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SHORT COMMUNICATIONS

Severe adverse reactions to Infliximab therapy are common in young children with inflammatory bowel disease

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Abstract

Since 2000 we have introduced 141 Infliximab infusions to 23 children with severe inflammatory bowel disease. A total of seven severe adverse reactions occurred in 26% (6 of 23) of the children. Four reactions were acute (anaphylaxis n = 2; allergic reaction n = 2) and 3/4 of these children were younger than 10 years of age. Two children developed an abscess and one child had septicaemia and brain lesions related to progressive multifocal leucoencephalopathy.

Conclusion: adverse reactions to Infliximab infusions are common. Young children seem to be prone to severe allergic reactions although they are on azathioprine and conventional glucocorticoid therapy.

Infliximab, a monoclonal human-murine chimeric antibody to tumour necrosis factor-α (TNF-α) has been a breakthrough in the therapy of severe inflammatory bowel disease (IBD) refractory to conventional treatment. Infliximab blocks both soluble and membrane-bound TNF-α thus reducing inflammation (1). In children with refractory Crohn's disease, Infliximab therapy benefits the majority but about one third of treated patients show no improvement (2). In those responsive, the effect of Infliximab is often transitory (3). Side effects are relatively common, ranging from 5% to 17% of paediatric patients (2–6) and hamper the use of this therapy in children.

We have used Infliximab infusions in our paediatric patients since year 2000 for treatment of severe Crohn's disease that is not responding to conventional treatment regimens with steroids, azathioprine, antibiotics or enteral feeding. We did a retrospective chart review in all our patients with IBD who had received one or more Infliximab infusions in Helsinki and Tampere university hospital that comprise the two major referral centres for the diagnostics and treatment of paediatric IBD with catchment area of 56% of the paediatric population in Finland (a population base of 2.9 million). We traced 23 children, 22 of them with Crohn's disease and 1 child with ulcerative colitis treated with Infliximab infusion.

The demographic data of the patients are presented in Table 1. Infliximab infusions were initiated with a regular dose of 5 mg/kg. Five children received infusion with lower dose of 3–4 mg/kg. The majority of patients were on azathioprine and on oral glucocorticoids (Prednisolone or Budesonide) at the time of their first infusion (Table 1).

The 23 children with IBD treated with Infliximab infusions received a total of 141 infusions during this 5-year period. Four children experienced a minor reaction (4 of 23; 17%; children no. 4–7 in Table 2) during infusion necessitating no medication. Five children (5 of 23; 22%) did not respond to the Infliximab infusion, and the therapy was discontinued soon. Six children had received 10 or more Infliximab infusions. The only child with UC experienced no adverse events during her seven Infliximab infusions.

Major adverse reactions occurred in 6 of 23 children (26%; children no. 1–4 and 8–9 in Table 2). The time interval to the preceding infusion was within 1–2 months in all children with an adverse reaction.

Severe acute reactions occurred in 4 children (4 of 23; 17%; children no. 1–3 and 8 in Table 2). The majority of these children were younger than 10 years of age (3 of 4; number of children ≤10 years of age in this study n = 3). All these children were on glucocorticoid therapy (Prednisolone 20 mg daily n = 1; 2.5 mg Prednisolone on alternate days n = 1; Budesonide 9 mg and 6 mg on alternate days n = 1; Budesonide 6 mg daily n = 1;) and two of these children were on azathioprine. The youngest child (2.7 years of age) had received 20 mg Prednisolone (2 mg/kg) 2–3 hour prior to infusion and she had been on azathioprine for 6 months.

The 2-year-old child, who had a severe acute reaction after her second infusion, had two abscesses necessitating revision under anaesthesia within 1 week after her first infusion. There was no bacterial growth. An 11-year-old boy had an abscess within 4 weeks in his buttock that needed surgical revision. None of the 23 children developed an opportunistic infection or tuberculosis.

The most severe adverse reactions occurred in a 16-year-old boy who after the second Infliximab infusion developed severe septicaemia necessitating treatment in the intensive care unit. His clinical condition deteriorated, and 3 months later, MRI examination revealed changes related to progressive multifocal leucoenkephalopathy. There were no specific findings in biopsy and no infective agent was found. The neurological symptoms vanished and brain lesions disappeared

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Table 1 Demographic data on the paediatric patients with inflammatory bowel disease treated with Infliximab infusions at our hospitals

Number of patients	n = 23
Age (median, range)	14 years (2.7–18)
Sex (male/female)	10/13
Diagnosis	Crohn's disease n = 22 Ulcerative colitis n =1
Therapy at the time of first infusion (no. of patients)	
Mesalazine	n = 13
Azathioprine	n = 17
Oral glucocortioid	n = 18
Antibiotics	n = 5

completely within 6 months after discontinuation of the Infliximab therapy.

