

Tocilizumab and adalimumab in an 18q deletion syndrome patient with chronic arthritis

Sirs,

A case of 18q deletion syndrome (18q-syndrome) was reported in 1964 by De Grouchy *et al.*; the syndrome exhibits diverse symptoms such as mental retardation, short stature, and poor muscle tone (1). Some studies have reported an association between chromosome 18 and immunocompetence. For example, the haplo-insufficiency of the 18q22.3-q23 gene region may be associated with the immunoglobulin A deficiency phenotype (2), and chromosome 18 may contain a locus that is responsible for the regulation of both Th1 and Th2 cytokine production (3). Here we report the case of a patient with 18q-syndrome and an autoimmune disease of chronic arthritis.

A 10-month-old girl who was unable to crawl underwent a genetic screening that revealed the presence of 18q-syndrome [46, xx, del (18)(q22-qter)]. She had delayed mental development, whereas no malformation and abnormality were observed in motor development. The girl developed nephrotic syndrome (NS) at the age of 1 year; her kidney function had a waxing and waning course until 7 years of age. The immunosuppressive drugs for the NS included methylprednisolone, mizoribine, and cyclosporine. After a successful course of treatment, the mizoribine and cyclosporine were discontinued at the age of 11 years and 7 months. One month later, she complained of general malaise, a loss of appetite, and

joint pain, and she was then referred to the pediatric department in our hospital.

Biochemical examination of her blood showed the following results: white blood cells, 8,900/ μ L; haemoglobin, 14.8 g/dL; platelets, 35.5×10^4 / μ L; erythrocyte sedimentation rate, 123 mm/h; C-reactive protein, 2.81 mg/dL; rheumatoid factor, 469.8 IU/mL; 50% haemolytic unit of complement, 61.9 U/mL; ferritin, 114 ng/mL; anti-nuclear antibody, <80 times the normal; matrix metalloproteinase-3 (MMP-3), 195 ng/mL; anti-cyclic citrullinated peptide antibody, 293 U/mL; immunoglobulin G, 830 mg/dL; immunoglobulin A, 188 mg/dL; immunoglobulin M, 411 mg/dL; immunoglobulin D, 10.7 mg/dL; interleukin-6, 113 pg/mL; soluble interleukin-2 receptor, 812 U/mL; and tumour necrosis factor- α , 1.4 pg/mL. The prototypes of the HLA allele were HLA-A*24:31, B*71:51, and DRB1*04:14. She complained of pain in her neck, both hands, and her wrists. Magnetic resonance imaging (MRI) revealed irregular patterns of the dens, bilateral carps, and the distal radius as well as synovial inflammation with fibrosis that contributed to the low signal intensity on the T1-weighted images and the high signal intensity on the T2-weighted images. Accordingly, the patient was diagnosed with inflammatory arthropathies. She was treated with methotrexate 5 mg/m²/week (Japanese initial dose), ibuprofen 10 mg/kg/day, and prednisolone 2 mg/kg/day; however, MRI showed more extensive synovial inflammation in the radius after 2 months because the methotrexate dose was extremely insufficient to manage her inflammation. Increas-

ing the dose of methotrexate to 14 mg/m²/week and ibuprofen to 20 mg/kg resolved her pain, but her movement was limited to walking with assistance. High dose methotrexate for a year did not decrease the limitations of her ankle joints; thus, tocilizumab was added to the methotrexate. After the tocilizumab (8 mg/kg/dose) was initiated, the joint limitation were resolved without any side effects, and the level of MMP-3 decreased by 53.7 ng/mL. However, she occasionally had pain in her wrists and right ankle; the ultrasound examination showed increased blood flow to the lunate bone and that the synovium of the right lateral malleolus had thickened. After 14 months of treatment with tocilizumab and one week of wash-out, the treatment was changed to adalimumab 40 mg (1.1 mg/kg/dose) every 2 weeks; she was free of any pain, stiffness, or recurrence just 2 months after its introduction. The level of MMP-3 decreased by 39.0 ng/mL, and the ultrasound examination showed no thickened synovium or increased blood flow.

This patient had also been treated for NS. Immunosuppressant treatment can potentially improve the pain in inflammatory arthropathies; however, she developed joint pain when the immunosuppressant was slowly tapered. Some studies have reported an association between chromosome 18 and immunocompetency; haplo-insufficiency of the 18q22.3-q23 gene region might cause the immunoglobulin A deficiency phenotype (2), and chromosome 18 has a locus that is responsible for the regulation of both Th1 and Th2 cytokine production (3). Moreover, single nucleotide polymorphisms have been

Table I. Clinical and genetic profiles, and treatments for reported patients with abnormal chromosome 18 and chronic arthritis.

Case	Age/sex	Breakpoint	Arthritis type	Treatment	Response
Petty 1987	11 years boy	Ring18	Oligoarticular	Aspirin Physical therapy	Complete response
Petty 1987	5.5 years girl	Del (18) (q21.2-22)	Oligoarticular	Aspirin	Complete response
Fujii 1988	13 years girl	Del (18) (q22-qter)	Polyarticular	Aspirin Indomethacin Sulindac	Complete response
Hansen 1994	4 years boy	Del (18) (q22-qter)	Oligoarticular	Acetylsalicylic acid Physical therapy Triamcinolone hexacetonide Naproxen, Auranofin Hydroxychloroquine	Partial response
Rosen 2004	8 years girl	Del (18) (q22-qter)	Oligoarticular	Naproxen	Complete response
Salavoura 2007	5 years girl	Telomere del 18q	Polyarticular	Methotrexate (15 mg/kg/week) Aspirin, Prednisolone	Unknown
Safi 2012	7 years girl	Del (18) (q22-qter)	Polyarticular	Methotrexate (0.6 mg/kg/week) Aspirin, Prednisolone	Complete response
Current	11 years girl	Del (18) (q22-qter)	Polyarticular	Methotrexate (14 mg/m ² /week) Ibuprofen, Prednisolone Tocilizumab, Adalimumab	Complete response

Del: deletion; p and q: short and long chromosome arms; ter: terminal.

associated with rheumatoid arthritis (4). Up to now, 7 patients with chromosome 18 abnormalities and chronic arthritis have been reported (5-10); the current patient was the eighth case (Table I). Although the arthritis in these patients might be juvenile idiopathic arthritis (JIA), it was not possible to discern whether the arthritis was secondary to the chromosome abnormality or the co-occurrence of JIA and the manifestations of the 18q abnormalities. The arthritis conditions in these patients were not considered to be JIA but chronic arthritis, because the latter could not be excluded. A meta-analysis of a genome scan revealed that 18q21 was associated with rheumatoid arthritis (4), whereas the breaking point of the chromosome in 5 of 7 patients was 18q22. Arthritis may be caused by points which have not been revealed. In this patient's case, high-dose methotrexate (14 mg/m²/week) failed to cure joint pain, whereas tocilizumab and adalimumab were successful in eliminating pain, resolving the limited joint mobility, and preventing the progression of bone destruction without adverse effects such as severe infection, myocardial damage, or dyslipidemia. The current case demonstrated that biological treatment can be effective for chronic arthritis in a patient with 18q-

syndrome. Our case may also support the association between chromosome 18 and chronic arthritis.

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