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References


Unusual Late Onset of X-linked Chronic Granulomatous Disease in an Adult Woman after Suspicous Childhood, Andreas Lun; Joachim Roessler; Harald Renz

The multisubunit enzyme NADPH oxidase [phagocyte oxidase (phox)] of phagocytic cells plays a central role in cellular host defense (1). Phagocytes release large amounts of superoxide in the respiratory extraburst after stimulation with microorganisms. The production and subsequent conversion of superoxide to microbicidal reactive oxygen metabolites ([ROMs]; e.g., H2O2) are critical for the elimination of pathogens such as Staphylococcus aureus, Serratia marcescens, and Aspergillus (2).

After activation of phagocytes, p47-phox and p67-phox, together with other proteins such as Rac, translocate from cytosol to the membrane, where they associate with two membrane-bound subunits of cytochrome b558, p22-phox and gp91-phox (3). This initiates an electron flux from NADPH via the activated phox to molecular oxygen leading to the generation of superoxide (4).

The central role of this oxidase in cellular host defense is clearly demonstrated in patients suffering from a rare inherited disorder known as chronic granulomatous disease (CGD) (5). Mutations affecting any of the four subunits gp91-phox, p22-phox, p47-phox, or p67-phox either render phagocytes from CGD patients incapable of superoxide generation after stimulation or strongly decrease its production (6). Typically, these patients suffer from recurrent and life-threatening bacterial and fungal infections (3).

Here we present the case of a 43-year-old female patient with recurrent serious conditions that are typical of CGD, including Aspergillus fumigatus infection and formation of intestinal granulomas. The history of the patient is remarkable because for the first 17 years of her life, no typical CGD infections and no typical symptoms of CGD occurred. In the following years, the patient experienced cutaneous abscesses in the anogenital and back region and recurrent bacterial pneumonia (ages 29, 36, 41, 42, and 43 years). At age 29 years, the patient suffered from a severe therapy-resistant salmonella sepsis with ensuing severe damage of the liver and hepatic coma.

The symptoms and history led to the differential diagnosis of CGD. Stimuli-induced ROM formation of her neutrophils was tested with dihydrorhodamine 123[Phago-Burst; Orpegen; see Ref. (7)]. Most of the patient’s neutrophils (98%) were unable to produce ROMs after maximal stimulation with phorbol-myristate-acetate. Only 2% at most of her neutrophils produced H2O2 at concentrations within the reference interval (Fig. 1). To
explained by age-related skewing of lyonization (10). This case supports the view that appropriate system, leading to enhanced susceptibility to further damage or alteration of further parts of her immune or infections may have triggered some discrete organ compensation of her phagocyte defect during her childhood, Alternatively, the patient may have had functional compensation of the phagocyte defect by the developmental stage. The mosaic of nonpathogenic and defective cells, as our patient did, attributable to lyonization. The patient’s carrier status, a molecular analysis of the gp91-phox gene was performed. The genomic DNA was prepared by standard methods with a commercially available product (QIAGEN). All exons of the gp91-phox gene (CYBB) and their intronic border regions were amplified by PCR and sequenced (9). A microdeletion of a base pair was detected on one of the two alleles of the X chromosomes, 6-A 409 in exon 5 of the gp91-phox gene (CYBB), which led to a shift of the reading frame and to a premature stop codon at position amino acid 139, Val139→stop. This carrier status, together with an extreme lyonization, appears to explain the clinical phenotype of CGD with severe recurrent infections. The late onset of this patient’s CGD could perhaps be explained by age-related skewing of lyonization (10). Alternatively, the patient may have had functional compensation of her phagocyte defect during her childhood, or infections may have triggered some discrete organ damage or alteration of further parts of her immune system, leading to enhanced susceptibility to further infections. This case supports the view that appropriate genotyping for CGD should be performed at any age whenever suspicious symptoms occur.

References

Hemolytic Uremic Syndrome Attributable to Streptococcus pneumoniae Infection: A Novel Cause for Secondary Protein N-Glycan Abnormalities, Femke de Loos,1 Karin M.L.C. Huijben,1 Nicole C.A.J. van der Kar,2 Leo A.H. Monnens,2 Lambertus P.W.J. van den Heuvel,3 Johanna E.M. Groener,3 Ronald A. de Moor,3 and Ron A. Wevers1*

To verify the patient’s carrier status, a molecular analysis of the gp91-phox gene was performed. The genomic DNA was prepared by standard methods with a commercially available product (QIAGEN; Qiagen) (9). All exons of the gp91-phox gene (CYBB) and their intronic border regions were amplified by PCR and sequenced (cycle sequencing; BIG-DYE PE and ABI 377; Perkin-Elmer) (9). A microdeletion of a base pair was detected on one of the two alleles of the X chromosomes, 6-A 409 in exon 5 of the gp91-phox gene (CYBB), which led to a shift of the reading frame and to a premature stop codon at position amino acid 139, Val139→stop. This carrier status, together with an extreme lyonization, appears to explain the clinical phenotype of CGD with severe recurrent infections.

The late onset of this patient’s CGD could perhaps be explained by age-related skewing of lyonization (10). Alternatively, the patient may have had functional compensation of her phagocyte defect during her childhood, or infections may have triggered some discrete organ damage or alteration of further parts of her immune system, leading to enhanced susceptibility to further infections. This case supports the view that appropriate genotyping for CGD should be performed at any age whenever suspicious symptoms occur.

Hypoglycosylation of glycoproteins is characteristic for congenital disorders of glycosylation (CDG) and may consist of partial or completely missing glycans (11). The major first test for CDG is isoelectric focusing (IEF) of plasma transferrin. The IEF pattern shows a cathodal shift because of the hypoglycosylation of the protein (2). Primary defects in the N-glycan biosynthetic pathway are known for nine CDG subtypes: CDG Iα–f and CDG Iα–c (3–8). Transferrin hypoglycosylation can also be secondary to chronic alcohol abuse (9,10), galactosemia (11), hereditary fructose intolerance (12), and severe liver

Fig. 1. Histogram plots of H2O2 production of neutrophils from a carrier with extreme lyonization (the CGD patient; left histograms) and a control (right histograms).

Top panels show the spontaneous and bottom panels the phorbol-myristate-acetate-stimulated ROM production as fluorescence intensity of the phagocytes.