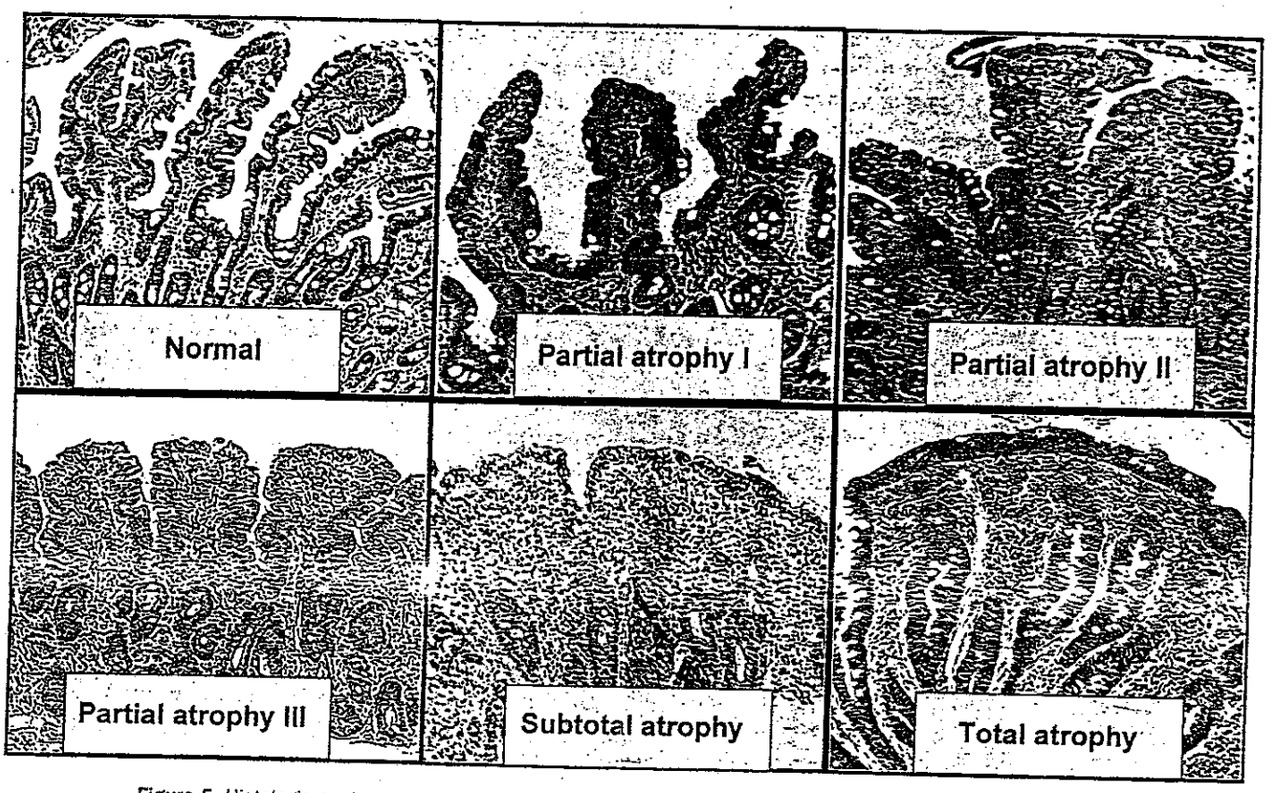


Figure 5. Histologic grades of intestinal mucosa damage in patients with CD (courtesy of Dr. Karoly Horvath).

A single negative result of the serologic markers cannot always rule out the possibility of CD on a lifelong basis. This has been elegantly shown by a recent follow-up study of 275 patients with type I diabetes,[103] in which only 2 of 9 patients found to have CD during a 6-year period had an AEA-positive test result at the time of diabetes onset.[103]

Finally, we suggest that serologic testing for CD should be performed routinely in people joining blood donor groups. Because the celiac enteropathy often impairs iron absorption, CD should be identified as soon as possible in these subjects to avoid the onset of a sideropenic anemia secondary to the combination of periodic blood drawings and the malabsorption condition typical of the disease.

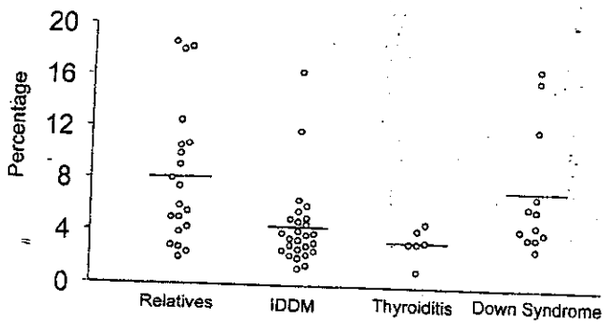
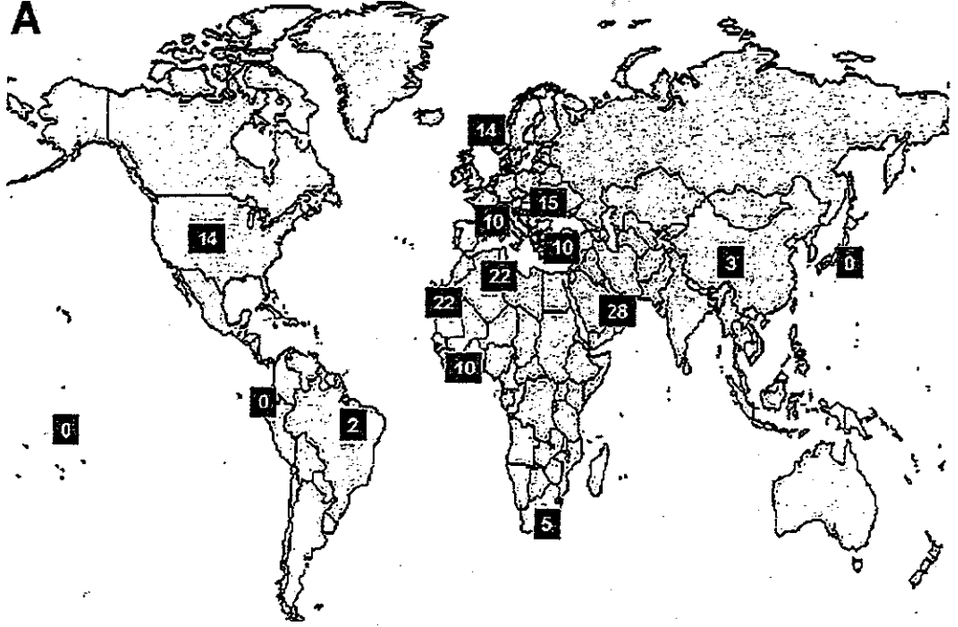
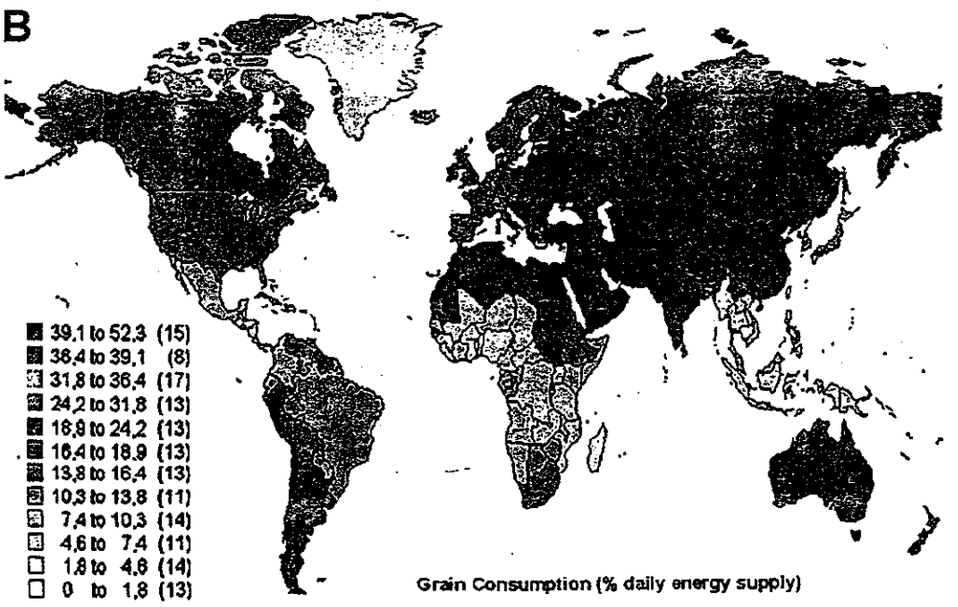


Figure 6. Prevalence of CD in some at-risk groups. *Dots* represent the prevalence found in different studies, and *lines* show the mean values.

Case finding or mass screening? How to deal with the submerged part of the celiac iceberg is currently a matter of debate in the scientific community. An increasing number of experts is in favor of early, mass screening of CD because this condition apparently fulfills the requirements for a worthwhile screening program: (1) it is a common disorder causing significant morbidity in the general population; (2) early detection is often difficult on a clinical basis; (3) if not recognized, the disease can manifest itself with severe complications that are difficult to manage (e.g., infertility, osteoporosis, lymphoma); (4) there is an effective treatment, the GFD; and (5) sensitive and simple screening tests are available, e.g., the anti-tTG test.