Acute infusion reactions during Infliximab infusion are relatively common, the frequency estimated from 4–5% (5,7) to 12–16% (2,6,8) and 23% (8) per number of patients treated. A total of 35% of our patients experienced an acute reaction during Infliximab infusion, and 50% of these acute events were anaphylaxis or severe urticaria, the majority of them (3 of 4) occurring in children under 10 years of age. It is remarkable that each child under 10 years of age experienced an acute adverse reaction. To our knowledge, there are no reports addressing the safety of Infliximab infusion in the very young children. In paediatric studies on Infliximab, the age of children has been over 10 years (2,8,10). In the large recent multi-centre study in paediatric patients (6), severe reactions were rare (anaphylaxis 2 of 243) but the age of the patients with adverse reactions was not commented.

Infliximab is a recombinant chimeric antibody including antigens originating from mouse. Infusion reactions are considered secondary to the formation of antibodies directed against Infliximab (11). In the study by Miele et al. (9), more than one third of the child patients developed human antichimeric antibodies (HACA) during the course of repeated infusions (9). To avoid the development of HACA, azathioprine on regular doses may show a preventive effect and is thus recommended in patients receiving Infliximab (11). The majority of allergic reactions occur during the first four infusions (6,10). Among our patients, the most severe anaphylaxis occurred during the seventh infusion (a girl of 6 years of age). It is remarkable that anaphylaxis and severe urticaria occurred although the children were concomitantly on glucocorticoids. One child had received a Prednisolone dose of 2 mg/kg 2–3 h before infusion, but this did not prevent the development of severe urticaria during infusion. This particular patient had received immunosuppressive medication for more than 4 months, a time interval considered to reduce the risk for infusions reactions (10). Others have reported that immunosuppressive therapy does not exclude severe infusion reactions (3,6).

The incidence of serious infections in all patients treated with Infliximab is estimated to reach 8% in adults (7). In this study, 8.7% of the children (2 children) developed sterile abscesses within 2–4 weeks of the infusion and 1 child presented with severe septicaemia. No other infections were detected.

Infliximab may cause neural changes suggestive of multiple sclerosis or other demyelinating processes as described in a 19-year-old girl with Crohn's disease. Fortunately, these changes seem to recover after the Infliximab therapy is discontinued (12). Our patient was a 16-year-old boy with extremely aggressive Crohn's disease not responding to any of the treatments. His brain lesions related to progressive multifocal leucoenkephalopathy with corresponding neural

Table 2 Adverse reactions to Infliximab infusions in 23 children with inflammatory bowel disease

No.	Age (years)	Sex	Diagnosis	Therapy at the time of adverse reaction	No. of infusions (5 mg/kg)	Adverse reactions
1	2.7	Female	Crohn	Prednisolone 20 mg	2	Abscess at the infusion site and in the leg (2 weeks after 1st infusion)
				Azathioprine 12.5 mg × 2		Severe urticaria (during 2nd infusion)
2	6.5	Female	Crohn	Mesalazine 500 mg × 2 Budesonide 6 mg*	7	Anaphylaxis (during 7th infusion)
3	9	Male	Crohn	Mesalazine 500 mg × 3 Azathioprine 25 mg × 2 Budesonide 6 mg	3 3	Severe urticaria (during 3rd infusion)
4	11	Male	Crohn	Prednisolone 20/5 mg on alternate days	4**	Dizziness and nausea (2nd infusion) Abscess in the buttock (4 weeks after 2nd infusion)
5	12	Female	Crohn	Azathioprine 25 mg × 2	12	Flu mild (1st infusion) Vertigo (2nd infusion) tiredness (3rd infusion)
6	13	Male	Crohn	Azathioprine 25 mg × 2 Mesalazine 500 mg × 3 Budesonide 9 mg/week	12	Low blood pressure (3rd infusion) with no subjective symptoms
7	14	Female	Crohn	Prednisolone 20 mg × 1 Azathioprine 50 mg × 2 Mesalazine 500 mg × 6	1	Difficulties to breath, chest pain (1st infusion)
8	14	Female	Crohn	Prednisolone 2.5 mg on alternate days Azathioprine 25 mg + 12.5 mg	5	Anaphylaxis (during 5th infusion)
9	16	Male	Crohn	Azathioprine 50 mg × 2	5	Severe septicaemia (after 2nd infusion) Multifocal leucoencephalopathy

*Azathioprine not tolerated.

