Clinical and Laboratory Manifestation of Selective IgM Deficiency

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Selective IgM deficiency

- First described in two patients with fulminant meningococcal septicemia (Hobbs et al. 1967).
- Associated with
  - Severe infections (septicemia. Brucella)
  - Mild RTI, UTI infections
  - Skin infections (pyoderma, generalised molluscum contagiosum), recurrent chalasia
  - Autoimmune diseases: SLE, Hashimotos´s disease
  - ?Allergy
- Frequency: not known

Selective IgM deficiency - pathogenesis

- sIgM cells present.
- Increased percentage of CD8+ cells (Inoue et al. l986).
- T-lymphocytes of IgM patients suppressed IgM production in normal persons (Inoue et al 1986, Vogelzang 1982), not confirmed by others (Endoh et al 1981, Kimura et al 1993).
- Addition of normal T -lymphocytes did not increase IgM production (Kimura et al 1993).

Patient No 1 (female, 67 years)

- „Eczema“ from childhood, disappeared at age of 50.
- Hay fever from childhood, treatment included allergen immunotherapy for more than 30 years, symptoms disappeared at the age of 55.
- Exertional dyspnoea. Lung function test: mild combined disorder.
- No joint pains, no xerostomy, no photosensitivity.
- Mildly decreased lacrimation.
- No frequent/severe infections.

Patient No 1: immunoglobulin levels

- **IgG: 23,40 g/l**
- **IgG1: 20,31 (4.9-11.40)**
- IgG2: 1,44 (1,50-6,40)
- IgG3: 0,63 (0,20-1,10)
- IgG4: 0,07 (0,8-1,40)
- IgA: 1,74 g/l
- **IgM: <0,05 g/l**
- anti T-tox, PCP, HIB antibodies: normal

Patient No 1: autoantibodies

- **ANA: 1:1280 (speckled type)**
- **anti SS-A, SS-B: positive**
- **RF (IgA isotype): positive**
- **anti-GPC: positive**
- Negative: ANCA, ds SCL 70, Jo-1, Sm/RNP, ACLA, anti-thyroid Abs...
- C3, C4, CRP: normal
- Renal functions: normal

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Patient No 2 (female, 66 years)

- From 20 years has been suffering from solar dermatitis, good response to antihistaminics or local steroids.
- For the last 2 years has been suffeering from intermittent pain of small joints of the hands without other signs of arthritis.
- Treated for hypertension.
- She never suffered from frequent/serious infections.

Patient No 2: laboratory tests

- **IgA: 4.56 g/l, IgM<0,05g/l,** IgG, IgG subclasses, anti T-tox, PCP, HIB antibodies: normal
- ANA: 1:160, homogenous type
- Anti SS-A, SS-B: positive
- Negative: anti - dsDNA, Jo, Sm/RNP, nucleosome, histones, GPC, thyroid, ASMA, RF, ACLA
- Normal CRP, normal C3, C4 levels
- Mildly decreased lactimation, normal salivation.
- Normal renal function.

Patient No 3 (male, 24 years)

- Followed-up for patellar chondropathy from puberty.
- Mild bronchial asthma was diagnosed at the age of 22 years, that time selective IgM deficiency was discovered.
- He does not suffer from frequent /severe infections.

Patient No 3: laboratory tests

- IgG: 8,41 g/l
- IgG subclasses: normal
- IgA: 2,32 g/l
- IgM:<0,05 g/l
- IgE: 157 IU/ml
- Normal anti-tetanic, HIB, PCP antibodies
- ANA, RF, ACLA, ASMA, anti GPC, anti-thyroid abs...: negative

Patient No 4 (male - 62 years)

- Recurrent furunculi from the age of 37.
- At the age of 40 treatment by low dose IMIG was initiated, (currently 1g/4 weeks), his clinical state markedly improved.
- Interruption of the treatment always lead to recurrence of clinical symptoms.
- At the age of 55 DM-II compensated by oral antidiabetics.
- From the age of 60 -ischemic disease of lower extremities.