However, several issues need further clarification to correctly establish the cost/benefit ratio for CD screening. Although it is well established that patients with untreated CD may develop complications, the natural history of undiagnosed CD is currently unclear. Available studies have necessarily been limited to patients with clinically diagnosed CD (i.e., the tip of the iceberg), eventually leading to biased estimate of the risks. For





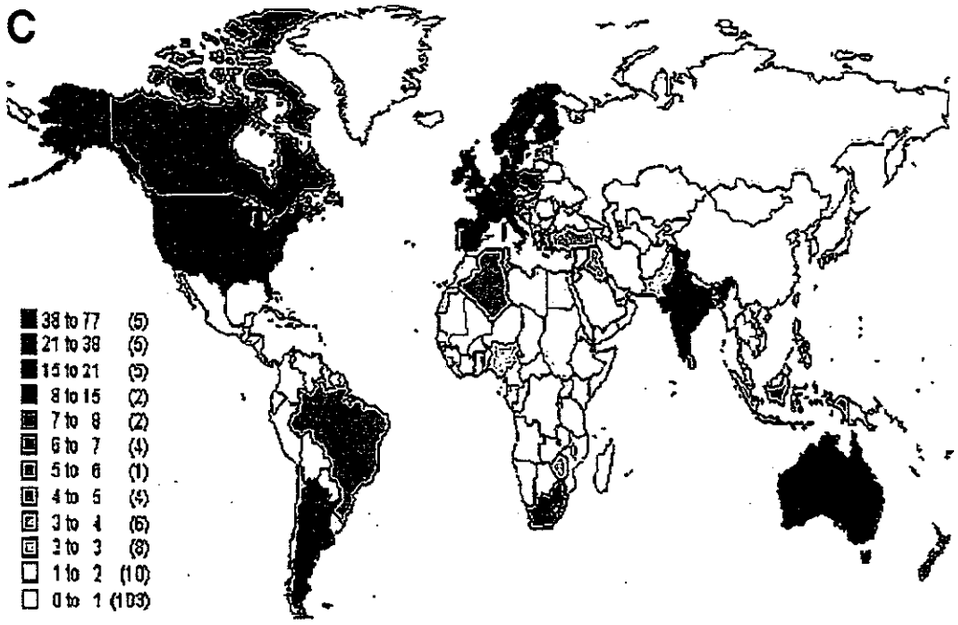


Figure 2. (*A*) CD-associated HLA-DR3. Percentage of genic frequency of HLA-DR3 in the world. (Data provided by Dr. Francesco Cucca, Department of Pediatrics, University of Cagliari, Cagliari, Italy.) (*B*) World distribution of grain consumption. The intensity of color is directly related to the amount of wheat products consumed (expressed as percent of daily energy supply). Numbers in parentheses represent the number of countries that have the wheat consumption shown on the left. (Data from The Sixth World Food Survey; Rome, Italy: Food and Agriculture Organization of the United Nations. 1996.) (*C*) Scientific production on CD worldwide during the period from 1966 to the present. The intensity of color is directly related to the number of articles found in a MEDLINE search for CD and the name of the country. Numbers in parentheses represent the number of countries that have published within the range of manuscripts shown on the left.

other factors (e.g., intestinal infections and nutrient intakes) on the clinical presentation and, even more intriguingly, whether environmental variables can influence the prevalence of CD, therefore assessing the fascinating possibility of primary prevention of this disorder.

How to Diagnose CD?

The diagnosis of CD is based on 3 key parameters: (1) case identification, (2) screening tests, and (3) definitive tests. These parameters have substantially changed during the past 50 years, thanks to better understanding of the clinical presentation of the disease and the advent of more sensitive and specific diagnostic tools and confirmative tests.

The Past

Until a few decades ago, there was the general perception that the clinical presentation of the disease was quite uniform. Case identification was based entirely on the search for symptoms such as chronic diarrhea, abdominal distention, and weight loss (or poor weight gain) occurring in young children a few months after the introduction of solid food to their diet. To confirm clinically suspected CD, unspecific screening tests aimed at establishing the digestive/absorptive functions of the proximal small intestine (i.e., glucose tolerance test, D-xylose test, fecal fat) were used. Given the lifelong nature of the disease, in 1970 the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) dictated specific guidelines by identifying 3 CD diagnostic phases (Figure 3).[90] To meet the criteria of the first phase, the presence of gastrointestinal symptoms compatible with CD, positive results of pathologic screening tests, and confirmation of the diagnosis by intestinal biopsy showing histologic evidence of flat mucosa were required (Figure 3). Upon establishment on a GFD, the clinical symptoms had to resolve, results of screening tests had to return to within normal limits, and a second intestinal biopsy showing complete healing of the histologic damage was recommended (phase 2) (Figure 3). Phase 3 was then started by a gluten challenge with subsequent return of symptoms, pathologic screening test results, and intestinal damage (Figure 3). The diagnosis was confirmed only if all the criteria listed in the 3 phases were completely satisfied.

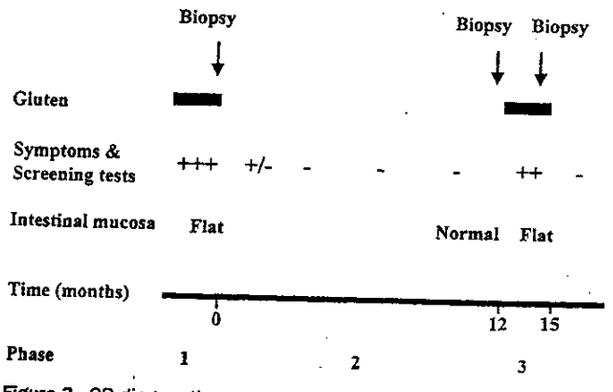


Figure 3. CD diagnostic protocol proposed by the ESPGHAN in 1970.

The Present

Development of serologic tests. In the past 10–15 years we have learned that the clinical expression of CD is more heterogeneous than previously thought.[86] Beside the classical gastrointestinal form, a series of other clinical manifestations of the disease have been described thanks to the advent of innovative serologic screening tests, such as assays for antigliadin antibody (AGA) and antiendomysium antibody (AEA). The combined use of serum AGA IgG (good sensitivity) and IgA (good specificity) resulted in a reliable screening test for diagnosis of CD.[91] Based on the use of this new tool, we have learned that the clinical presentation of CD is more protean than previously thought, including previously unrecognized atypical and asymptomatic forms (see above). Moreover, these studies show that CD is not limited to the pediatric population; the onset of disease may occur during adulthood, after years of silent disease.

Because it has been demonstrated recently that tTG is the target of a specific autoimmune response (see below),[11] this enzyme has also been used to develop innovative diagnostic tools. The routine use of the AEA assay is limited by elevated costs, time-consuming protocols unsuitable for testing large numbers of samples, poor sensitivity in young children (<2 years of age) and in IgA-deficient individuals (the AEA assays routinely performed are of the IgA class), and use of the esophagus of an endangered species (such as the monkey) as the substrate for the immunofluorescent analysis. Even if this last issue has been resolved by using the human umbilical cord as a valid alternative to the monkey esophagus,[80] it has been reported that the subjective interpretation of the AEA assay may lead to unacceptable variability among laboratories that perform this test.[92] Therefore, major effort has been concentrated on developing a tTG-based ELISA, using either the commercially available guinea pig tTG[93,94] or human recombinant tTG.[95,96]

The currently available serologic tests for the diagnosis of CD remain within the province of the specialized diagnostic laboratory. Given the projected high prevalence of the disease and its protean nature, a simple

Table 2. Prevalence of CD Based on Clinical Diagnosis or Screening Data

Geographic area	Prevalence on clinical diagnosis[a]	Prevalence on screening data
Brazil	?	1:400
Denmark	1:10,000	1:500
Finland	1:1000	1:130
Germany	1:2300	1:500
Italy	1:1000	1:184
Netherlands	1:4500	1:198
Norway	1:675	1:250
Sahara	?	1:70
Slovenia	?	1:550
Sweden	1:330	1:190
United Kingdom	1:300	1:112
United States	1:10,000	1:111
Worldwide (average)	1:3345	1:266

[a]Classical gastrointestinal symptoms.
Data from references 81–85, 125–131.

lation at a certain point). Screening studies show a high prevalence of CD among both healthy children[62–64] and adults.[65] The prevalence of CD throughout the old continent seems to be more homogeneous than previously thought (Table 2). Furthermore, these screenings showed that CD is one of the most frequent genetically based diseases,[62,66] occurring in 1 of 130–300 in the European population[67,68] (Table 2). In a serologic screening study involving more than 17,000 Italian schoolchildren, the prevalence of CD was 1 in 184,[48] and the ratio of known to undiagnosed CD cases was 1 to 7. The European experience taught that, despite common genetic and environmental factors, the clinical presentation of CD in neighboring countries may greatly diverge. A typical example of this phenomenon is the Danish epidemiologic case. Until a few years ago, CD was regarded as rare in Denmark, with an estimated incidence based on clinical evidence (i.e., presence of classical symptoms) of 1/10,000[69] (Table 2). At the same time, the incidence of the disease in neighboring countries (including Sweden and Finland) that share similar genetic backgrounds increased after a decrease in breast feeding practice and increased consumption of gluten during infancy.[70,71] Subsequent serologic screening studies suggested that CD is as frequent in Denmark as in Sweden, with a reported prevalence of 1/500[72] (Table 2). These results suggest that in Denmark most cases of CD were previously undiagnosed, presumably because of lack of typical gastrointestinal symptoms. Factors such as type of cow's milk formulas, breast feeding, age at gluten introduction, quantity of gluten and quality of cereals, and quantity of wheat gluten may all influence the clinical presentation of the disease.[71]

Epidemiology of CD in the United States

In the American scientific community, CD is generally believed that CD is a rare disorder in the United States, which is reflected by the limited number of scientific papers published from the new continent in the 30-year period from 1965 to 1995.[73] Only 2 epidemiologic studies of CD were published during this period, both between 1993 and 1994. The first study was conducted by Rossi et al.[74] in 1993 on a pediatric population from the western New York area with symptoms possibly related to CD, such as chronic diarrhea, failure to thrive, short stature, and diabetes.[74] Although the prevalence of CD among patients with symptoms possibly associated to the disease was lower than reported in Europe, the concurrence of CD and insulin-dependent diabetes mellitus was comparable to that previously reported from the old continent. These data suggest that other atypical presentations of CD and eventually late onset of the disease after an asymptomatic phase during childhood may account for the low occurrence of CD reported in this study. The second American epidemiologic study published in 1994 was based on a retrospective evaluation (1960–1990) of the incidence of CD among the population of Olmsted County, Minnesota, using the medical record of the Rochester Epidemiological Project.[75] Case definition was limited to those individuals presenting typical gastrointestinal symptoms (i.e., chronic diarrhea and weight loss) or dermatitis herpetiformis whose intestinal biopsies showed flat mucosa.[75] Using these restrictive parameters, the authors identified only 3 cases among the pediatric population (calculated incidence rate, 0.4 per 100,000 person-years), whereas the overall age- and gender-adjusted incidence was 1.2 per 100,000 person-years. Based on these results, the authors concluded that CD is relatively rare in the United States (prevalence ~1:10,000). Unfortunately, both studies failed to consider the protean clinical manifestations of CD. By focusing on specific symptoms, the authors may have missed what is currently defined as the submerged part of the so-called celiac iceberg (Figure 1). Recently, a series of epidemiologic studies conducted using more appropriate experimental designs and powerful screening tools showed that CD is as frequent in the United States as in Europe in both risk groups[76–78] and the general population[79,80] (Table 2). Our center for celiac research is currently conducting a large, multicenter study on the prevalence of CD in both risk groups (i.e., subjects with either symptoms or complications associated with CD, first- and second-degree relatives of patients with biopsy-proven CD, etc.) and the general population. The results generated on a large number of

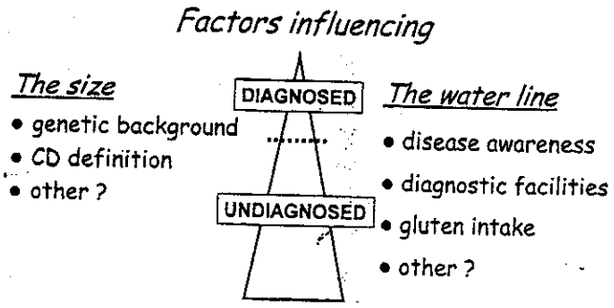


Figure 1. The CD iceberg model.

individuals screened so far suggest that the prevalence of CD in the United States is similar to that reported in Europe if not even higher, both among risk groups and in the general population[81] (Table 2).