**Infliximab dose 3.5 mg/kg.

symptoms developed within 3 months after introduction of Infliximab therapy. Within 6 months after discontinuation of Infliximab therapy, his brain MRI was completely normal and he presented no neurological symptoms.

In conclusion, adverse reactions to Infliximab infusions are common. The majority of reactions are mild and enable continuation of the therapy. However, young children seem to be prone to severe adverse reactions although they are on azathioprine and conventional glucocorticoid therapy. It is advisable that this therapy should be limited to specialized paediatric centres.

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Identification of a novel compound heterozygote SCO2 mutation in cytochrome c oxidase deficient fatal infantile cardioencephalomyopathy

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Abstract

Fatal infantile cardioencephalomyopathy (OMIM No. 604377) is a disorder of the mitochondrial respiratory chain and is characterised by neonatal progressive muscular hypotonia and cardiomyopathy because of severe Cytochrome c oxidase deficiency. Here we report a novel mutation in the Cytochrome c oxidase assembly gene SCO2 in an infant with fatal infantile cardioencephalomyopathy despite normal initial metabolic screening.

Conclusion: In newborns with unexplained muscular hypotonia and cardiomyopathy genetic testing of mitochondrial respiratory chain disorders might be helpful to establish a final diagnosis and guide treatment decisions.

Cytochrome c oxidase (COX) is a multimeric enzyme of the inner mitochondrial membrane and catalyses the reduction of molecular oxygen by reduced cytochrome c, the terminal step in the respiratory chain. The incidence of respiratory chain disorders is 1 in 10 000 newborns of which isolated COX deficiency constitutes around 1/3 (1). COX deficiency presents with a wide range of multi-system symptoms. Several pathogenic mutations have been reported in the three mitochondrial-encoded COX subunits and in genes involved in the assembly of the COX holoenzyme (2).

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The human *SCO2* gene (GenBank AF177385) encodes a mitochondrial protein that has been shown to chaperone copper to the catalytic Cu_A site of COX (3). Pathogenic mutations in *SCO2* have been associated with *fatal infantile cardioencephalomyopathy* (OMIM No. 604377), a disorder with progressive muscular hypotonia, hypertrophic cardiomyopathy and encephalopathy (4). Here we report a novel *SCO2* mutation in a 4-month-old girl with *fatal infantile cardioencephalomyopathy* due to COX deficiency.

After an uneventful pregnancy, the child was born at term without complications. At the age of 4 weeks, the girl presented with generalized muscular hypotonia and tachydyspnea. Echocardiography at this time showed severe hypertrophic obstructive cardiomyopathy. Extensive metabolic screening of serum, urine and liquor including repeated determination of lactate levels at this time was normal. Despite the normal metabolic screening, a mitochondrial disorder was suspected on the basis of the clinical findings. Subsequent analysis of mitochondrial respiratory chain enzyme activity from a skeletal muscle biopsy showed a significantly decreased COX activity and supported the suspected diagnosis of *fatal infantile cardioencephalomyopathy* due to SCO2 deficiency.

Direct sequencing of the entire coding regions and flanking intron boundaries of the *SCO2* gene revealed two heterozygous single base pair mutations in exon 1 (Fig. 1). The first mutation was a change of guanine to adenine at position 1541 (1541G>A) leading to an amino acid substitution (E140K). This mutation has been identified previously in all patients with SCO2 deficiency either in the homozygote or compound heterozygote state, and is therefore called 'common mutation'. The second mutation changed thymine 1602 to guanine (1602T>G), leading to a yet unknown amino acid exchange (V160G). The mutation is located in a conserved region of the *SCO2* gene, although this particular amino acid residue has changed during phylogeny (isoleucine in yeast vs. valine in human). *SCO2* gene analysis of the parents showed inheritance with the heterozygote 1541G>A mutation in the mother and the 1602T>G mutation in the father. Neither the 1541G>A nor the 1602T>G mutation was detected in 100 healthy control individuals.

