HEPATOENCEPHALOPATHY CAUSED BY *SENECIO JACOBAEA* INTOXICATION IN FIVE HORSES

Hepato-encefalopathie door Senecio jacobaea-vergiftiging bij vijf paarden

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ABSTRACT

Acute hepatoencephalopathy due to ingestion of *Senecio jacobaea* is described in five horses. Diagnosis was based on history, clinical findings, ultrasonography, laboratory results and postmortem examination. Blood analysis revealed decreased levels of urea and increased levels of ammonia, gamma-glutamyl transferase, bile acids and total bilirubin. As no specific treatment for pyrrolizidine alkaloid intoxication exists, therapy was mainly supportive. None of the five horses survived. Because of the poor prognosis, prevention of the disease, by means of pasture management and exclusion of these plants from hay or silage, is mandatory.

SAMENVATTING

In dit artikel worden vijf paarden beschreven die een fatale hepato-encefalopathie ontwikkelden als gevolg van opname van *Senecio jacobaea* (jakobskruiskruid). De diagnose werd gesteld aan de hand van de anamnese, de klinische symptomen, het bloedonderzoek, het echografisch onderzoek van de lever en de lijkschouwing. Bij bloedonderzoek vielen vooral het lage ureumgehalte en de sterk verhoogde gehaltes van ammoniak, gamma-glutamyltransferase, galzuren en totale bilirubine op. Aangezien geen specifieke therapie voor deze pyrrolizidinealkaloïde-intoxicatie bestaat, werd hoofdzakelijk symptomatisch behandeld met evenwel een fatale afloop bij alle patiënten. Wegens de slechte prognose van de aandoening zijn vooral preventieve maatregelen aangewezen. Deze omvatten een aangepast weidebeheer en het verhinderen van de aanwezigheid van deze planten in hooi of ingekuild gras.

INTRODUCTION

Poisoning of animals by pyrrolizidine alkaloids is well-documented and is the main cause of chronic liver damage in the horse (Olsman and van Oldruitenborgh-Oosterbaan, 2004). Pyrrolizidine alkaloids (PAs) are found in many plant species, especially in plants of the genus *Senecio*, with common ragwort (*Senecio jacobaea*) by far the most frequently implicated (Clarke *et al.,* 1981). Disease caused by *Senecio* is also known as "Walking disease" (USA), "Sirasyke" (Norway), "Dunsiekte" (South Africa) and "Winton disease" (New Zealand) (Grabner, 1990).

Fortunately, herbivores seldom eat mature plants (Fig. 1), but poisoning can occur when seedlings (Fig. 2) are grazed accidentally along with other forage or when there is a lack of other feed. Dried plants, which have only a minimal reduction in their alkaloid content, are more palatable and less easily avoided during eating, making them a particular risk when present in hay.

Although acute poisoning and death can already occur within a few days of feeding plants high in PAs, chronic poisoning is the most common form of PA intoxication. The latter only becomes apparent several weeks or months after the animals have eaten toxic quantities of PA-containing plants. Consequently, diagnosis may be difficult as the toxic plants may no longer be present in the pasture or feed by the time clinical signs become evident.

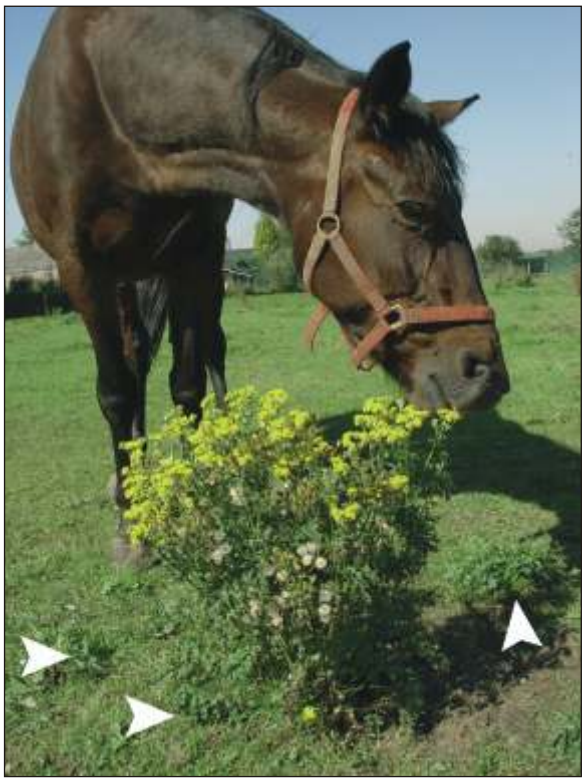

Figure 1. Seedlings (white arrow heads) and mature plants with yellow flowers in a horse's pasture.

