A Mutation in the IL-2 Receptor γ Chain Gene Associated with X-linked Severe Combined Immunodeficiency Accompanying Opisthotonus

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Severe combined immunodeficiency (SCID) is an inherited disease with profoundly defective T cells, B cells, and NK cells. X-linked severe combined immunodeficiency (X-SCID) is its most common form. In this report, we describe a 4-month old male with X-SCID who also showed opisthotonic posturing. Opisthotonus represents abnormal motor posturing and is defined as the posturing, in which the neck and back are arched posteriorly. The patient was referred to our hospital with liver dysfunction, respiratory distress, anal abscess, poor feeding and wasting; the patient appeared to suffer from severe and persistent infections. In fact, circulating T cells were not detectable, despite that the number of B cells was maintained in the normal ranges. Diagnosis of X-SCID was established by DNA analysis of the interleukin (IL)-2 receptor γ chain gene; namely, we detected the novel mutation within exon 2 (221 C→A), which leads to the substitution of tyrosine codon for stop codon (Y69stop). Computed tomography of the brain revealed mild atrophy, but no hemorrhage and no malformation. There were no pathological findings in the cerebrospinal fluid. Thus, the cause of opisthotonic posturing remains unknown. The patient died due to severe infection at the age of 7 months. It remains to be investigated to clarify the relationship between the mutation and clinical manifestations. In conclusion, we have identified the novel mutation in the IL-2 receptor γ chain gene, which is associated with X-SCID. Furthermore, this is the first report that describes the patient with X-SCID accompanying opisthotonus. ——— X-SCID; opisthotonic posturing; point mutation; RT-PCR; infant.

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Severe combined immunodeficiency (SCID) is an inherited disease with profoundly defective T cells, B cells, and NK cells. X-linked severe combined immunodeficiency (X-SCID) is the most common form, and accounts for approximately half of the patients with SCID (Fisher and Notarangelo 2004). X-SCID gene was mapped to Xq13.1, and mutations of the interleukin (IL)-2 receptor γ chain have been recognized to be the cause of the disorder (Noguchi et al. 1993b). The γ chain, initially identified as a third subunit of the IL-2 receptor (Takeshita et al. 1992; Kumaki et al. 1993), was subsequently found to be a common component of the IL-4, IL-7, IL-9, and IL-15 receptors (Kondo et al. 1993; Noguchi et al. 1993a; Russell et al. 1993; Kondo et al. 1994; Giri et al. 1994). Therefore, a mutation in the common γ chain gene results in a marked reduction in the number of mature T cells and NK cells. In addition, a severe humoral deficiency is seen due to the defective T cell response, although B cells are usually present in normal numbers.

Patients with X-SCID have severe and persistent infections, such as pneumonia and diarrhea, leading to failure to thrive (Stephan et al. 1993), usually die early in life unless treated by bone marrow transplantation (Buckley et al. 1997). Here, we describe a 4-month old male with X-SCID, who showed opisthotonic posturing and carried a novel mutation in exon 2 of the IL-2 receptor γ chain gene. To the best of our knowledge, this is the first report that describes the patient with X-SCID complicating opisthotonus.

Patient and Clinical Findings

The patient, a 4-month-old male, was referred to our hospital with liver dysfunction, respiratory distress, anal abscess, poor feeding and wasting. His weight was 5680 g, and the height was 63 cm. The patient was born after a normal pregnancy and delivery. His birth weight was 2785 g, and the neonatal period was normal. In his family history, two maternal brothers died in early infancy due to pneumonia. Additional details are unknown.

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Fig. 1. The patient with opisthotonic posturing

When the patient was 2 months old, he was admitted to another hospital for intractable diarrhea and poor feeding for 1 week.

When he was referred to our hospital, he showed opisthotonic posturing (Fig. 1). He was unable to hold up his head, and lay in a totally opisthotonic posture, but he could suck a bottle and smile at the appearance of his mother. However, clinical examination did not reveal any muscle weakness. Computed tomography (CT) of the brain revealed mild atrophy. Radiological studies of the cervical spine revealed considerable reduction not only of flexion, but also of extension of the neck. Cerebrospinal findings were normal, and the infection with herpes virus, cytomegalovirus or enterovirus was negative, as judged with polymerase chain reaction (PCR).

In his peripheral blood, there were no detectable circulating T cells, although the number of B cells was normal. The responsiveness of the lymphocytes to phytohemagglutinin and concanavalin A were markedly reduced.

