Down-Syndrome associated with MBL-deficiency, IgG-deficiency, vasculitis and mutated prothrombin

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The association of Down syndrome with mannose-binding lectin (MBL)-deficiency, recurrent infections and vasculitis has not been reported. We report a 30 year-old female with Down-syndrome associated with MBL-deficiency with the genotype LXA/HYD, IgG-deficiency, recurrent uro-genital infections, cutaneous vasculitis, G20.210A prothrombin mutation, deep venous thrombosis, and pulmonary embolism. MBL-deficiency in combination with IgG deficiency might have favored the development of recurrent uro-genital infections. Immunodeficiency might be also involved in the pathogenesis of cutaneous vasculitis. Deep venous thrombosis and pulmonary embolism were attributed to the genetically determined prothrombotic state and intake of oral contraceptives (Rev Méd Chile 2009; 137: 94-7).

(Key words: Down syndrome; Severe combined immunodeficiency; Prothrombin)

Síndrome de Down asociado a deficiencia de lectina de unión a manosa, deficiencia de IgG, vasculitis y mutación de la protrombina. Informe de un caso

La asociación de síndrome de Down con deficiencia de lectina de unión a manosa, infecciones recurrentes y vasculitis no ha sido informada. Presentamos una mujer de 30 años de edad con síndrome de Down asociado a deficiencia de lectina de unión a manosa, con el genotipo LXA/HYD, deficiencia de IgG, infecciones urogenitales recurrentes, vasculitis cutánea, mutación de protrombina G20.210A, trombosis venosa profunda y embolia pulmonar. La deficiencia de lectina de unión a manosa combinada con la deficiencia de IgG puede haber favorecido las infecciones urogenitales recurrentes. La inmunodeficiencia puede también tener relación con la patogenia de la vasculitis cutánea. La trombosis venosa profunda y la embolia pulmonar pueden deberse al estado protrombótico derivado de la mutación de protrombina y el uso de contraceptivos orales.

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Mannose-binding lectin (MBL)-deficiency is due to mutations in the MBL2 gene on chromosome 10, encoding for MBL. MBL is a calcium-dependent serum protein that plays a role in the innate immune response by binding to carbohydrates on the surface of viruses, bacteria, fungi, or protozoa, where it activates the complement system or acts directly as an opsonin. Individuals with MBL deficiency have an increased susceptibility to infectious diseases, particularly for infections of the lower urinary tract, vaginitis, or the lung¹⁻³. MBL deficiency may be also associated with non-infectious diseases, such as lupus erythematosus, rheumatoid arthritis, cystic fibrosis, or common variable immunodeficiency. The association of MBL-deficiency, IgG-deficiency, vasculitis, Down-syndrome, and a prothrombin mutation has not been reported to occur together in a single patient.

CASE REPORT

The patient is a 30-yo HIV-negative, Caucasian female, with typical features of a Down-syndrome, including epicanthus, long palpebral fissures, low-set ears, saddle nose, brachycephaly, flat face, eversion of the lateral portion of the lower eyelids, arched eyebrows with sparse lateral regions, long eyelashes, small ears, protruding tongue, muscular hypotonia, developmental delay, hyperflexibility of joints, brachydactyly, hypothyroidism, and dermatoglyphic abnormalities⁴. The diagnosis had not been genetically confirmed. Since age 25y she experienced recurrent infections of the lower urinary tract and vulvitis. Cutaneous vasculitis of the lower legs occurred for the first time at age 28y but was definitively diagnosed upon the histological and immunohistological appearance of a skin biopsy not earlier than at age 30y. Since corticosteroids were only partially effective, immunoglobulins were initiated for the first time at age 29y and repeatedly given with success. At age 29y, one month after initiation of an oral contraceptive (levonorgestrel 0.15 mg, ethinylestradiol 0.03 mg), she experienced a deep venous thrombosis of the left lower leg and bilateral, peripheral pulmonary embolism, which required oral anticoagulation with phenprocoumon during one year. Also at age 29y MBL-deficiency and IgG-deficiency were detected during extensive investigation for the cause of re-

current cutaneous vasculitis (Table 1). At age 30y she developed a local infection of digit one of the left foot after a minimal trauma, for which she received fusidic acid, orally. After two days and intake of 5 tablets she developed a severe, generalized erythrodermia and fever, and required hospitalization. After discontinuation of fusidic acid, and administration of corticosteroids and antihistaminics, the allergenic skin reaction resolved completely. Her history was also noteworthy for recurrent uro-genital infections.

Concerning the laboratory findings, IgG was repeatedly reduced (Table 1). There was also a reduction of the subclass IgG2. Antibodies against tetanus were not determined but pneumococcal antibodies were normal. Other immunological parameters, which were normal or negative, include anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies (c-ANCA, p-ANCA, atypical ANCA, proteinase-3 ANCA, myeloperoxidase ANCA, lactoferrin ANCA, elastase ANCA, cathepsin G ANCA, BPI-ANCA), cardiolipin IgG, IgM, and IgA, beta2-glycoprotein, circulating immune complexes, ADNase B, CH'50, AH'50, anti-thyroid microsomal antibodies, anti-thyroglobulin antibodies, anti-TPO antibodies, anti-TSH receptor IgG antibodies, phosphatidylserin antibodies, beta2-glycoprotein-I G/A, nRNP antibodies, SM-antibodies, RO/SS-A-antibodies, LA/SS-B antibodies, SCL-70-antibodies, Jo-1-antibodies, histone antibodies, ds-DNA antibodies, ss-DNA antibodies, and prothrombin A antibodies. Lupus anticoagulant was not determined. MBL, however, was markedly decreased (Table 1). MBL-deficiency was confirmed upon the presence of the MBL-genotype LX/HYD. Screening for thrombophilia revealed the heterozygous G20210A mutation in the prothrombin gene. Upon assessment of thyroid function hypothyroidism was detected and a therapy with L-thyroxin (0.05 mg/d) initiated. Radiologic investigations of the lower urinary tract, such as intravenous urography and ultrasound, were normal.