Patient No 4: laboratory tests

- IgG: 7,28 g/l
- IgG subclasses: normal
- IgA: 3,24 g/l
- IgM: <0,05 g/l
- IgE: 153 IU/ml
- IgD: 6 IU/ml
- Anti-tetanic, PCP, HIB: abs: normal
- Autoantibodies: negative

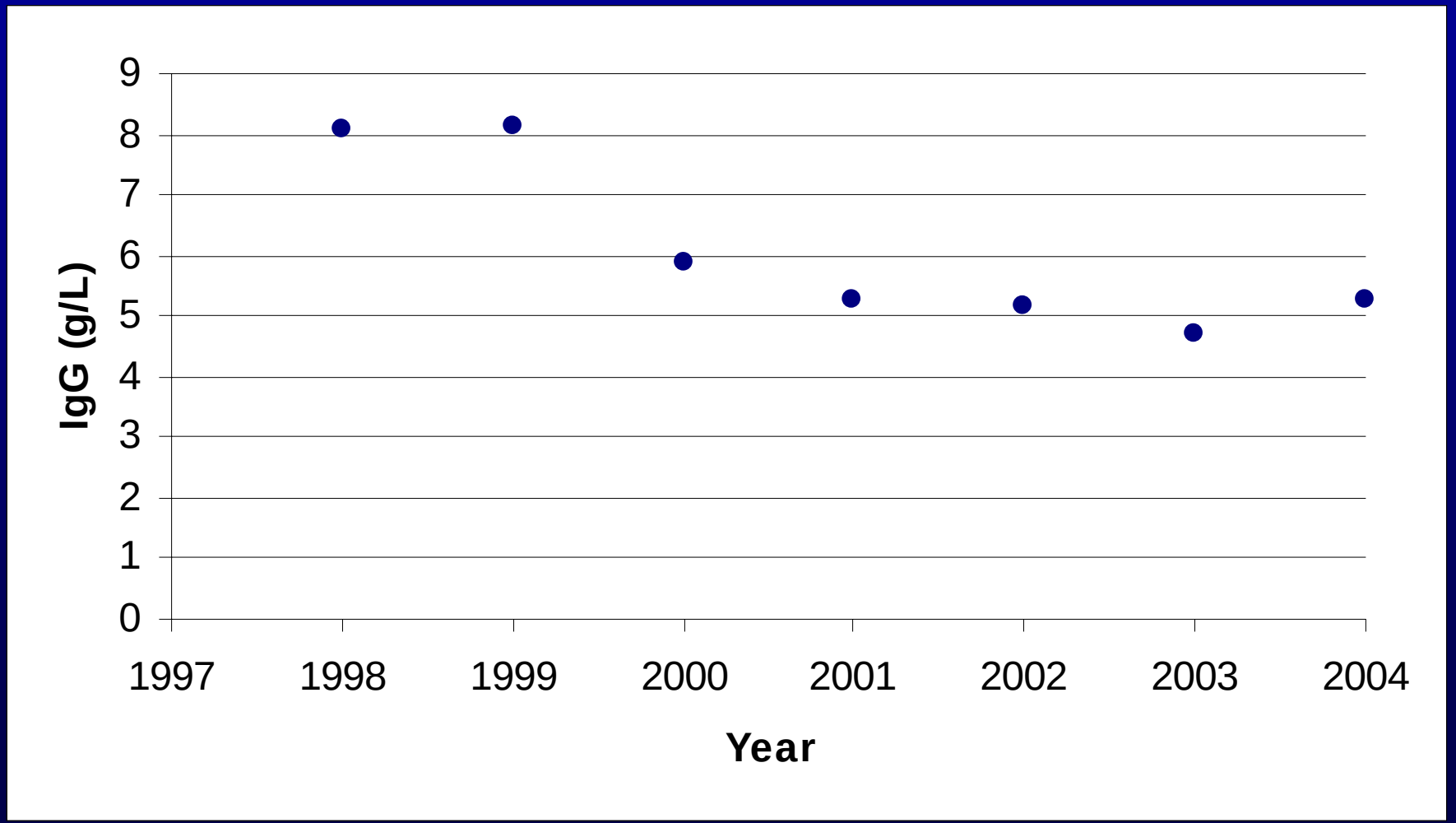
Patient No 5 (female 56 years)

- Trombocytopathy, without bleeding tendency.
- From 53 years intermittent vertigo + intermittent parestesiae, diplopy - from 55 years treated by carbamazepine.
- From 53 years abdominal pain: chronic pancreatitis, diverticulosis.
- From childhood increased frequency of respiratory tract infections, no serious infections occurred.

