Could their **Asthma** or **COPD** be **Hereditary?**

A guide to Alpha-1 Antitrypsin Deficiency

for Physicians

ALPHA-1 CANADA

ALPHA-1 ANTITRYPSIN DEFICIENCY CANADA INC.

Could their Asthma or COPD be **hereditary?**

Knowing that your patient has alpha-1 antitrypsin deficiency opens up a number of lifestyle and treatment options as well as avoidance of risk factors that can improve their quality of life.

Characteristics of A1AD

Alpha-1 antitrypsin deficiency (also known as A1AD, α1ATD, AATD) is characterized most commonly by COPD in adults and liver disease in children and adults. COPD, specifically emphysema, tends to occur much earlier and with less tobacco smoke exposure in individuals with alpha-1 antitrypsin deficiency; thus it is commonly misdiagnosed as difficult-to-manage asthma. Smoking is the major factor influencing the course of COPD.The onset of respiratory disease in smokers with A1AD is between age 30 and 50 years; in non-smokers, the onset can be delayed to the sixth decade. Non-smokers often have a normal life span. Knowing that your patient has alpha-1 antitrypsin deficiency opens up a number of lifestyle and treatment options as well as avoidance of risk factors that can improve their quality of life. A1AD-associated liver disease, present in only a small portion of affected children, manifests as obstructive jaundice and raised serum aminotransferase levels in the early days and months of life or may be identified by the incidental finding of elevated liver enzymes in children of any age.

The incidence of liver disease increases with age; liver disease in adults, manifests as cirrhosis and fibrosis, and is not necessarily associated with a history of neonatal liver disease.

Diagnosis and Testing

The World Health Organization, the American Thoracic Society and Alpha-1 Canada recommend that everyone with COPD be tested for alpha-1 antitrypsin deficiency.

Clinical Diagnosis

A1AD is suspected in individuals with evidence of:

- pulmonary disease (i.e., emphysema, asthma, persistent airflow obstruction, and/or chronic bronchitis) and/or
- evidence of liver disease at any age, including obstructive jaundice in infancy
- individuals with bronchiectasis
- A1AD is also observed rarely in individuals with Wegener granulomatosis and necrotizing panniculitis

The diagnosis of A1AD relies on the following:

- Demonstration of low plasma concentration of alpha-1 antitrypsin (AAT)
  AND
- observation of a deficient variant of the protein AAT by protease inhibitor (PI) typing
  OR
- detection by molecular genetic testing of mutations in both copies of SERPINA1, the gene encoding AAT.

Measurement of AAT level is the first step

The diagnosis of A1AD relies on demonstration of low plasma concentration of AAT, followed by (when low) either observation of a deficient variant of the protein AAT by protease inhibitor (PI) typing or detection of mutations in both copies of the gene SERPINA1, which encodes AAT. PI*Z is the most common deficiency allele. Ninety-five percent of A1AD results from the presence of two Z alleles. Genetic testing is clinically available.

Measurement of AAT is done inexpensively in many labs in all provinces. Some routinely refer low results to one of four Canadian labs that perform PI typing or directly to a DNA diagnostic laboratory for genotyping of SERPINA1, the gene responsible for A1AD. The exception is Alberta where both procedures are done by DynaLIFE.

In some provinces, AAT serum level and phenotyping or genotyping can be ordered on a single requisition. On a laboratory requisition you may order “alpha-1 antitrypsin level” and specify “Phenotype if <1.5g/L” this will authorize total assay and pre-authorize phenotyping if appropriate and if available through that laboratory.

In other provinces, phenotyping (PI typing, Protease Inhibitor typing or genotyping) can be ordered separately, however, is usually done only when previously measured AAT is 1.5 g/L or less (or below the normal mean for the testing laboratory), OR the patient is a first-degree relative/spouse of a known AAT deficient subject. Your request for PI typing or genotyping when ordered separately should specify the previous result or the subject’s name and relationship for phenotyping to proceed. Typically, a requisition specific for the laboratory doing the testing is needed. (Please note that genotyping requires a blood sample collected in an EDTA tube).

Interpretation of Results

The normal plasma concentration of AAT is 80% to 20% of normal. Mean is 1.3 g/L (range: 1.06 g/L to 1.58 g/L).

For adults with the PI ZZ genotype the concentration is usually 13% to 23% of normal (mean: 18%±5% of normal).

For children with the PI ZZ genotype and liver disease the plasma concentration can be as high as 40% of normal.

If a low serum level is found it does not establish adiagnosis of clinically important severe deficiency. In fact, the majority of abnormal results are mildly reduced values found in carriers at low risk of having clinical disease, confirmatory phenotyping or genotyping is needed.