Epidemiology of CD in the Rest of the World

Because CD is the result of the interaction between genetic (both HLA and non–HLA-associated genes) and environmental factors (gluten-containing grains), it would be reasonable to evaluate the world distribution of these 2 components to identify areas "at risk" for CD. The coincidence of the CD HLA aplotypes (Figure 2*A*) and the level of wheat consumption (Figure 2*B*) clearly confirm Europe as a region at risk for CD. However, the coexistence of the 2 key components involved in CD pathogenesis (Figure 2*A* and *B*) is also notable in regions where CD has been historically considered rare. This apparent paradox can be explained by the limited number of scientific studies performed in some of those countries in which CD is perceived as a rare disorder (Figure 2*C*). Recent epidemiologic studies conducted in areas at risk (Figure 2*A* and *B*), such as South America,[82] North Africa,[83] and Asia,[84,85] suggest that CD was indeed underdiagnosed.

Combined together, these studies suggest that CD is still underestimated in areas where large epidemiologic studies are lacking. The European experience taught us that despite common genetic and environmental factors, the clinical presentation of CD in neighboring countries may greatly diverge and could explain the different disease prevalence previously reported. A comparison between the estimated prevalence (based on the occurrence of typical symptoms) and the serologic screening data (where available) shows that CD is a common disease but its gastrointestinal presentation is relatively rare, particularly in countries in which CD was considered a negligible pathology (Table 2). Worldwide, CD "out of the intestine" is 15 times more frequent than CD "in the intestine" (Table 2), making the diagnosis extremely challenging.

The Iceberg Model

The epidemiological changes of CD are efficiently conceptualized by the iceberg model, originally introduced by Richard Logan in 1991.[86] The prevalence of CD can be conceived as the overall size of the iceberg, which is primarily influenced by the frequency of the predisposing genotypes in the population. Indeed, CD seems to be more common wherever the frequency of the HLA-DR3 (and DQ2) is high, such as in Europe, the United States, and North Africa. The dimension of this iceberg also depends, to a lesser extent, on disease definition, i.e., whether subjects with so-called latent or potential CD[47] or those with gluten sensitivity and mild enteropathy[87] are "counted" as affected individuals. In countries where a substantial part of the population is of European origin, the prevalence of CD is likely to be more stable than previously thought, roughly in the range of 0.5%–1% of the general population. A sizable number of these cases are properly diagnosed because of suggestive complaints (e.g., chronic diarrhea, unexplained iron deficiency) or other reasons (e.g., family history of CD). These cases make up the visible part of the celiac iceberg, in quantitative terms expressed by the incidence of the disease. However, as previously reported, screening studies show that in Western countries, for each diagnosed case of CD, an average of 5–10 cases remain undiagnosed (the submerged part of the iceberg). The "water line," namely the ratio of diagnosed to undiagnosed cases, depends on several factors: (1) awareness of CD: "think of CD and you will find it" is an aphorism worth remembering[88]; differing awareness, and consequently variable thresholds for serologic CD testing, is likely to explain a substantial part of the wide differences in incidence between countries; (2) availability of diagnostic facilities: lack of both laboratory equipment and personnel trained in CD diagnosis is a major problem in large areas of the world, e.g., North Africa, the Middle East, and India, where the frequency of CD is currently underestimated; (3) variations in clinical intensity: at both individual and population levels, the higher the amount of ingested gluten, the higher the intensity of the clinical picture, thereby increasing the chances that CD can be diagnosed on clinical grounds. This has been clearly shown by the "epidemic" of CD observed in Sweden during the 1980s and early 1990s, in relationship with the gluten load that infants received with follow-up formulas.[89] Because of the variable relevance of these factors, the water line is much more unstable than the overall size of the iceberg, thereby explaining the reported wide fluctuations in space and time of CD incidence. What remains to be evaluated is the effect of

Atypical Forms

In recent years there has been a noticeable change in the age of onset of symptoms and the clinical presentation of CD. Mäki et al.[12] first reported an up-shift of age at diagnosis in Finland to 5–6 years, with fewer than 50% of new cases presenting with typical gastrointestinal symptoms. Reports from Scotland,[13] England,[14] Canada,[15] and the United States[16] have also shown that almost 50% of patients with newly diagnosed CD do not present with gastrointestinal symptoms.

Dermatitis herpetiformis. Dermatitis herpetiformis is currently regarded as a variant of CD ("skin CD"). It is a blistering skin disease characterized by pathognomonic granular immunoglobulin (Ig) A deposits in uninvolved skin.[17] The most typical sites of the rash are the elbows, knees, and buttocks. Intestinal symptoms are not common, but a varying degree of enteropathy, ranging from the infiltrative-type lesion to flat mucosa, can be found on small intestinal biopsy in almost 100% of cases. Both the enteropathy and the rash slowly clear with a gluten-free diet (GFD) and relapse when patients return to a regular diet.[18]

Iron-deficiency anemia. Iron deficiency with or without anemia, typically refractory to oral iron supplementation, can be the only presenting sign of CD.[19]

Short stature. Short stature is well described as the only symptom of CD in some older children and adolescents, and it is believed that as many as 9%–10% of those with "idiopathic" short stature have CD.[20–22] In these patients, both the bone age and growth velocity are significantly impaired.[20,22,23] Some patients have also demonstrated impaired growth hormone production after provocative stimulation testing.[23] This value returns to normal after introduction of a GFD.[24]

Dental enamel hypoplasia. Dental enamel hypoplasia has been found in up to 30% of untreated patients with CD.[25,26]

Arthritis and arthralgia. CD has been described in 1.5%–7.5% of patients with rheumatoid arthritis.[27–29] These symptoms were reported by Mäki et al.[30] as the only presentation of CD in 7 adolescent patients. In each case, the symptoms resolved on introduction of a GFD and all other anti-inflammatory medications could be discontinued.

Chronic hepatitis and hypertransaminasemia. Idiopathic chronic hepatitis as the initial presentation of CD has been reported occasionally.[31,32] Vajro et al.[33] describe 3 children with cryptogenetic chronic hepatitis secondary to CD. In all cases, GFD induced complete remission with normalization of the biochemical and histologic changes of hepatitis. Resolution of the biochemical abnormalities associated with hepatic damage has been reported in a high percentage of pediatric patients with CD who adhered to a strict GFD.[34]

Osteoporosis. Patients with CD are at high risk for developing low bone mineral density and bone turnover impairment. Persistent villous atrophy is associated with low bone mineral density. In adult patients responsive to diet, the bone density seems comparable to that of healthy individuals.[35] Children who followed a GFD for at least 5 years had normal bone mineralization and bone turnover.[36] Of 86 consecutive patients with newly diagnosed, biopsy-confirmed CD, 40% had osteopenia and 26% osteoporosis.[36] No differences between male and female patients or between fertile and postmenopausal women were observed. Even in postmenopausal women, GFD led to significant improvement in bone mineral density.[37] In these cases, supplement treatment with vitamin D and Ca^{2+} is indicated.

Neurologic problems. Gluten sensitivity is common in patients with neurological diseases of unknown cause and may have etiologic significance.[38] Pellecchia et al.[39] recently reported that 3 of 24 patients with idiopathic cerebellar ataxia had CD.

Other extragastrointestinal symptoms. A delay in onset of puberty secondary to CD has been described in a number of adolescent patients.[12,22,40,41] Recurrent abortions[42,43] and reduced fertility[40,42] caused by CD have also been reported in this age group. Recently, Ciacci et al.[44] have reported that the relative risk of abortion in women affected by CD is 8.9 times higher than in healthy subjects, and a GFD reduced the relative risk of abortion.[44]

Asymptomatic (Silent) Form

This form is characterized by the presence of histologic changes, probably limited to the proximal intestine, that occur in individuals who are apparently asymptomatic.[45–47] Most cases in this category have been identified through screening programs involving apparently healthy subjects. However, a more careful clinical anamnesis typically reveals that many of these "silent" cases are indeed affected by low-intensity illness often associated with decreased psychophysical well-being. Common findings include (1) iron deficiency with or without anemia; (2) behavioral disturbances, such as tendency to depression, irritability, or impaired school performance in children; (3) impaired physical fitness, "feeling always tired," and easy fatigue during exercise; and (4) reduced bone mineral density.[48,49] A 24-month follow-up study showed that adolescents with screening-detected CD who were apparently symptomless at diagnosis often reported improved physical and psychologic

conditions once they began following a GFD.[50] The most common changes included increased weight and height velocity, increased appetite, mood amelioration, and improved physical and school performance.[50] Finally, current evidence suggests that subjects with "silent" CD are at risk to develop the same long-term complications experienced by individuals with typical symptoms.

Associated Diseases

A number of medical conditions are significantly associated with CD (Table 1). For some of these conditions, sensitivity to gliadin has been conclusively proven or may be implicated (Table 1).

Complications Associated With Unrecognized CD

Malignancies. The persistence of mucosal injury with or without typical symptoms can lead to serious complications, and gastrointestinal malignancies (particularly lymphoma) have been reported in 10%–15% of adult patients with known CD who do not strictly comply with a GFD.[51] However, the increased risk for malignancy in the gastrointestinal tract in patients with CD has been questioned recently; therefore, the precise magnitude of this complication remains uncertain (see diagnosis section below). Nevertheless, it has been reported that the mortality rate in CD patients is almost double (1.9×) the rate calculated for the general population, mainly because of the occurrence of neoplasms.[52] Data from Logan et al.[52] have shown that when appropriate treatment for CD was instituted in childhood and strictly followed, the mortality rate of these subjects was no different from that expected in the general population, and no deaths from intestinal lymphoma were recorded.