The further clinical course was complicated by persistent severe neutropenia. Bone marrow histopathology revealed defective maturation of myeloid progenitor cells (promyelocyte arrest) similar to the findings in inherited infantile agranulocytosis (Kostmann syndrome). Consecutively, the patient developed progressive neurological symptoms including uncontrolable seizures and finally died of septic shock in neutropenia due to *Serratia marcescens* sepsis at the age of 4 months.

Among the previously described patients with mutations of the *SCO2* gene, clinical phenotypes vary considerably depending on the genotype (5). Patients homozygote for the 1541G>A mutation have been found to show less COX deficiency and present with a milder clinical phenotype than patients with compound heterozygote mutations (6). In the analysis reported here, the newly identified point mutation 1602T>G occurred in close proximity to the 1541G>A mutation, in a conserved region which has been shown to be functionally critical for biogenesis of the holoenzyme (7) and lead to a rapidly progressive disease phenotype compared to other reported patients with *SC02* mutations (5,6). This emphasizes that a severe disease phenotype can occur despite a relatively conserved amino acid exchange (valine160 is replaced by glycine which is also neutral and non-polar) in a region with predominately mild disease phenotype.

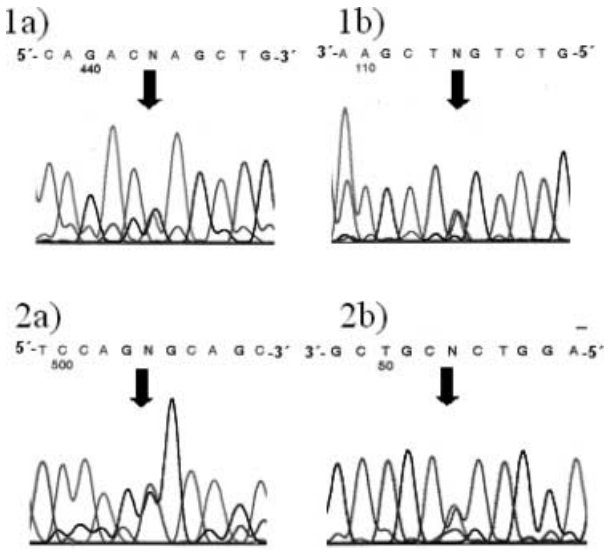

Figure 1 Direct sequencing of the SCO2 gene revealed compound heterozygosity for a G1541A (1a + 1b) and T1602G (2a + 2b) mutation in both strands.

As SCO2 mutations result in impaired copper incorporation in the COX holoenzyme, it has been hypothesized that alimentary supplementation might re-establish COX activity. Freisinger et al. (6) reported on two patients with homozygous SCO2 deficiency in which copper-histidine supplementation seemed to improve cardiac function and defer clinical progression. However, after administering copper-histidine to the patient reported here on the same protocol, there was no therapeutic benefit. This might be due to a more severe genotype, overruling potential beneficial effects of copper supplementation.

In conclusion, we identified a novel *SCO2* gene mutation in an infant with rapid progressive *fatal infantile cardioencephalomyopathy* despite normal initial metabolic screening. This points out the importance of genetic testing in infants with muscular hypotonia and cardiomyopathy. Further studies are necessary to gain deeper insights in the genotype–phenotype relationship of SCO2 mutations and to further evaluate potential benefits of copper-histidine therapy in these patients.

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Is there a connection between severe cerebral palsy and increased gluten sensitivity?

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Keywords
Antigliadin antibodies (AGA), Celiac disease, Cerebral palsy (cerebral pareses), Feeding difficulties

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Abstract

In nine children with severe cerebral palsy (CP), feeding difficulties and poor development of weight and height, laboratory markers for metabolic and enteral dysfunction were studied.

Conclusion: Four of the nine patients with CP had increased levels of antigliadin antibodies AGA (IgA), a finding which calls for further studies concerning the possible connection between increased celiac markers and CP.

Malnourishment is often seen in children with severe neurological diseases, including cerebral palsy (CP) (1,2). Generally, this has been regarded as a natural effect of the disease and no specific measures have been taken. Weight and height have only sparsely been measured in these children, although it is well known that long periods of starvation can affect the neurodevelopment (3–6). The spasticity in children with severe CP increases their need of nutrients. Apart from the spasticity, however, several additional factors can worsen the nutritional status, for instance swallowing difficulties, vomiting, gastroesophageal reflux with or without aspiration, delayed stomach emptying, constipation and refusal to eat on account of constant pain. The insufficient calorie intake in these children is an increasingly recognised problem and more active efforts to improve this situation are now being made (7–12).