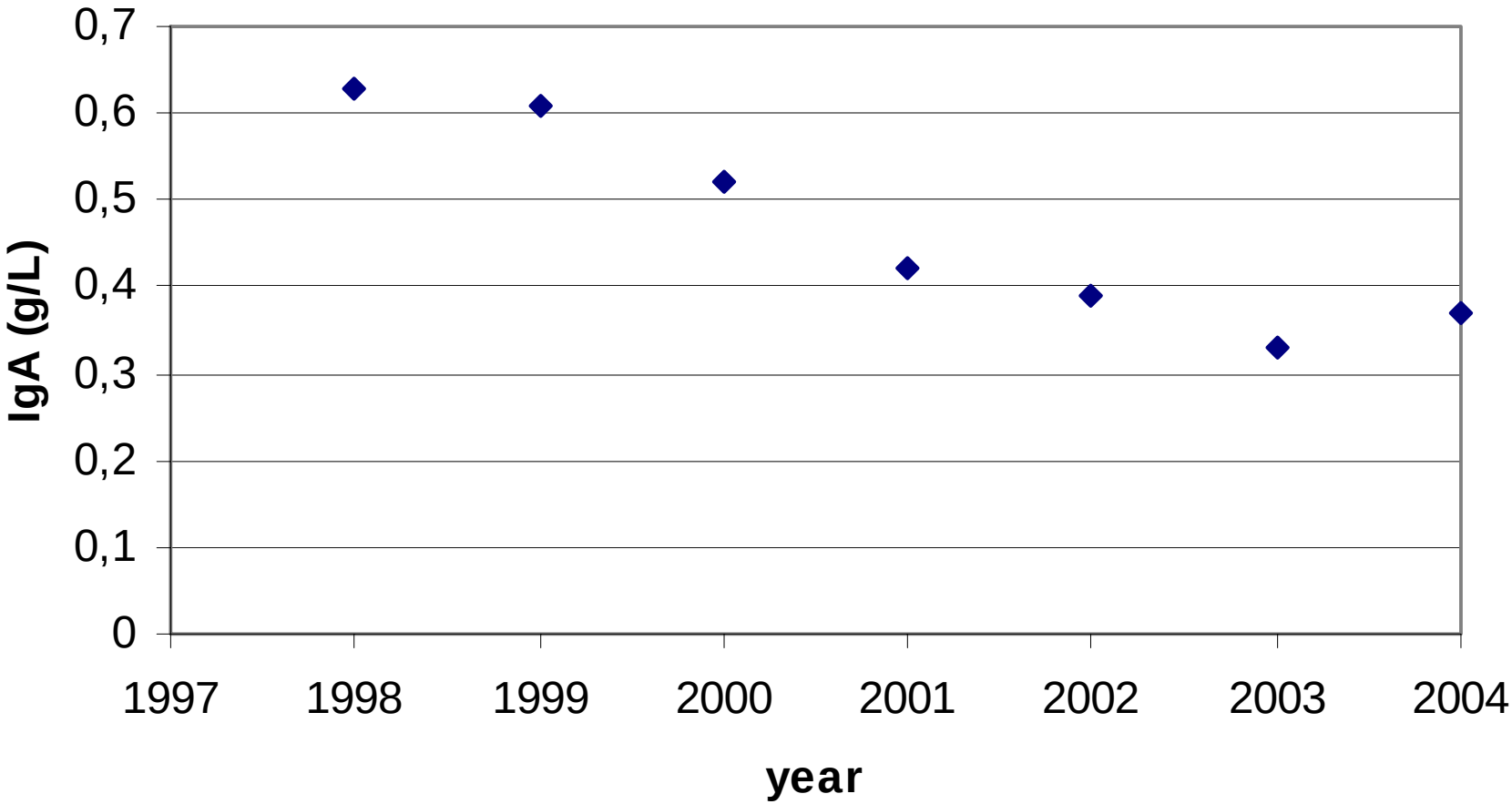
Patient No 5: laboratory tests

- IgG: 8,13 g/l
- **IgA: 0,61g/l**
- **IgM<0,08 g/l**
- IgG subclasses: normal
- anti PCP, HIB: normal,
- Normal response after tetanus vaccination.
- No autoantibodies were detected.