Autoimmune diseases. CD seems to meet the criteria of a true autoimmune disease for which the genetic predisposition (HLA), exogenous trigger (gluten), and autoantigen (tTG) are known. It seems that tTG is only one of the autoantigens involved in gluten-dependent autoimmune reactions. Other autoantigens that are normally "cryptic" can be unmasked and cause a self-aggressive immunologic response following the gliadin-initiated inflammatory process. In fact, persistent stimulation by some proinflammatory cytokines such as interferon γ and tumor necrosis factor α can cause further processing of autoantigens and their presentation to T lymphocytes by macrophage-type immunocompetent cells (the so-called antigen-presenting cells). The phenomenon of antigen spreading has been described in well-defined natural models such as insulin-dependent diabetes mellitus, whose clinical manifestations appear after the patient has produced an autoimmune response to various autoantigens (i.e., anti-insulin, anti–β cell), and might also be present in CD. This could explain the high incidence of autoimmune diseases (Table 1) and the presence of a large number of organ-specific autoantibodies in a certain number of celiac subjects on a gluten-containing diet.

Based on this evidence, it is tempting to hypothesize that the range of gluten-dependent autoimmune disorders present in genetically predisposed individuals goes well beyond the classic enteropathy of CD (Table 1). Furthermore, recent data suggest that the prevalence of autoimmune diseases among patients with CD is proportional to the time of exposure to gluten.[7]

The Epidemiology of CD

Epidemiology of CD in Europe

In the past 3 decades, a substantial number of epidemiologic studies have been conducted in Europe to establish the frequency of CD, and interesting controversies have arisen. Earlier investigations measured the incidence of CD, namely the number of "new" diagnoses in the study population during a certain period. One of the oldest epidemiologic studies on CD conducted in 1950 established that the cumulative incidence of the disease in England and Wales was 1/8000, whereas an incidence of 1/4000 was detected in Scotland.[53] The diagnosis at that time was entirely based on the detection of typical symptoms and confirmed by complicated and sometimes nonspecific tests. The awareness of the disease greatly increased in the 1960s when more specific tests for malabsorption and the pediatric peroral biopsy technique became available.[54] Consequently, an elevated incidence of the disease (which in the middle 1970s reached peaks of 1/450–500) was reported in studies from Ireland,[55] Scotland,[56] and Switzerland.[57] This increased incidence of CD prompted changes in the dietary habit, based on the hypothesis that delayed exposure to gluten could prevent the onset of the disease. For the first time in 25 years, a decrease in the incidence of CD was reported in the United Kingdom and Ireland[58–60] after a late introduction of gluten in infant diet. Unfortunately, this decrease was deceptive because subsequent screening studies showed that the reduction in typical cases in infants was counterbalanced by the increase of atypical forms of CD with the onset of the symptoms occurring in older children or in adults.[61] Because of the development of sensitive serologic tests, it has recently become possible to evaluate the prevalence of CD (number of affected persons, including subclinical cases, in a defined popu-

Current Approaches to Diagnosis and Treatment of Celiac Disease: An Evolving Spectrum

ALESSIO FASANO* and CARLO CATASSI†

*Center for Celiac Research and Division of Pediatric Gastroenterology and Nutrition, University of Maryland, Hospital for Children, Baltimore, Maryland; and †Department of Pediatrics, University of Ancona, Ancona, Italy

Celiac disease (CD) is a syndrome characterized by damage of the small intestinal mucosa caused by the gliadin fraction of wheat gluten and similar alcohol-soluble proteins (prolamines) of barley and rye in genetically susceptible subjects. The presence of gluten in these subjects leads to self-perpetuating mucosal damage, whereas elimination of gluten results in full mucosal recovery. The clinical manifestations of CD are protean nature and vary markedly with the age of the patient, the duration and extent of disease, and the presence of extraintestinal pathologic conditions. In addition to the classical gastrointestinal form, a variety of other clinical manifestations of the disease have been described, including atypical and asymptomatic forms. Therefore, diagnosis of CD is extremely challenging and relies on a sensitive and specific algorithm that allows the identification of different manifestations of the disease. Serologic tests developed in the last decade provide a noninvasive tool to screen both individuals at risk for the disease and the general population. However, the current gold standard for the diagnosis of CD remains histologic confirmation of the intestinal damage in serologically positive individuals. The keystone treatment of CD patients is a lifelong elimination diet in which food products containing gluten are avoided.

Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten-containing grains in susceptible individuals. The gliadin fraction of wheat gluten and similar alcohol-soluble proteins in other grains are the environmental factors responsible for the development of the intestinal damage. The disease is associated with HLA alleles DQA1*0501/DQB1*0201, and in the continued presence of gluten the disease is self-perpetuating.[1] The typical intestinal damage characterized by loss of absorptive villi and hyperplasia of the crypts completely resolves upon elimination of gluten-containing grains from the patient's diet.

It is now evident that CD is the result of an inappropriate T cell–mediated immune response against ingested gluten.[2] Under physiologic circumstances, the intestinal epithelium with its intact intercellular tight junctions serves as the main barrier to the passage of macromolecules such as gluten. During this healthy state, quantitatively small but immunologically significant fractions of antigens cross the defense barrier. These antigens are absorbed across the mucosa along 2 functional pathways. The vast majority of absorbed proteins (up to 90%) cross the intestinal barrier through the transcellular pathway, followed by lysosomal degradation, which converts proteins into smaller, nonimmunogenic peptides. The remaining portion of peptides is transported as intact proteins, resulting in antigen-specific immune responses. This latter phenomenon uses the paracellular pathway that involves a subtle but sophisticated regulation of intercellular tight junctions that leads to antigen tolerance. When the integrity of the tight junction system is compromised, such as in CD,[3,4] an immune response to environmental antigens (i.e., gluten) may develop. The up-regulation of zonulin, a recently described intestinal peptide involved in tight junction regulation,[5] seems to be responsible, at least in part, for the increased gut permeability characteristic of the early phase of CD.[6] This zonulin-dependent increased permeability may also be responsible for the increased incidence of autoimmune disorders reported in untreated CD patients.[7]

Another important factor for the intestinal immunologic responsiveness is the major histocompatibility complex (MHC). Human leukocyte antigen (HLA) class I and class II genes are located in the MHC on chromosome 6. These genes code for glycoproteins, which bind peptides, and this HLA–peptide complex is recognized by certain T-cell receptors in the intestinal mucosa.[8,9] Susceptibility to at least 50 diseases, including CD, has been associated with specific HLA class I or class II

Abbreviations used in this paper: AEA, antiendomysium antibody; AGA, antigliadin antibody; CD, celiac disease; ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology, and Nutrition; GFD, gluten-free diet; Ig, immunoglobulin; tTG, tissue transglutaminase.

0016-5085/01/$35.00
doi:10.1053/gast.2001.22123

Table 1. Possible Clinical Manifestations of CD

Typical symptoms	Atypical symptoms	Associated conditions
Chronic diarrhea	Secondary to malabsorption	Possibly gluten dependent
Failure to thrive	Sideropenic anemia	IDDM
Abdominal distention	Short stature	Autoimmune thyroiditis
	Osteopenia	Autoimmune hepatitis
	Recurrent abortions	Sjögren syndrome
	Hepatic steatosis	Addison disease
	Recurrent abdominal pain	Autoimmune atrophic gastritis
	Gaseousness	Autoimmune emocytopenic diseases
	Independent of malabsorption	Gluten independent
	Dermatitis herpetiformis	Down syndrome
	Dental enamel hypoplasia	Turner syndrome
	Ataxia	Williams syndrome
	Alopecia	Congenital heart defects
	Primary biliary cirrhosis	IgA deficiency
	Isolated hypertransaminasemia	
	Recurrent aphthous stomatitis	
	Myasthenia gravis	
	Recurrent pericarditis	
	Psoriasis	
	Polyneuropathy	
	Epilepsy (with or without intracranial calcifications)	
	Vasculitis	
	Dilatative cardiomyopathy	
	Hypo/hyperthyroidism	

alleles. The primary HLA association in CD is to the HLA-DQA1*0501, DQB1*0201 genes encoding DQ2 molecules.[1] Non-HLA genes together appear to contribute more to genetic susceptibility than do the HLA genes, but the contribution from each single, predisposing non-HLA gene appears to be modest.[10] Dieterich et al.[11] recently demonstrated that one of the targets of the autoimmune response in CD is the tissue transglutaminase (tTG).[11] The deamidating activity of this enzyme seems to generate gliadin peptides that bind to DQ2 to be recognized by disease-specific intestinal T cells.[10]

Clinical Presentations

The clinical manifestations of CD vary markedly with the age of the patient, the duration and extent of disease, and the presence of extraintestinal pathology (Table 1). Depending on the features at the time of presentation, together with the histologic and immunologic abnormalities at the time of diagnosis, CD can be subdivided into the following clinical forms.

Classical (Typical) Form

The onset of symptoms in the classical form generally occurs between 6 and 18 months of age. This form is typically characterized by chronic diarrhea, failure to thrive, anorexia, abdominal distention, and muscle wasting. Growth is usually normal during the first months of life. Symptoms begin within weeks to a few months after the introduction of weaning foods containing prolamines, and soon there is a progressive decrease in weight gain with a decline in the child's percentile for weight and weight for height. On examination, the children are often pale and noticeably thin with a protuberant abdomen, decreased subcutaneous fat, and reduction in muscle mass. The stools are characteristically pale, loose, bulky, and highly offensive because of fat malabsorption. In the very young infant with early onset of symptoms there may be frank watery diarrhea with dehydration and electrolyte imbalance. A small number of these infants also have severe hypoproteinemia and edema and may present in a shocklike state that has been termed "celiac crisis." Laboratory signs of the malabsorption include iron deficiency anemia, hypoalbuminemia, hypocalcemia, and vitamin deficiencies. The pathologic changes are most marked in the duodenum and upper jejunum, but the extent of mucosal damage is highly variable, and in some cases the entire small intestine may be involved. The histologic changes in CD range from minor villous blunting to subtotal or total villous atrophy (see below, Figure 5), decreased villous height-to-crypt depth ratio, crypt hyperplasia with increased mitosis, significantly increased plasma cell and lymphocyte infiltration in the lamina propria, and a pronounced increase in the number of intraepithelial lymphocytes.