Much is still unknown, however, about the food intake and nutritional status in these children. One clinical observation that has been made occasionally in children with severe CP and slow growth is that they have an increased level of antigliadin antibodies (AGA). What this means is not clear. Our aim was, therefore, to conduct a small pilot study to investigate laboratory markers for metabolic and enteral dysfunction in children with severe CP.

The study was comprised of nine children with severe CP from a county (Södermanland, 250 000 inhabitants) in the middle of Sweden. In the county there are about 100 children with CP with an incidence rate of 2.1/1000 newborn children. Approximately 25% of the children with CP are in need of nutritional support and the nine children in the study were chosen because they had the most feeding problems in the cohort of children with CP. Five of the nine children included in the study had tetraplegia, three dyskinesia and one hemiplegia. All nine showed a poor development of weight and height. The children were between 1.5 and 18 years of age at the time of the study. In addition to CP, all patients had a diagnosis of mental retardation and six patients had epilepsy (see Table 1).

In all children, test results were normal or near normal for haemoglobin (Hb), hematocrit (EVF) albumin, creative protein (CRP), asparate transaminase (AST), alanine aminotransferase (ALT), transferrin, ferritin, Immunoglublin G (IgG), IgA and IgM, sodium, potassium, thyroid-stimulating harmone (TSH) thyroxine, and U-sodium.

Abnormal laboratory findings are presented in Table 1. Four of the nine patients had increased levels of AGA (IgA) and two out of five tested had elevated serum values for

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Table 1 Abnormal laboratory findings among nine patients with cerebral palsy

Patient number	1	2	3	4	5	6	7	8	9
Age (years)	10	3	10	6	18	1.5	3	2	14
S-Fe (10–33)		7.5	6.9			2.9			8.2
Creatinine (47–100)		25	35	38		35	29		
Total IgE (<20)	24	103			42		76		
B_{12} (150–700)			1290	882					
Gliadin IgA (<20)	24	53	64	73					
Occult blood test				pos	pos				pos

All patients had mental retardation. Patients 2, 3, 4, 5 and 6 had epilepsy.

vitamin B_{12}. Small bowel biopsies were performed in two patients and showed villous atrophy in one of them. Four out of seven had elevated total IgE values and four out of eight had low S-Fe. Osophageal pH was measured in seven patients and was abnormal in six of them indicating gastroesophageal reflux. One patient had a positive serological test for *Helicobacter pylori*. All patients with abnormal findings were treated medically or surgically.

The major finding in this small pilot study was that a relatively large number of children with CP also had increased levels of AGA (IgA). This observation raises the question of whether this is merely a coincidence, in a study of such a small size, or whether this group might have an increased risk of developing celiac disease. If there is no such association, it may be speculated that the increased values might be a result of a damaged intestinal mucosa due to other factors such as malnutrition, disturbed bacterial ecology or neurological dysfunction of the gut. It might also be due to an abnormal immunological response in these children.

A possible association between increased gluten antibodies and CP could be explained not only by a cross-reaction between gluten antibodies and neural tissue giving brain lesions, but also by a true medical association.

Up to 20% of children with celiac disease have been shown to have a lesion in the white matter in the brain and it may be speculated whether this is caused by an extra-intestinal manifestation of an increased amount of AGA (13).

Also, malnourishment/undernutrition early in life affects the brain and the neurodevelopment (3–6). Therefore, malabsorption early in life caused by celiac disease could contribute to the brain lesions as well.

In adults with gluten ataxia who also have antibodies against the Purkinje cells, Hadjivassiliou et al. discuss the possibility of a cross-reaction between antibodies to gliadin and epitopes on the Purkinje cells. Also, cerebral atrophy could be found in these patients (14). As a possible explanation, it is suggested that there might be a cell-mediated inflammation compromising the blood–brain barrier, allowing entry of AGA into the CNS (15).

Although this issue is still speculative, other reports and our results call for further studies concerning the possible connection between increased AGA and CP. Is there a disorder of both the enteral and neuronal systems? And if there is a connection, can the neurodevelopment be improved by treatment with a gluten-free diet?

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