Protease Inhibitor (PI) Types

- PI ZZ: Plasma concentration of AAT approximately 18% of normal (0.23 g/L)
- PI SZ: Not usually associated with a high risk for liver or lung disease; higher risk of developing COPD among smokers
- PI MZ: Slightly increased risk for decreased lung function
- PI MM: Observed in normal individuals with normal plasma concentration of AAT

For more information on having your patients tested contact **Alpha-1 Canada** at 1-888-669-4583 or visit our web site at **www.alpha1canada.ca.** The Alpha-1 Canadian Registry provides information on research and testing, you can visit their website at **www.alpha1canadianregistry.com** or call 1-800-352-8186

Prevalence

A1AD affects all racial groups worldwide. It is most common among Caucasians and least common in Asian and black populations, among whom rare deficiency variants other than PI ZZ also occur.

The prevalence of A1AD in the white population of North America ranges between one in 5,000 and one in 7,000

Management

Intravenous augmentation therapy (regular infusion of purified human AAT to augment deficient ATT serum concentrations) is widely prescribed in the United States and other countries and has been recommended by the Canadian Thoracic Society for affected individuals whose FEV1 is 25% to 80% of predicted and have never smoked or have quit smoking yet continue to show rapid decline in FEV1 despite optimal medical therapy; however, definitive controlled trials have not been carried out.

Intravenous augmentation therapy is not useful for A1AD liver disease.

It is recommended that patients:

- Contact **Alpha-1 Canada**
- avoid smoking (both personal and passive)
- avoid an occupation with exposure to environmental pollutants
- avoid exposure to mineral dust, gas and fumes

Lifestyle

Expression of the disorder can be modified in asymptomatic individuals by lifestyle changes, including avoidance of smoking and occupations with exposure to environmental pollutants used in agriculture, mineral dust, gas and fumes.

Regular exercise and good nutrition are expected to be beneficial in maintaining lung health, as are careful maintenance of fat-soluble vitamins.

Surveillance

Liver function should be evaluated periodically in all individuals with PI ZZ, including those who did not manifest childhood liver disease

Resources

Patients

Patients diagnosed with alpha-1 antitrypsin deficiency should be referred to the following resources:

- **Alpha-1 Canada** at 1-888-669-4583 or **www.alpha1canada.ca**
- Alpha-1 Canadian Registry at 1-800-352-8186 or **www.alpha1canadianregistry.com**

Physicians

- For further information, physicians can also contact the organizations above as well as members of the **Alpha-1 Canada** Medical Advisory Board at 1-888-669-4583.

Genetic Facts

A1AD is inherited in an autosomal codominant manner. When both parents are heterozygotes, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier. In the rare instance in which one parent is homozygous (PI ZZ) and one parent is heterozygous, the risk for each sib to be affected is 50%.

Unless an individual with A1AD has children with a reproductive partner who is affected or a carrier, his/her offspring will be obligate heterozygotes (carriers) for the disease-causing mutation. Carrier testing is available on a clinical basis by PI typing or mutation analysis for sibs and offspring of affected individuals.

Testing of the sibs of affected individuals is strongly recommended. However, predictive genetic tests should ideally be preceded by genetic counselling, particularly when considering genetic testing of minors. In all cases, the focus should be on the child's best medical interests.

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Medical Advisory Board

Alpha-1 Canada is pleased and proud to have four of Canada's leading researchers and clinicians in the field of alpha-1 antitrypsin deficiency as members of our Medical Advisory Board. They are:

Dr. Kenneth R. Chapman, MD, MSc, FRCPC, FACP, FCCP, Chair
Dr. Chapman is the Chair of the Medical Advisory Board, a Professor of Medicine at the University of Toronto and an internationally respected researcher in the field of asthma and airway diseases. Dr. Chapman is also Director of the Canadian Registry for Alpha-1 Antitrypsin Deficiency

Dr. Jean Bourbeau, MD, MSc
Dr.Bourbeau is an associate professor in the Department of Medicine and the Department of Epidemiology and Biostatistics and Occupational Health at McGill University in Montreal.

Dr. Simon Ling, MB, ChB
Dr. Ling is Associate Professor of Paediatrics at the Hospital for Sick Children, University of Toronto. Dr. Ling collaborates in studies of the genetic determinants of liver disease due to cystic fibrosis and alpha-1 antitrypsin deficiency

Dr. Marsha Speevak, BSc, PhD, FCCMG, FACMG
Dr.Speevak is Assistant Professor at the University of Toronto, Department of Laboratory Medicine and Pathobiology. Dr.Speevak's laboratory at Credit Valley Hospital provides targeted genotyping (S and Z variants) as well as full gene sequencing of SERPINA1, the gene responsible for alpha-1 antitrypsin deficiency

Alpha-1 Canada

Alpha-1 Canada is committed to providing information and support to people affected by alpha-1 antitrypsin deficiency; informing and educating the medical community about alpha-1 antitrypsin deficiency; and to generating broad awareness about this genetic liver, lung and skin disease.

Please refer your patients to **Alpha-1 Canada** for information, education and support.

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