1 case in 99 children. One explanation for this high prevalence might be that the population studied may have had an unusually high genetic risk of celiac disease. However, the fact that the distribution of HLA genotypes in this population corresponds to that in the Finnish population in general suggests that the study population was representative of the Finnish population as a whole. The true prevalence of celiac disease is likely to be even higher than 1 in 99. Not all our antibody-positive subjects consented to undergo biopsy, and some may have had a mucosal lesion or gluten-induced disease despite the presence of morphologically normal mucosa.[19-21] The presence of gluten-induced autoantibodies in subjects with initially normal villous architecture on small-bowel biopsy who are eating normal amounts of gluten predicts subsequent mucosal deterioration and celiac disease.[22,23] Five subjects who were initially positive for such autoantibodies were negative on follow-up testing, despite the fact that they were eating a normal, gluten-containing, diet. This finding might point to a minor variant of the natural history of celiac disease, in which gluten sensitivity fluctuates over time.[24] We have previously observed that intolerance to cereals is not a specific sign of celiac disease, and only 10 percent of patients who spontaneously report abdominal symptoms after consuming cereals are found to have celiac disease.[25]

An important finding of this study is that most antibody-positive subjects carried the HLA-DQ2 or DQ8 molecules that are characteristic of celiac disease.[10] The HLA-dependency of the production of autoantibodies associated with celiac disease has been reported in a study of the first-degree relatives of patients with celiac disease.[3,26] We found that the risk associated with the HLA-DR3–DQ2 haplotype was much greater than that associated with the HLA-DR4–DQ8 haplotype, and it is striking that a compound heterozygote (one who carried both haplotypes) had a lower risk than a person who carried only the HLA-DR3–DQ2 haplotype.

We used the IgA-class serum endomysial antibody test, which has been validated in Europe,[27] to identify untreated celiac disease, but the drawback of this test remains its subjectivity. After the identification of tissue transglutaminase as the target of celiac disease–specific autoantibodies in both rodent and primate tissues,[28] a non–observer-dependent enzyme-linked immunosorbent assay was developed to detect the antibodies.[29-31] We found that this assay was as reliable and sensitive as the endomysial antibody test, which is based on indirect immunofluorescence.

Our findings suggest that these assays are a reliable and simple means of screening children for clinically silent celiac disease and genetically inherited gluten intolerance before symptoms or signs of chronic malabsorption develop. The crucial question now is whether population-based screening should be considered outside research programs. In our study, one third of the subjects in whom celiac disease was detected by screening had no symptoms and did not have any risk factors for celiac disease. In other clinical settings, even those in which serologic testing for celiac disease is routine, prevalence figures similar to ours are not obtained.[32] Nonetheless, whether treatment benefits clinically silent celiac disease should be thoroughly assessed. Undetected celiac disease increases the risk of several complications, including osteoporosis.[1,2,18] On the other hand, the lifelong need to follow a gluten-free diet may be burdensome, especially if the patient is asymptomatic.[33] Further studies of the effect of asymptomatic celiac disease, including cost-effectiveness evaluations, are needed before population-based screening studies can be recommended. However, given our finding that celiac disease is underdiagnosed, clinicians should keep in mind the complex clinical picture of the disease and have a high index of suspicion and a low threshold for ordering serologic tests.

In summary, we found that celiac disease was highly prevalent in an unselected population of schoolchildren and adolescents. The results of serum endomysial and tissue transglutaminase antibody tests were highly correlated with the HLA genotype. The tissue transglutaminase antibody test offers an objective means of detecting celiac disease early, when it is clinically silent.

The Celiac Disease Study Group is supported by grants from the Päivikki and Sakari Sohlberg Foundation, the Foundation of the Friends of the University Children's Hospitals in Finland, the Medical Research Fund of Tampere University Hospital, and the Academy of Finland Research Council for Health (73489). The study was also funded by the Commission of the European Communities in the form of the Research and Technology Development programs "Quality of Life and Management of Living Resources" (QLRT-1999-00037) and "Evaluation of the Prevalence of Celiac Disease and its Genetic Components in the European Population." The study does not necessarily reflect the current views or future policies of the Commission of European Communities.

Dr. Höpfl, Dr. Hansson, and Ms. Dahlbom are employees of Pharmacia Diagnostics. Pharmacia did not sponsor the study but did provide the immunoassays for the detection of tissue transglutaminase antibodies.

REFERENCES

1. Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med 2002;346:180-8.
2. Collin P, Kaukinen K, Välimäki M, Salmi J. Endocrinological disorders and celiac disease. Endocr Rev 2002;23:464-83.
3. Mäki M, Holm K, Lipsanen V, et al. Serological markers and HLA genes among healthy first-degree relatives of patients with coeliac disease. Lancet 1991;338:1350-3.
4. Csizmadia CG, Mearin ML, von Blomberg BM, Brand R, Verloove-Vanhorick SP. An iceberg of childhood coeliac disease in the Netherlands. Lancet 1999;353:813-4.
5. George EK, Mearin ML, van der Velde EA, et al. Low incidence of childhood celiac disease in the Netherlands. Pediatr Res 1995; 37:213-8.
6. Korponay-Szabo IR, Kovacs JB, Czinner A, Goracz G, Vamos A, Szabo T. High prevalence of silent celiac disease in preschool children screened with IgA/IgG antiendomysium antibodies. J Pediatr Gastroenterol Nutr 1998;28:26-30.
7. Meloni G, Dore A, Fanciulli G, Tanda F, Bottazzo GF. Subclinical coeliac disease in schoolchildren from northern Sardinia. Lancet 1999;353:37.
8. Rossi TM, Albini CH, Kumar V. Incidence of celiac disease identified by the presence of serum endomysial antibodies in children with chronic diarrhea, short stature, or insulin-dependent diabetes mellitus. J Pediatr 1993;123:262-4.
9. Hill I, Fasano A, Schwartz R, Counts D, Glock M, Horvath K. The prevalence of celiac disease in at-risk groups of children in the United States. J Pediatr 2000;136:86-90.
10. Sollid LM. Coeliac disease: dissecting a complex inflammatory disorder. Nat Rev Immunol 2002;2:647-55.
11. Kulmala P, Rahko J, Savola K, et al. Beta-cell autoimmunity, genetic susceptibility, and progression to type 1 diabetes in unaffected schoolchildren. Diabetes Care 2001;24:171-3.
12. Sulkanen S, Collin P, Laurila K, Mäki M. IgA- and IgG-class antihuman umbilical cord antibody tests in adult coeliac disease. Scand J Gastroenterol 1998;33:251-4.
13. Hansson T, Dahlbom I, Rogberg S, et al. Recombinant human tissue transglutaminase for diagnosis and follow-up of childhood coeliac disease. Pediatr Res 2002;51: 700-5.
14. Iltanen S, Holm K, Partanen J, Laippala P, Mäki M. Increased density of jejunal gammadelta+ T cells in patients having normal mucosa — marker of operative autoimmune mechanisms? Autoimmunity 1999;29:179-87.
15. Nejentsev S, Sjöroos M, Soukka T, et al. Population-based genetic screening for the estimation of Type 1 diabetes mellitus risk in Finland: selective genotyping of markers in the HLA-DQB1, HLA-DQA1 and HLA-DRB1 loci. Diabet Med 1999;16:985-92.
16. Pagano M, Gauvreau K. Principles of biostatistics. Belmont, Calif.: Duxbury Press, 1993.
17. Catassi C, Rätsch IM, Fabiani E, et al. Coeliac disease in the year 2000: exploring the iceberg. Lancet 1994;343:200-3.
18. Mäki M, Collin P. Coeliac disease. Lancet 1997;349:1755-9.
19. Valdimarsson T, Franzen L, Grodzinsky E, Skogh T, Ström M. Is small bowel biopsy necessary in adults with suspected celiac disease and IgA anti-endomysium antibodies? 100% Positive predictive value for celiac disease in adults. Dig Dis Sci 1996;41:83-7.
20. Kaukinen K, Collin P, Holm K, Karvonen A-L, Pikkarainen P, Mäki M. Small bowel mucosal inflammation in reticulin or gliadin antibody-positive patients without villous atrophy. Scand J Gastroenterol 1998; 33:944-9.
21. Kaukinen K, Mäki M, Partanen J, Sievänen H, Collin P. Celiac disease without villous atrophy: revision of criteria called for. Dig Dis Sci 2001;46:879-87.
22. Collin P, Helin H, Mäki M, Hällström O, Karvonen A-L. Follow-up of patients positive in reticulin and gliadin antibody tests with normal small-bowel biopsy findings. Scand J Gastroenterol 1993;28:595-8.
23. Troncone R, Greco L, Mayer M, et al. Latent and potential coeliac disease. Acta Paediatr Suppl 1996;412:10-4.
24. Kutlu T, Brousse N, Rambaud C, Le Deist F, Schmitz J, Cerf-Bensussan N. Numbers of T cell receptor (TcR) alpha beta+ but not of TcR gamma delta+ intraepithelial lymphocytes correlate with the grade of villous atrophy in coeliac patients on a long term normal diet. Gut 1993;34:208-14.
25. Kaukinen K, Turjanmaa K, Mäki M, et al. Intolerance to cereals is not specific for coeliac disease. Scand J Gastroenterol 2000; 35:942-6.
26. Mustalahti K, Sulkanen S, Holopainen P, et al. Coeliac disease among healthy members of multiple case coeliac disease families. Scand J Gastroenterol 2002;37:161-5.
27. Stern M. Comparative evaluation of serologic tests for celiac disease: a European initiative toward standardization. J Pediatr Gastroenterol Nutr 2000;31:513-9.
28. Dieterich W, Ehnis T, Bauer M, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med 1997;3:797-801.
29. Dieterich W, Laag E, Schöpper H, et al. Autoantibodies to tissue transglutaminase as predictors of celiac disease. Gastroenterology 1998;115:1317-21.
30. Sulkanen S, Halttunen T, Laurila K, et al. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. Gastroenterology 1998;115:1322-8.
31. Sblattero D, Berti I, Trevisiol C, et al. Human recombinant tissue transglutaminase ELISA: an innovative diagnostic assay for celiac disease. Am J Gastroenterol 2000; 95:1253-7.
32. Collin P, Reunala T, Rasmussen M, et al. High incidence and prevalence of adult coeliac disease: augmented diagnostic approach. Scand J Gastroenterol 1997;32: 1129-33.
33. Mustalahti K, Lohiniemi S, Collin P, Vuolteenaho N, Laippala P, Mäki M. Gluten-free diet treatment and quality of life in patients with screen-detected celiac disease. Eff Clin Pract 2002;5:105-13.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal*'s Web site at http://www.nejm.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.

CELIAC DISEASE DETECTED BY SCREENING

In 2001 the remaining 46 antibody-positive subjects who had not previously received a diagnosis of celiac disease were invited to undergo small-bowel biopsy and antibody testing. Thirty-six (78.3 percent) agreed to undergo biopsy, and 27 had mucosal villous atrophy with crypt hyperplasia typical of celiac disease. Morphometric studies revealed a mean ratio of villous height to crypt depth of 0.87 (range, 0.11 to 1.68; a ratio of less than 2 is indicative of celiac disease). In addition, the intraepithelial densities of γ/δ T-cell receptor–bearing lymphocytes exceeded the threshold for positivity (3.5 cells per millimeter), with a mean of 20 cells per millimeter (range, 3.5 to 71.6). Aberrant up-regulation of the expression of HLA-DR was seen in 25 of 27 mucosal specimens.