The patient's family history, clinical course, and results of his laboratory data indicated a congenital immunodeficiency. After informed consent was obtained from the parent, DNA analysis using peripheral blood mononuclear cells (PBMC) of patient was performed. Methods for cDNA preparation and sequence analysis were described elsewhere (Kumaki et al. 1995). The PCR primer pair used to isolate the entire coding region of the γ chain gene and PCR conditions were the same as previously reported (Kumaki et al. 1995). The PCR products were purified by gel filtration and subjected to direct sequencing using the ABI Taq DyeDeoxy Terminator Cycle Sequencing kit (Perkin-Elmer Corp., Foster City, CA). Both strands were sequenced. The results were confirmed by sequence analysis of genomic DNA.

We detected the novel mutation within exon 2 (221 C $\rightarrow$ A), leading to the substitution of tyrosine codon for stop codon (Y69stop) (Fig. 2). Diagnosis of X-SCID was made by DNA analysis of the IL-2 receptor γ chain gene.

The patient was transferred to another hospital for bone marrow transplantation; however, he died due to severe infection before transplantation at the age of 7 months.

Fig. 2. Sequence analysis showing a nonsense mutation of the IL-2 receptor γ chain gene. Shown is the genomic sequence encompassing a point mutation (C to A) in exon 2 of the γ chain gene.

Arrow indicates the C-to-A transversion.

Discussion

The patient showed opisthotonic posturing. Abnormal motor posturing, classified as decorticate, decerebrate and opisthotonic posturing, is characterized by generalized extension of the trunk and lower limbs with increased muscular tone (Plum and Posner 1972). Decorticate posturing is defined as semi-flexion, adduction and internal rotation at the shoulders and semi-flexion or flexion at the elbows. Decerebrate posturing is defined as extension of upper limbs, adduction and internal rotation of the shoulders, with pronation of the forearms. Opisthotonic posturing is defined as abnormal motor posturing, in which the neck and back are arched posteriorly (Brown et al. 1973). There are a large number of underlying disorders, which may result in abnormal posturing, such as intracranial hemorrhage (subdural hemorrhage, intraventricular hemorrhage, arteriovenous malformation etc), infections (meningitis, encephalitis, abscess etc), hypoxia (cardiac arrest, neonatal hypoxia, drowning etc), metabolic disturbance (hypernatremic dehydration, alkalosis etc), birth trauma and congenital malformation (Brown et al. 1973). In the present case, brain CT

showed mild atrophy, but no hemorrhage and congenital malformation. The patient had no evidence for infections such as herpes virus, cytomegalovirus, and enterovirus, and had no metabolic disorders. The cause of opisthotonic posturing is unknown.

Kumaki et al. (2000) reported that 27 unrelated Japanese patients with X-SCID were examined in terms of their genetic mutations and expression of the IL-2 receptor γ chain. Among the 25 patients examined, 23 different mutations were identified in the IL-2 receptor γ chain gene. Overall, 84% of patients lacked the expression of the γ chain, leading to a diagnosis of X-SCID. In the present patient, a C-to-A point mutation at nucleotide position 221 resulted in substitution of tyrosine for stop codon.

To date, 147 unique mutations in the IL-2 receptor γ chain gene, associated with X-SCID, have been reported in the database at the website <http://nhgri.nih.gov/DIR/GMBB/SCID/IL2RGbase.html>. Mutations have been identified throughout all eight exons of the γ chain gene, including missense mutations, nonsense mutations, and splicing defects that give rise to aberrant transcripts. However, there are no reports that describe X-SCID patients complicating opisthotonic posturing.

In conclusion, we have identified the novel mutation of the IL-2 receptor γ chain gene that is associated with X-SCID accompanying opisthotonus. Further analyses of mutant γ chains obtained from X-SCID patients are needed to clarify the relationship between mutations and clinical manifestations.