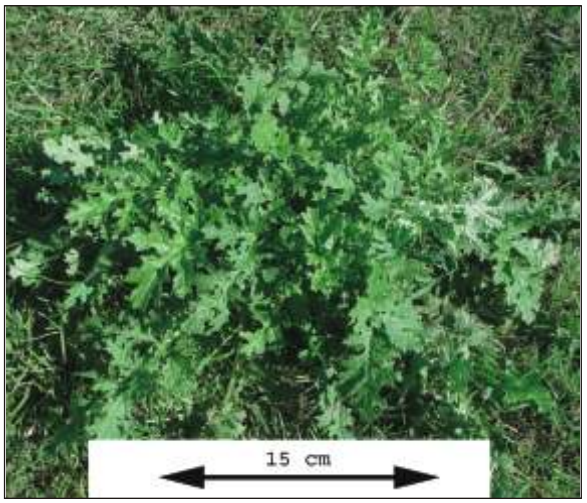

Figure 2. Seedlings remain as rosettes until maturity.

CASE DETAILS

History

Between May and August 2004 five horses (A - E) with clinical symptoms of hepatoencephalopathy were presented at the Faculty of Veterinary Medicine, Ghent University.

Clinical findings

Horse A, a fifteen-year-old Quarter Horse gelding was presented with ataxia, weakness, salivation and depression. Temperature, heart rate and circulation were normal. The horse was kept in a pasture overgrown with *Senecio jacobaea*. Hepatic ultrasound indicated a generalized hyperechogenicity of the liver parenchyma. Abdominal ultrasound showed fluid contents in the caecum and reduced motility of the small intestine.

Horse B, a fifteen-year-old Belgian Warmblood mare, showed severe nervous symptoms characterized by aggressive behavior, excitation, transpiration, salivation and trembling. The heart rate was 60 beats per minute (bpm) and the rectal temperature was 36.6 °C. The owner of the horse had found *Senecio* plants in the pasture. An ultrasonographic examination of thorax and abdomen showed no abnormalities. On rectal examination, dry feces were present in the rectum and no other abnormalities were detected except for a contracted spleen.

Horse C, an eighteen-year-old Shetland pony mare, was presented because of weight loss, weakness, dehydration and dysphagia after she had been dewormed two days before. The heart rate was increased to 76 bpm and the rectal temperature was 37.8°C. The owners reported that *Senecio jacobaea* had been found in the pasture and that another pony had died 2 months before, presenting similar symptoms. Abdominal ultrasound demonstrated fluid contents in the caecum and colon.

Horse D, an eleven-year-old Warmblood gelding, and horse E, a twelve-year-old Fjord mare, were presented because of a suspicion of intoxication by *Senecio Jacobaea* or pesticides used to combat *Senecio Jacobaea*. They were grazing in the same pasture that had been treated with dimethylamine-containing pesticides ten days before. Both horses were trembling, weak and had mild colic symptoms. The temperature of horse D was 37.9°C, and the heart rate was 44 bpm. Auscultation, ultrasonography and rectal examination showed no abnormalities. Horse E was lethargic, had a heart rate of 80 bpm and a rectal temperature of 38.3°C. The mucous membranes were congested. On rectal examination, a mild caecal tympany was found.

Laboratory findings

On admission, blood samples were taken from all horses, the results of which are shown in Table 1. Mild to moderate increases in packed cell volume were seen in horses C and E. The most consistent abnormalities were decreased urea values and obvious increases

Table 1. Results of blood analysis of 5 horses with pyrrolizidine alkaloid toxicosis.

	Packed cell volume %	Total bilirubin µmol/l	γGT IU/l	Ammonia µg/dl	Bile acids µmol/l	AP IU/l	AST IU/l	Urea mmol/l
Reference values	**35-45**	**17 - 51**	**< 30**	**13 - 108**	**< 15**	**71-508**	**127-427**	**4-8**
Horse A	40	130	129	115	55	503	681	3
Horse B	45	52	259	707	153	> 1500	583	2.8
Horse C	49	71	109	392	90	489	343	2.2
Horse D	39	125	119	467	69	588	488	<1.8
Horse E	56	178	88	559	65	443	608	1.9

in gamma-glutamyl transferase (γGT), ammonia and bile acids. The total bilirubin was markedly increased in 4 of the horses. The highest value, 178 µmol/l, was found in horse E and additional analysis showed it to be mainly indirect bilirubin.