A second blood sample was obtained at the time of biopsy in 2001. Altogether 24 of 27 patients with celiac disease detected by screening had both IgA-class endomysial antibodies (median titer, 1:1000; range, 1:50 to 1:4000) and IgA-class tissue transglutaminase antibodies (median titer, 37.8; range, 6.8 to 624). Both antibody tests were negative in one subject. Two subjects had IgA deficiency but were positive for IgG-class antibodies alone. A gluten-free diet was prescribed for all 27 subjects with newly diagnosed celiac disease, and 25 agreed to follow the diet.

NORMAL MUCOSAL MORPHOLOGY

Table 1 summarizes the findings in the nine subjects with normal mucosal architecture on small-bowel biopsy. Five subjects who were initially antibody-positive were negative for antibodies during follow-up in 2001. All but one of them had an increased density of γ/δ T-cell receptor–bearing lymphocytes, and all had enhanced expression of HLA-DR, indicating ongoing mucosal inflammation in the morphologically normal mucosa. Two subjects who were initially negative for endomysial antibodies but who had low levels of tissue transglutaminase antibodies had negative tests for both types of antibodies in 2001. Eight of the nine subjects were positive for HLA-DQ2.

ANTIBODY-POSITIVE SUBJECTS WHO DECLINED TO UNDERGO BIOPSY

Ten of the antibody-positive subjects declined to undergo small-bowel biopsy. In the 1994 serum

Table 1. Results of Serum Antibody Tests and Small-Bowel Biopsy in Nine Subjects with Normal Mucosal Architecture on Small-Bowel Biopsy.*

Subject No.	1994 Serum Sample		2001 Serum Sample		Morphometric Findings on Biopsy			Immunohistochemical Findings on Biopsy		HLA Haplotype
	EMA	tTG†	EMA	tTG†	VH	CrD	VH:CrD‡	Density of γ/δ T-Cell Receptor–Bearing Lymphocytes§	Expression of HLA-DR¶	
	titer	*U/ml*	*titer*	*U/ml*	*μm*			*cells/mm*		
1	1:200	13.7	1:500	20.3	430	140	3.07	12.5	Enhanced	DR3–DQ2
2	1:200	28.9	1:100	5.6	430	200	2.15	3.2	Enhanced	DR3–DQ2
3	1:100	13.4	1:<5	0.5	550	180	3.06	5.6	Enhanced	DR3–DQ2 and DR4–DQ8
4	1:100	14.8	1:<5	1.5	480	160	3.00	34.4	Enhanced	DR3–DQ2
5	1:50	76.6	1:<5	0.6	460	190	2.42	9.1	Enhanced	DR3–DQ2
6	1:200	16.6	1:<5	1.4	450	170	2.65	0	Enhanced	DR3–DQ2
7	1:500	51.0	1:<5	2.3	430	190	2.26	12.7	Enhanced	DR3–DQ2
8	1:<5	7.0	1:<5	0.5	550	200	2.75	1.4	Enhanced	DR3–DQ2
9	1:<5	5.7	1:<5	4.1	500	200	2.50	0.7	Normal	Neither DR3–DQ2 nor DR4–DQ8

* EMA denotes IgA-class endomysial antibodies, tTG IgA-class tissue transglutaminase antibodies, VH villous height, and CrD crypt depth.
† A value above 5 U per milliliter was considered positive.
‡ A ratio of less than 2 is considered to indicate celiac disease.
§ The normal value is fewer than 3.5 cells per millimeter of epithelial tissue.
¶ The expression of HLA-DR is considered to be enhanced if it is expressed only in crypt cells or is expressed strongly in epithelium.

samples, the median endomysial antibody titer was 1:200 (range, 1:5 to 1:4000), and the median level of tissue transglutaminase antibodies was 70.6 U per milliliter (range, 4.8 to 169.7). Four subjects agreed to provide a second blood sample in 2001, and all four had increased levels of IgA-class endomysial antibodies (1:1000, 1:2000, 1:2000, and 1:4000) and IgA-class tissue transglutaminase antibodies (66.7, 89.0, 91.1, and 101 U per milliliter, respectively).

HLA TYPING

The distribution of the HLA genotypes associated with celiac disease in the 3627 subjects who underwent genotyping is shown in Table 2. Altogether 655 schoolchildren (18.1 percent) carried the HLA-DQA1*05-DQB1*02 (HLA-DR3–DQ2) haplotype, and 1411 (39 percent) carried either the HLA-DR3–DQ2 or the HLA-DQ-A1*03-DQB1*0302 (HLA-DR4–DQ8) haplotype. All but two of the antibody-positive subjects were positive for one or both of these haplotypes, irrespective of the findings on small-bowel biopsy (Fig. 1). The majority (85.7 percent) carried the HLA-DR3–DQ2 haplotype. There was no correlation between the various haplotypes and the severity of mucosal abnormalities.

CLINICAL ASPECTS OF CELIAC DISEASE DETECTED BY SCREENING

All 27 subjects with newly diagnosed, biopsy-proved celiac disease and the 9 subjects with normal mucosal architecture on small-bowel biopsy completed a questionnaire concerning symptoms related to celiac disease. None had another autoimmune disease. Four of the 27 patients with newly diagnosed celiac disease had an affected first-degree relative. When specifically asked, 11 reported recurrent abdominal pain and intermittent diarrhea or constipation, 1 reported tiredness, and 1 had skin symptoms. Ten subjects had clinically silent celiac disease. Two of the subjects with normal mucosal architecture on small-bowel biopsy reported abdominal pain.

PREVALENCE OF CELIAC DISEASE

Among the 3654 schoolchildren, 37 had biopsy-proven celiac disease, for a minimum prevalence of 1 case in 99 children (95 percent confidence interval, 1 in 146 to 1 in 75) (Fig. 1). The prevalence of subjects who were positive for both antibodies and HLA-DQ2 or DQ8 was 1 in 67 (95 percent confidence interval, 1 in 89 to 1 in 52).

DISCUSSION

This population-based screening study showed that celiac disease is underdiagnosed. Simple, noninvasive serologic tests detected celiac disease in schoolchildren who had not previously been given a diagnosis of the disease.

Clinical celiac disease represents the tip of the iceberg.[17,18] According to our findings, the prevalence of biopsy-proven celiac disease is at least

Table 2. Prevalence of HLA-DR and DQ Genotypes Associated with Celiac Disease among the 3627 Schoolchildren Who Underwent Genotyping, Including the 56 Subjects Who Were Positive for Serum Endomysial or Tissue Transglutaminase Antibodies.

HLA Genotype	All Children (N=3627)	Antibody-Positive Children (N=56)	Odds Ratio (95% CI)*	Positive Predictive Value†
	no. (%)			
DR3–DQ2 and any other haplotype except DR4–DQ8	575 (15.9)	46 (82.1)	26.45 (11.81–51.85)	8.00
DR4–DQ8 and any other haplotype except DR3–DQ2	756 (20.8)	6 (10.7)	0.45 (0.18–1.11)	0.79
DR3–DQ2 and DR4–DQ8	80 (2.2)	2 (3.6)	1.66 (0.02–7.03)	2.50
Other genotypes	2216 (61.1)	2 (3.6)‡	0.02 (0.01–0.09)	0.09

* The odds ratio is the risk that a subject who carried a certain HLA genotype was positive for celiac disease–specific autoantibodies. CI denotes confidence interval.
† The positive predictive value is the percentage of all subjects with a specific genotype who were positive for antibodies.
‡ One subject with confirmed celiac disease carried the HLA-DQB1*02 allele (DR7 haplotype). The other was negative for both HLA-DQ2 and DQ8 (Subject 9 in Table 1).

SERUM ANTIBODY TESTS

The serum samples from all 3654 schoolchildren were simultaneously assessed in a blinded fashion in two different laboratories: tests for endomysial antibodies were conducted in Tampere, Finland, and tests for tissue transglutaminase antibodies were performed in Freiburg, Germany. Serum IgA- and IgG-class endomysial antibodies were determined by an indirect immunofluorescence method as previously described.[3,12] Determinations of IgA-class tissue transglutaminase antibodies were carried out with a Celikey assay (Pharmacia Diagnostics) in accordance with the manufacturer's instructions. The limit of detection of the assay was 0.1 U per milliliter, and we chose 5 U per milliliter as the cutoff point for positivity. Serum samples with IgA-class tissue transglutaminase antibody levels below the limit of detection were further tested for the determination of IgG-class tissue transglutaminase antibodies with an enzyme-linked immunosorbent assay (Pharmacia Diagnostics), as previously described.[13] The same microplates and test procedure used for IgA-class antibodies (Celikey) were used in this subgroup of serum samples. Values above 5 U per milliliter were considered positive.

In subjects who were positive for IgG-class tissue transglutaminase antibodies, an IgG-class endomysial antibody test was performed.[12] In such subjects, the total serum IgA was determined nephelometrically, and serum levels below 0.05 g per liter were considered indicative of selective IgA deficiency.

ENDOSCOPY

Upper gastrointestinal endoscopy was performed with an Olympus endoscope (model GIF-IT140) at the Department of Pediatrics, Oulu University Hospital. During the procedure, multiple duodenal-biopsy samples were obtained for routine histologic analysis. One sample was prepared for immunohistochemical staining.

DIAGNOSIS OF CELIAC DISEASE

Formalin-fixed biopsy specimens stained with hematoxylin and eosin were studied with the use of light microscopy and morphometric techniques. Villous height and crypt depth were measured, and the ratio of villous height to crypt depth was calculated. A ratio of less than 2 was considered to be indicative of celiac disease (i.e., villous atrophy with crypt hyperplasia).

IMMUNOHISTOCHEMICAL STAINING

Frozen biopsy samples of the small intestine were stained for intraepithelial lymphocytes bearing γ/δ T-cell receptors, and cell densities were determined as previously described.[14] The biopsy specimens were also stained for HLA class II molecules, and the expression of HLA-DR was considered to be enhanced when epithelial staining was strong or was confined to crypt cells.[14]

HLA TYPING

HLA typing was performed with the use of a screening test developed to detect alleles associated with an increased risk of type 1 diabetes and those associated with protection against it.[15] Samples were analyzed for selected HLA-DQB1 alleles, including DQB1*02 and DQB1*0302, and samples that were positive for the HLA-DQB1*02 allele were further analyzed for the presence of associated alleles: HLA-DQA1*0201 and DQA1*05.