DISCUSSION

The presented patient is interesting for the concurrent occurrence of Down-syndrome, MBL-deficiency, IgG-deficiency, cutaneous vasculitis, and the G20210A prothrombin mutation. Whether these abnormalities were causally related or their common occurrence a mere coincidence remains speculative. A Medline

Table 1. Remarkable laboratory tests in a patient with Down syndrome MBL-deficiency and other mutations

Parameter	Reference limits	Test result
CRP	0-0,5 mg/dl	2,42
Latex rheumafactor	0-20 IU/ml	8,5
ASLO	65-200 E/ml	188
Circulating immunocomplexes	0-2 ug/ml	0,58
IgG	790-1700 mg/dl	737
IgA	76-450 mg/dl	394
IgM	90-350 mg/dl	82
IgE	<100 IU/ml	369
IgG1	500-880 mg/dl	610
IgG2	150-600 mg/dl	131
IgG3	20-100 mg/dl	44
IgG4	8-120 mg/dl	9
C3	90-180 mg/dl	124
C4	13-50 mg/dl	30
Alpha-1-antitrypsin	160-350 mg/dl	162
Alpha-glycoprotein	55-140 mg/dl	138
ANF (ANA)	neg	neg
P-ANCA	neg	neg
C-ANCA	neg	neg
Hepatitis antibodies	neg	neg
IgG-pneumococcus antibodies	neg	1:43
IgM-pneumococcus antibodies	neg	1:86
Hemophilus IgG antibodies	<1 µg/ml	2.05
C1-inhibitor	0,22-0,34 g/l	0,37
MBL	60-5500 ng/ml	19

Abnormal results are highlighted

search did not detect previous reports about the association of Down-syndrome with MBL-deficiency or the G20210A prothrombin-mutation. Repeatedly, however, an association of Down-syndrome with vasculitis has been reported⁵⁻⁷. Rarely, Down-syndrome was also associated with deficiency of IgG subclasses^{8,9}. No reports were detectable when combining "MBL-deficiency" with "G20210A prothrombin-mutation", but MBL-deficiency has been reported in association with IgG-deficiency^{10,11}. According to these reports reduction of IgG in MBL-deficiency might be due to binding of IgG to MBL¹¹. Rarely, MBL-deficiency has been also reported in association with vasculitis, particularly ANCA-associated small vessel vasculitis¹² and vasculitis in Behcet's disease¹³. The G20210A prothrombin-mutation has not been reported together with IgG deficiency, but repeatedly together with vasculitis, most frequently in Behcet's vasculitis¹⁴ but also together with cutaneous livedoid vasculitis¹⁵. In single cases IgG deficiency was related

to vasculitis^{16,17}. An argument against a common cause of the described abnormalities is that Down syndrome is usually due to trisomy of chromosome 21 and that the genes for MBL, prothrombin, and IgG are located all on chromosomes other than chromosome 21.

Whether the recurrent infections of the uro-genital tract were causally related to MBL-deficiency or IgG-deficiency remains speculative. However, it is well known that both conditions predispose for recurrent infectious disease^{8,18}. Additionally, the recurrent infections could be due to urinary tract abnormalities, frequently found in Down-syndrome¹⁹. However, in our patient no urinary tract abnormality has been found on cystoscopy or imaging of the lower or upper urinary tract. Possibly, urinary tract infections were due to colonization of the urinary tract by fungi, a complication of recurrent antibiotic therapy. They could be also attributed to corticosteroid therapy but an argument against this is that uro-genital tract

infections occurred already long before the initiation of corticosteroids. Low IgG was interpreted as IgG-deficiency since also subclass IgG2 was reduced. Low IgG due to MBL-deficiency was excluded, since such a causal relation has rarely been reported and since also subclass IgG2 was reduced. Though vasculitis was also rarely related to MBL-deficiency^{12,13} or IgG-deficiency^{16,17}, it cannot be definitively excluded that immunodeficiency contributed to the development of the dermal abnormalities, since cutaneous vasculitis has been previously reported in a patient with Down syndrome⁵ and since patients carrying MBL-haplotypes are at risk of developing systemic lupus erythe-

mtosus²⁰. Whether deep venous thrombosis and pulmonary embolism were due to the prothrombin mutation or the oral contraceptives, or both, remains speculative. To reduce the risk of recurrent thromboembolism the patient was recommended to withdraw oral contraceptives but no oral anticoagulation was initiated.

This case shows that Down-syndrome, MBL-deficiency, IgG-deficiency, recurrent uro-genital infections, vasculitis and the prothrombin mutation may concur in the same patient. Recurrent infections and vasculitis may be attributable to immunodeficiency from low IgG or low MBL.

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