Serum IgG level in patient No 5



Serum IgA levels in patient No 5



Patient No 6 (male, 26 years)

- Perennial rhinitis with watery nasal discharge from the age of 24.
- Allergy tests were negative.
- Referred at the age of 25.
- No frequent/serious infections.

Patient No 6: laboratory tests

- **IgG: 4,54 g/l**
- **IgG1: 2.50 g/l (4.90-11,40)**
- **IgG2: 0,82 g/l (1,50-6,40)**
- IgG3: 0,52 g/l (0,20-1,10)
- IgG4: < 0,04 g/l (0,08-1,40)
- **IgA: 0,52 g/l**
- **IgM: <0,05 g/l**
- Normal anti-tetanus, HIB, PCP antibodies
- No autoantibodies were detected.

Isohaemagglutinin titres

Patient No	Blood group	Isohaemagglutinin titre
1	AB	
2	A	Anti-B 1:4
3	A	anti-B 0
4	A	anti-B 1:8
5	O	anti-A 1:8, anti-B 1:16
6	A	anti-B 0

IgM levels measured by ELISA (in mg/l)

- Patient No 1: 21..24
- Patient No 2: 34..5
- Patient No 3: 20
- Patient No 4: 34..53
- Patient No 5: 6
- Patient No 6: 25..35

B-lymphocytes in IgM-deficient patients

Patient	CD19	IgM+ % of CD19	IgD-27+ % of PBL	IgM+21- % z CD19	Warnatz´s group
1	6,5	86,8	0,46	6,5	II
2	9,5	86,2	1,34	8,9	II
3	10	86,9	1,52	1,9	II
4	7	77,6	2,16	0,6	II
5	7,3	93,3	0,17	5,9	Ib
6	7	92,7	0,48	8	II
Controls	9,5(3,7)	74,4(18,7)	1,37(0,73)	6,4(3,3)	

T-lymphocytes in IgM-deficient patients

Patient	CD3+ (%)	CD4+ (%)	CD8+ (%)	CD45RA+ of CD4+(%)	CD45RO+ of CD4+(%)	CD16/56+ (%)
1	81	36	41	25	74	10
2	74	41	29	25	74	16
3	76	39	33	36	47	8
4	81	46	34	6	86	9
5	72	38	31	38	60	14
6	66	44	16	58	43	21
Controls	74(5,9)	47,2(7,7)	18,3 (5,12)	46,2(13,9)	55,8(14,3)	14,1(6,3)

In vitro IgM production in IgM deficient patients

Patient No	PWM (ng/10^6 cells)	SAC (ng/10^6 cells)
1	3	3
4	42	41
5	31	6
Controls (4)	116-461	176-404

$1x10^6$ PBM stimulated by PWM (20μg/ml) or SAC (1: 10 000) for 10 days.

Abdominal sonography

- Available in 4 patients, no abnormalities were detected.
- Normal spleen size in all 4 patients.

Serum immunoglobulin levels in relatives of IgM deficient patients

- Altogether 2 parents, one brother and two sons were investigated - in all normal serum Ig levels were observed.

Summary of 6 IgM deficient patients

- Frequency: 6/ $2x10^6$
- Clinical manifestation:
  - Mild immunodeficiency: 2
  - Autoimmune phenomena: 2
  - Allergy 1
- Family history: no immunoglobulin abnormalities in all relatives available.
- sIgM positive B-cells present in all patients, IgM secretion decreased in all 3 patients investigated.
- Gradual decrease in IgG and IgA in at least one patient.