References

- Brown, J.K., Ingram, T.T.S. & Seshia, S.S. (1973) Patterns of decerebration in infants and children: defects in homeostasis and sequelae. *J. Neurol. Neurosurg. Psychiatry*, **36**, 431-444.
- Buckley, R.H., Schiff, R.I., Schiff, S.E., Markert, M.L., Williams, L.W., Harville, T.O., Roberts, J.L. & Puck, J.M. (1997) Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. *J. Pediatr.*, **130**, 378-387.
- Fischer, A. & Notarangelo, L.D. (2004) Combined immunodeficiencies. *Immunological disorders in infants and children*, 5th ed., edited by Stiehm, E.R., Ochs, H.D. & Winkelstein, J.A. Elsevier Saunders, Philadelphia, Pennsylvania, pp. 447-479.
- Giri, J.G., Ahdieh, M., Eisenman, J., Shanebeck, K., Grabstein, K., Kumaki, S., Namen, A., Park, L.S., Cosman, D. & Anderson, D. (1994) Utilization of the beta and gamma chains of the IL-2 receptor by the novel cytokine IL-15. *EMBO J.*, **13**, 2822-2830.
- Kondo, M., Takeshita, T., Higuchi, M., Nakamura, M., Sudo, T., Nishikawa, S. & Sugamura, K. (1994) Functional participation of the IL-2 receptor gamma chain in IL-7 receptor complexes. *Science*, **263**, 1453-1454.
- Kondo, M., Takeshita, T., Ishii, N., Nakamura, M., Watanabe, S., Arai, K. & Sugamura, K. (1993) Sharing of the interleukin-2 (IL-2) receptor gamma chain between receptors for IL-2 and IL-4. *Science*, **262**, 1874-1877.
- Kumaki, S., Ishii, N., Minegishi, M., Ohashi, Y., Hakozaki, I., Nonoyama, S., Imai, K., Morio, T., Tsuge, I., Sakiyama, Y., Miyanoshita, A., Miura, J., Mayumi, M., Heike, T., Katamura, K., Takada, H., Izumi, I., Kamizono, J., Hibi, S., Sasaki, H., Kimura, M., Kikuta, A., Date, Y., Sako, M., Tanaka, H., Sano, K., Sugamura, K. & Tsuchiya, S. (2000) Characterization of the γ c chain among 27 unrelated Japanese patients with X-linked severe combined immunodeficiency (X-SCID). *Hum. Genet.*, **107**, 406-408.
- Kumaki, S., Kondo, M., Takeshita, T., Asao, H., Nakamura, M. & Sugamura, K. (1993) Cloning of the mouse interleukin 2 receptor gamma chain: demonstration of functional differences between the mouse and human receptors. *Biochem. Biophys. Res. Commun.*, **193**, 356-363.
- Kumaki, S., Ochs, H.D., Timour, M., Schooley, K., Ahdieh, M., Hill, H., Sugamura, K., Anderson, D., Zhu, Q., Cosman, D. & Giri, J.G. (1995) Characterization of B-cell lines established from two X-linked severe combined immunodeficiency patients: interleukin-15 binds to the B cells but not internalized efficiently. *Blood*, **86**, 1428-1436.
- Noguchi, M., Nakamura, Y., Russell, S.M., Ziegler, S.F., Tsang, M., Cao, X. & Leonard, W.J. (1993a) Interleukin-2 receptor gamma chain: a functional component of the interleukin-7 receptor. *Science*, **262**, 1877-1880.
- Noguchi, M., Yi, H., Rosenblatt, H.M., Filipovich, A.H., Adelstein, S., Modi, W.S., McBride, O.W. & Leonard, W.J. (1993b) Interleukin-2 receptor γ chain mutation results in X-linked severe combined immunodeficiency in humans. *Cell*, **73**, 147-157.
- Plum, F. & Posner, J.B. (1972) The diagnosis of stupor and coma. *Contemp. Neurol. Ser.*, **10**, 1-286.
- Russell, S.M., Keegan, A.D., Harada, N., Nakamura, Y., Noguchi, M., Leland, P., Friedmann, M.C., Miyajima, A., Puri, R.K., Paul, W.E. & Leonard, W.J. (1993) Interleukin-2 receptor gamma chain: a functional component of the interleukin-4 receptor. *Science*, **262**, 1880-1883.
- Stephan, J.L., Vlekoba, V., Le, Deist, F., Blanche, S., Donadieu, J., De Saint-Basile, G., Durandy, A., Griscelli, C. & Fischer, A. (1993) Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 patients. *J. Pediatr.*, **123**, 564-572.
- Takeshita, T., Asao, H., Ohtani, K., Ishii, N., Kumaki, S., Tanaka, N., Munakata, H., Nakamura, M. & Sugamura, K. (1992) Cloning of the gamma chain of the human IL-2 receptor. *Science*, **257**, 379-382.