The levels of alkaline phosphatase (AP) and aspartate aminotransferase (AST) were either normal or mildly increased.

Therapy

Differential diagnosis included (cholangio)hepatitis, heavy metal intoxication and PA poisoning. Because *Senecio jacobaea* plants were found in the pasture of these horses (Figures 1 and 2), PA poisoning was the most likely diagnosis. Treatment was mainly supportive. All horses received dextrose supplemented (5%) perfusion to correct dehydration and to maintain adequate tissue perfusion. Broad-spectrum antibiotics (ceftiofur (Excenel®), trimethroprim-sulfonamides (Borgal®) or enrofloxacine (Baytril®)) were given parenterally throughout the treatment period, while NSAIDs (Flunixine meglumine (Finadyne®)) were given for three to five days. All horses were offered a diet with high carbohydrate content and small quantities of easily digestible protein. Attempts were also made to reduce the intestinal absorption of neurotoxic molecules by administering paraffin oil via nasogastric intubation. In every horse, the temperature, heart rate and venous blood gas values were checked several times per day. Blood samples for liver enzymes were analyzed at regular intervals.

Temporary stabilization was obtained in horses A and B, though severe nervous symptoms recurred and necessitated euthanasia after 16 and 14 days, respectively. In horse C, the liver and blood values progressively normalized and the animal was discharged after 14 days. However, two weeks later the horse's condition suddenly deteriorated. Because the animal was presenting severe nervous symptoms, euthanasia was performed. Horses D and E showed no improvement at all and were euthanized 6 and 2 days after admission, respectively.

Postmortem findings

Horses B, D and E were examined postmortem. All livers were pale with a hard and irregular surface and showed macroscopic and microscopic evidence of fibrosis. Histological examination showed extensive portal liver fibrosis with a slight proliferation of the bile ducts. In the periportal area, a few binuclear hepatocytes and megalocytes could be found, as well as diffuse infiltration of neutrophils. In addition, focal zones of fatty degeneration were present. An accumulation of intracytoplasmatic pigment with a granular aspect was found in the hepatocytes at the level of the Kupffer cells.

The consistency of the liver of horse E was hard and the parenchyma was riddled with multiple yellow foci up to 3 mm in diameter. Histology revealed centrilobular and periportal fibrosis. The liver of horse D showed macroscopic evidence of liver fibrosis. However, due to postmortem degeneration, further analyses could not be performed.

DISCUSSION

Although pyrrolizidine alkaloid (PA) intoxication in animals has been known for a long time, it still remains a threat to horses and cattle because the effects of the toxin are often underestimated.

PAs are absorbed by the digestive tract and transported to the liver, where they are metabolized to pyrroles. These pyrroles cross-link double-stranded DNA and bind to proteins and nucleic acids within hepatocytes (Schmitz, 1998). The cross-linking of DNA has an antimitotic effect on hepatocytes, resulting in megalocyte formation. As the megalocytes die, these cells are replaced with fibrous tissue instead of normal hepatocytes. Finally, the liver fails due to hepatocellular death and fibrosis (Schmitz, 1998; Cheeke, 1998).

While the liver is the primary organ affected, reactive metabolites may also damage the lungs, leading to cor pulmonale or right heart failure. Renal damage may result in megalocytosis of renal tubular epithelium and glomerulosclerosis (Jones *et al.,* 1997).

In horses and cattle, daily ingestion of *Senecio* plant material equivalent to 1% to 5% of their bodyweight causes hepatic disease within a few weeks (Talcott, 2003). Acute toxicosis occurs after ingestion of a large amount of toxic material and commonly produces centrilobular liver necrosis with hemorrhage. Clinically, those animals may show depression, coma and death as a result of severe liver damage.

Chronic PA poisoning, which is more common, is characterized by hepatocellular necrosis in the portal areas, megalocytosis, fibrosis, biliary hyperplasia and obstruction of hepatic veins (Schmitz, 1998). After a variable period of time (weeks to months), affected horses usually develop encephalopathy, a neurological syndrome with clinical signs of central nervous dysfunction, incoordination, uncharacteristic aggression, blindness and head pressing, as well as weight loss, diarrhea and icterus (Ford, 1973; Craig *et al.* 1930). This neurological syndrome is associated with the toxic effects of hyperammonemia, although other substances, including mercaptans, gamma-aminobutyric acid and short-chain fatty acids, are probably also involved in the pathogenesis of encephalopathy. Ammonia is produced in abundance in the intestinal tract, especially in the caecum and colon, by the bacterial degradation of luminal proteins, amino acids and endogenous urea. This ammonia diffuses into the portal circulation and is transported to the liver, where it should be converted to urea. Hepatic encephalopathy in part reflects the failure of this important detoxification process and is caused be extensive liver cell necrosis (Mair and Jones 1995).