STATISTICAL ANALYSIS

We calculated 95 percent confidence intervals for prevalence rates and odds ratios.[16] The odds ratio was calculated with use of the equation $(a \times d) \div (b \times c)$, and the positive predictive value was calculated with use of the equation $a \div (a+c) \times 100$. In these equations a and c represent the numbers of subjects with genotypic risk factors with and without celiac disease–specific autoantibodies, respectively, and b and d represent the numbers of subjects without genotypic risk factors who do and do not have autoantibodies, respectively.

RESULTS

SEROLOGIC TESTS

The correlation between the results of the two methodologically different autoantibody tests was almost perfect: 3651 of 3654 results were concordant. Fifty subjects were positive for both IgA-class endomysial antibodies (median titer, 1:500; range, 1:5 to 1:4000) and IgA-class tissue transglutaminase antibodies (median titer, 70.3 U per milliliter; range, 8.8 to 680), and 3601 were negative for both tests (Fig. 1). One subject who was negative for tissue transglutaminase antibodies (titer, 4.8 U per milliliter) was positive for IgA-class endomysial antibodies at the lowest titer, 1:5. Two subjects who were negative for IgA-class endomysial antibodies

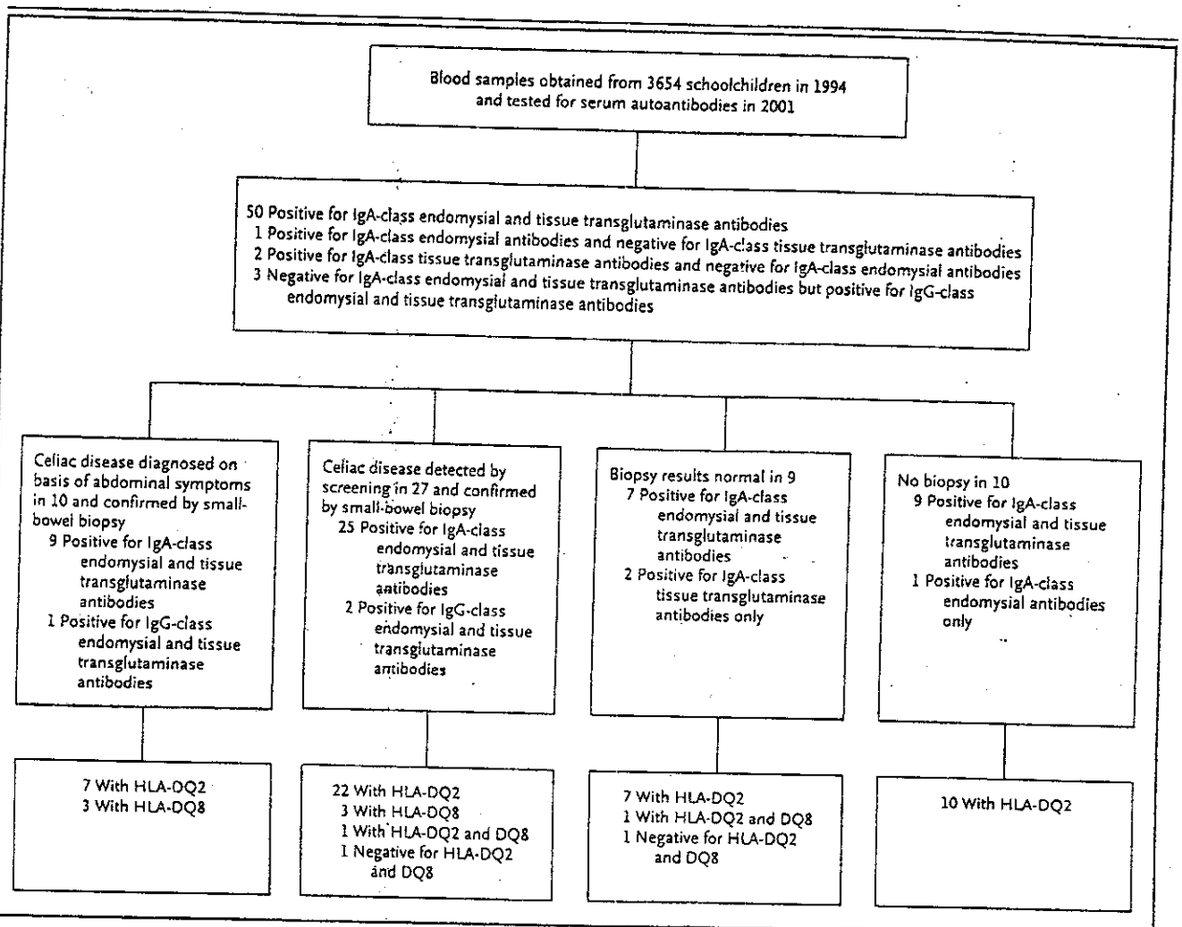


Figure 1. Results of Screening for Autoantibodies Associated with Celiac Disease in a Population of Finnish Schoolchildren.

Blood samples obtained in 1994 were tested for serum endomysial antibodies and tissue transglutaminase antibodies in 2001. Subjects with positive results who had not previously been given a diagnosis of celiac disease were invited to undergo upper gastrointestinal endoscopy. The results of small-bowel biopsy and typing for HLA-DQ2 and DQ8 are shown. The overall prevalence of biopsy-proven celiac disease in the cohort was 1 case in 99 children.

were positive for IgA-class tissue transglutaminase antibodies, with titers of 5.7 and 7.0 U per milliliter.

Seventeen subjects had undetectable serum levels of IgA-class tissue transglutaminase antibodies (less than 0.1 U per milliliter). Fourteen were negative for IgG-class tissue transglutaminase antibodies, with a median titer of 1.2 U per milliliter (range, 0.8 to 3.1), and three were clearly positive, with serum titers of 160.6, 148.2, and 26.4 U per milliliter (Fig. 1). All three proved to have IgA deficiency.

CELIAC DISEASE DETECTED ON THE BASIS OF SYMPTOMS

As of 1994, no cases of celiac disease had been identified in this cohort. Between 1994 and 2001, 10 cases were detected on the basis of abdominal symptoms and confirmed by biopsy (median age, 16 years; range, 14 to 20) (Fig. 1). Nine of the subjects were positive for both serum IgA-class endomysial antibodies (median titer, 1:1000; range, 1:500 to 1:4000) and IgA-class tissue transglutaminase antibodies (median titer, 119 U per milliliter; range, 37.9 to 634.4), and 1 had IgA deficiency but was positive for IgG-class endomysial antibodies (titer, 1:2000) and IgG-class transglutaminase antibodies (26.4 U per milliliter). The antibody results were obtained retrospectively from tests of serum samples obtained in 1994, before the clinical diagnosis had been made.

ORIGINAL ARTICLE

Prevalence of Celiac Disease among Children in Finland

Markku Mäki, M.D., Ph.D., Kirsi Mustalahti, M.D., Jorma Kokkonen, M.D., Ph.D., Petri Kulmala, M.D., Ph.D., Mila Haapalahti, M.Sc., Tuomo Karttunen, M.D., Jorma Ilonen, M.D., Ph.D., Kaija Laurila, M.Sc., Ingrid Dahlbom, M.Sc., Tony Hansson, Ph.D., Peter Höpfl, Ph.D., and Mikael Knip, M.D., Ph.D.

ABSTRACT

BACKGROUND

Wheat, rye, and barley proteins induce celiac disease, an autoimmune type of gastrointestinal disorder, in genetically susceptible persons. Because the disease may be underdiagnosed, we estimated the prevalence of the disease and tested the hypothesis that assays for serum autoantibodies can be used to detect untreated celiac disease and that positive findings correlate with specific HLA haplotypes.

METHODS

Serum samples were collected from 3654 students (age range, 7 to 16 years) in 1994 and screened in 2001 for endomysial and tissue transglutaminase antibodies. HLA typing was also performed on stored blood samples. All antibody-positive subjects were asked to undergo small-bowel biopsy in 2001.

RESULTS

Of the 3654 subjects, 56 (1.5 percent) had positive antibody tests, as determined in 2001. Results of the two antibody tests were highly concordant. As of 1994, none of the subjects had received a clinical diagnosis of celiac disease, but 10 who had positive tests for both antibodies in serum obtained in 1994 received the diagnosis between 1994 and 2001. Of the 36 other subjects with positive antibody assays who agreed to undergo biopsy in 2001, 27 had evidence of celiac disease on biopsy. Thus, the estimated biopsy-proved prevalence was 1 case in 99 children. All but two of the antibody-positive subjects had either the HLA-DQ2 or the HLA-DQ8 haplotype. The prevalence of the combination of antibody positivity and an HLA haplotype associated with celiac disease was 1 in 67.

CONCLUSIONS

The presence of serum tissue transglutaminase and endomysial autoantibodies is predictive of small-bowel abnormalities indicative of celiac disease. There is a good correlation between autoantibody positivity and specific HLA haplotypes. We estimate that the prevalence of celiac disease among Finnish schoolchildren is at least 1 case in 99 children.

From the Pediatric Research Center, Medical School, University of Tampere, Tampere, Finland (M.M., K.M., K.L.); the Department of Pediatrics, Tampere University Hospital, Tampere, Finland (M.M., K.M., M.K.); the Departments of Pediatrics (J.K., P.K., M.H.) and Pathology (T.K.), Oulu University Hospital, Oulu, Finland; Turku Immunology Center and Department of Virology, University of Turku, Turku, Finland (J.I.); Pharmacia Diagnostics, Uppsala, Sweden (I.D., T.H.); Pharmacia Diagnostics, Freiburg, Germany (P.H.); and the Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland (M.K.). Address reprint requests to Professor Mäki at the Celiac Disease Study Group, Pediatric Research Center, Medical School, Bldg. FM3, FIN-33014 University of Tampere, Tampere, Finland, or at markku.maki@uta.fi.

N Engl J Med 2003;348:2517-24.

CELIAC DISEASE IS A DISORDER INDUCED by wheat, rye, and barley proteins, and its classic form is characterized in children by malabsorption and failure to thrive. During the past two decades, however, the clinical picture of the disease has changed to include milder forms, thus resulting in an upward shift of the age at diagnosis. Screening for active celiac disease with the use of serum autoantibodies usually focuses on patients with mild gastrointestinal symptoms, isolated iron deficiency, atypical or extraintestinal manifestations, or autoimmune diseases or on the first-degree relatives of affected patients.[1-3] Screening programs within populations indicate that the disease is underdiagnosed,[4-7] but because of the rather small number of subjects studied, the confidence intervals for the true prevalence are wide. In the United States, the disease is extremely rare when the criteria for diagnosis rely on classic symptoms such as diarrhea and short stature.[8] By broadening the clinical indication, however, antibody screening seems to indicate that the prevalence in the United States is similar to that in Europe.[9]

Approximately 90 percent of patients with celiac disease carry the HLA-DQ2 heterodimer encoded by the HLA-DQA1*05 and DQB1*02 genes. Such patients have at least one copy of the extended HLA-DR3–DQ2 haplotype (encoding both the α and β chains of the major histocompatibility complex [MHC]) common to many autoimmune diseases, or they are heterozygous for the HLA-DR5–DQ7 haplotype (encoding the α chain of the MHC) and the HLA-DR7–DQ2 haplotype (encoding the β chain of the MHC), in which the heterodimer molecule is encoded in the *trans* position.[10] Most of the remaining 10 percent of patients have the HLA-DR4–DQ8 haplotype.

Evidence suggests that celiac disease is underdiagnosed in children. Serologic testing has the potential to detect otherwise undiagnosed disease. Evidence is also accumulating that daily ingestion of wheat, rye, and barley results in long-term extraintestinal sequelae in subjects with undiagnosed or untreated celiac disease.[1,2] Early detection of the disease and subsequent dietary elimination of gluten might be the appropriate method for averting complications later in life.

We sought to determine the prevalence of celiac disease in Finland and specifically to test the hypothesis that celiac disease can be identified by serologic testing in children who have not previously received a clinical diagnosis. We used two serologic tests simultaneously — endomysial and tissue transglutaminase autoantibody tests — to screen a geographically defined, unselected population of schoolchildren. We also assessed whether positivity for disease-specific autoantibodies correlates with the HLA haplotypes associated with celiac disease.

METHODS

SUBJECTS

We tested serum samples collected in 1994 as part of a study of risk factors for type 1 diabetes among schoolchildren.[11] All 4280 schoolchildren who were 7 to 16 years old and who lived in five municipalities in northern Finland were invited to participate in the study. The cohort represents 8 percent of the area's school population. Whole blood for HLA typing and serum were obtained from 3662 subjects (85.6 percent), and the samples were stored at −20°C until studied. Eight subjects were excluded because the volume of their serum samples was not sufficient for analyses. The median age of the remaining study cohort of 3654 subjects (1826 of whom were boys) was 12 years (range, 7 to 16) at the time of initial sampling.

The ethics committee of the Faculty of Medicine, University of Oulu, approved the original study protocol to screen for risk factors associated with type 1 diabetes and for the collection of blood samples in 1994. Written informed consent was also obtained from the subjects, their parents, or both. In 2001 the new protocol, which included serologic screening, upper gastrointestinal endoscopy, and mucosal biopsies, was evaluated and approved by the same committee. A new informed-consent document regarding blood testing and small-bowel biopsies was signed by the subjects, their parents, or both.

STUDY PROTOCOL

The cohort was screened for endomysial and tissue transglutaminase antibodies in blood samples obtained in 1994, and all subjects with a positive result who had not previously received a diagnosis of celiac disease were asked to undergo upper gastrointestinal endoscopy in 2001. At the visit for endoscopy, a second serum sample was obtained for antibody testing. Serum testing began on August 31, 2000, and the last biopsy specimen was obtained on December 14, 2001. Clinical symptoms were assessed with use of a semistructured questionnaire completed at the visit with the study clinician in 2001. A clinical dietitian assessed the diet of the subjects.

challenge to show the resultant deterioration of the small intestinal villous architecture. However, gluten challenge should be performed if there is any doubt concerning the correct diagnosis.

Routine full blood count, urea and electrolytes, liver function tests, serum iron or ferritin, folate or red blood cell folate, and B_{12} should be measured at initial diagnosis. Liver function tests may be mildly abnormal in patients with celiac disease, even when associated hepatic disorders are absent. Specific deficiencies of iron and folic acid should be therapeutically corrected, although they will not normally be required long-term after introduction of a gluten-free diet. B_{12} levels usually normalize without specific therapy. A DEXA scan should be undertaken to seek evidence of osteoporosis because this usually improves on a gluten-free diet, although specific therapy may required.

Treatment

The cornerstone of treatment is a gluten-free diet. This should involve the advice of a dietician who is experienced in this field. Patients should omit wheat, rye, and barley from their diet. Oats may be permitted, although it should not be forgotten that the majority of commercially available oat flour is contaminated with wheat gluten.

It is important to explain the disease and the toxicity of gluten-containing foods to the patient. This should include information on the avoidance of future ill health or reversal of current problems including anemia, depression, and infertility. Explaining the increased risk of malignancy, particularly small intestinal lymphoma, is debatable and should be decided with discretion on a patient-by-patient basis. Physicians should not frighten patients into dietary compliance but provide them with the necessary facts for them to decide themselves.

It is advisable for patients to join a celiac sprue group that usually publishes lists of locally available gluten-free products. There are now a wide range of gluten-free breads, biscuits, "pasta," etc. that are commercially available in the United States and many European countries, where they can be obtained on a prescription. Specific foods that require some mention include beer and malted breakfast cereals, which should be avoided because they contain celiac toxic barley hordein. Patients with celiac sprue usually experience a rapid symptomatic improvement within a matter of weeks of the exclusion of dietary gluten, and this provides additional diagnostic confirmation.

Nutrient Deficiency

At the time of diagnosis, routine blood tests including full blood count and biochemical profile (which includes albumin concentration, ferritin, serum folate or red cell, and B_{12}) should be measured. Supplements to replace iron and folate and B_{12} may be required if reduced serum levels of ferritin and folate are found, although levels frequently correct on treatment with a gluten-free diet. Monitoring of antiendomysial or tissue transglutaminase antibody titers, which usually normalize with the institution of a gluten-free diet, may prove useful to check dietary compliance. Occasionally, calcium and vitamin D supplementation may be required. Similarly, life-threatening hypokalemia or hypomagnesemia may occur and should be appropriately corrected.

Nonresponsive Celiac Sprue

The most common cause of nonresponsiveness is continued gluten intake. Should the biopsy remain abnormal, a wheat-free, gluten-free diet should be initiated in which there is avoidance of wheat starch–based gluten-free foods in addition to the standard gluten-free diet. It is important to stress that clinicians should rule out other treatable diseases with similar histology that do not respond to a gluten-free diet.

Steroids can be used, and an acute crisis is managed with parenteral hydrocortisone. Oral corticosteroids may be used in nonresponsive disease but only when other causes of small intestinal villous atrophy have been excluded. 6-Mercaptopurine or azathioprine may be used as steroid-sparing agents if a dose of more than 10 mg/day of prednisolone is required.

Ulcerative Jejunitis

In this condition, there are ulcers affecting the jejunum or ileum. Scarring can lead to stricture formation with intervening areas of dilated bowel. There is a variable degree of villous atrophy in adjacent and distant mucosa. There is a high mortality rate with death often following hemorrhage, perforation, or obstruction possibly on a background of malnutrition. Diagnosis can be difficult, with small intestinal radiology often being unhelpful. If ulceration or lymphoma beyond the second part of the duodenum is thought likely, enteroscopy may be useful to obtain biopsy specimens for histologic assessment.

Surgical resection of the ulcer, especially if localized to one part of the intestine, can be curative. Stricturoplasty may be undertaken. A strict gluten-free diet should be initiated, and steroids are often used, sometimes with

benefit. If a diagnosis of enteropathy-associated T-cell lymphoma is made, the patient should be referred to an oncologist for appropriate chemotherapy.

Malignancy

There is an increase in overall mortality in celiac sprue. The excess deaths are mainly caused by malignancy, the majority of which involve intestinal lymphoma. Holmes and colleagues found a 5-fold increased risk of developing malignancy in a celiac population with a relative risk of developing non-Hodgkin lymphoma of 40. This risk fell to the level of the normal population after patients had taken a gluten-free diet for 5 years.

Small bowel radiology, enteroscopy, and a computer-aided tomographic radiographic scanning should be undertaken if lymphoma is suspected. Laparotomy may be required. Treatment for enteropathy-associated T-cell lymphoma is unsatisfactory with a low survival rate. After lymphoma, the most common malignancy is adenocarcinoma of the intestine. Presentation may involve anaemia, gastrointestinal blood loss, weight loss, obstruction, vomiting, and abdominal pain.

Follow-up

Some physicians contend that after introduction of a gluten-free diet, most patients remain well. It is generally advocated that yearly weight, full blood count, ferritin, folate, calcium, and alkaline phosphatase should be recorded. Follow-up should be life-long, and this permits reinforcement of the continuing need for strict adherence to the gluten-free diet.

Screening first degree relatives may be undertaken and other associated conditions may be sought in affected individuals. It is wise, therefore, that follow-up should be undertaken by a physician.

Suggested Reading

Ciclitira PJ. Celiac disease. In: Textbook of gastroenterology. Yamada T, et al., eds. Chapter 74. Philadelphia: Lippincott-Raven, 1999.

Holmes GKT, Prior P, Lane MR, Poke D, Allan RN. Malignancy in coeliac disease: effect of a gluten-free diet. Gut 1989;30:333–338.

Howdle P, ed. Coeliac disease. Baillieres Clin Gastroenterol 1995;9: 211–230.

Janatuinen EK, Pikkarainen PH, Kemppainen TA, Kosma V-M, Jarvinen MK, Uusitupa MIJ, Julkenen RJK. A comparison of diets with and without oats in adults with celiac disease. N Engl J Med 1995; 333:1033–1037.

Maki M, Collin P. Coeliac disease. Lancet 1997;349:1755–1759.

Marsh MN. Mucosal pathology in gluten sensitivity. In: Coeliac disease. Marsh MN, ed. Oxford: Blackwell Scientific, 1992:136–191.

Walker-Smith JA, Guandalini S, Schmitz J, Schmerling DM, Visakorpi JK. Revised criteria for diagnosis of coeliac disease. Arch Disease Child 1990;77:891–894.

Additional Information

Coeliac Disease Foundation, 13251 Ventura Boulevard, Studio City, California 91604-1038. e-mail: cdf@primenet.com; website: http://www.celiac.org; fax: (818) 990-2379.

Address requests for reprints to: Chair, Clinical Practice and Practice Economics Committee, AGA National Office, c/o Membership Department, 7910 Woodmont Avenue, 7th Floor, Bethesda, Maryland 20814. Fax: (301) 654-5920.

This work was supported by the American Gastroenterological Association.

The Clinical Practice and Practice Economics Committee acknowledges the following individuals whose critiques of this review paper provided valuable guidance to the authors: Sumner Bell, M.D.; Peter H. R. Green, M.D.; Martin F. Kagnoff, M.D.

0016-5085/01/$35.00
doi:10.1053/gast.2001.24055