While central nervous symptoms are the most obvious symptoms, other clinical signs such as colic, stomach impaction, abnormal intestinal motility and dysphagia are also commonly observed. Especially in cattle, secondary photosensitization can occur.

The diagnosis of PA toxicosis is based on clinical signs, history (access to pyrrolizidine containing plants), laboratory tests (signs of liver failure), ultrasonography and histological examination of the liver (megalocytosis, fibrosis). The demonstration of high amounts of PAs in blood or tissue of the patient would be a conclusive diagnostic method, but this test is not yet available.

The horses presented to the clinic showed central nervous symptoms and weakness or disturbances of the digestive tract which, together with the history of grazing in *Senecio jacobaea* contaminated pastures, required further investigation of liver function. A range of laboratory tests have been described as being useful for the diagnosis and prognosis of PA toxicosis in horses. Curran *et al.* (1996), Durham *et al* (2003c) and Amory *et al.* (2005) reported γGT activity to be a useful screening test for detecting subclinical and clinical liver disease in horses exposed to pyrrolizidine alkaloids. Alkaline phosphatase was also found to be useful, though it showed a lower sensitivity. High plasma levels of ammonia have been used to confirm a diagnosis of hepatoencephalopathy, although there seems to be a poor correlation between plasma ammonia levels and the severity of the symptoms in horses (Byars 1983; Divers 1993). The same authors suggested that the low concentrations of serum urea in association with liver failure reflected the reduced hepatic synthesis of urea from ammonia. McGorum *et al.* (1999) and West (1996), however, found no significant association between urea concentration and hepatoencephalopathy or hyperammonaemia in 40 cases of equine hepatopathy. Serum bile acids can also be used in the diagnosis of liver failure due to PA toxicosis, as mentioned by Pearson and Craig (1993) and Curran *et al*. (1996). Total and unconjugated bilirubin levels are other markers for liver damage, because the loss of a substantial percentage of the functional hepatocyte mass reduces the hepatic uptake and conjugation of bilirubin (Tennant and Hornbuckle 1980; Duncan and Prasse 1986).

In our five horses with liver damage due to PA toxicosis, the most pronounced alterations in blood parameters were urea, γGT, ammonia, and serum bile acids.

However, formulating a prognosis based on blood values remains difficult since a large variation in these values has been reported in *Senecio* intoxicated horses. Other tests, such as the determination of amino acid profiles, the measurement of bromosulphophtalein halfclearance time and liver biopsy, have been described in the literature, though they were not used in our cases.

Transabdominal ultrasonography was performed in all five horses. The fact that hyperechogenicity of the liver was detected in only one of the five horses implies that ultrasonography is not a sensitive method for the diagnosis of acute PA toxicosis. Durham *et al*. (2003b) found that horses with moderate hepatic fibrosis and severe biliary hyperplasia were significantly more likely to have ultrasonographic abnormalities than horses without such changes. Increased echogenicity has been reported previously in cases of hepatic fibrosis and lipidosis (Rantanen 1986; Divers *et al*. 1988).

Treatment of PA toxicosis is difficult and in most cases unrewarding. Therapy is based on supportive treatment until the liver has regenerated sufficiently to resume its functions. The regenerative capacity of the liver, however, is reduced by the antimitotic effect of PAs on hepatocytes, and the ensuing fibrosis is the main reason why the prognosis for PA intoxication is much worse than for most other liver diseases. Supportive therapy consists of correction of dehydration, acid-base disturbances and electrolyte imbalances. To meet energy requirements, dextrose can be added to perfusion solutions. Reduction of the production and absorption of neurotoxic products in the intestinal tract might be achieved by oral administration of lactulose, paraffin oil or antibiotics (neomycin). With our horses, paraffin oil was used, as it is known that oral lactulose and neomycin can cause diarrhea and probably induce salmonellosis. Further therapy consists of parenteral administration of antibiotics. A diet with high carbohydrate content and small quantities of protein of high biological value should be offered.

As therapy is often not successful, prevention of PA toxicosis is of particular importance. Public awareness must be increased and veterinarians should play a key role in this process by informing horse owners about the possible dangers of *Senecio* and how to recognize the mature plants and especially the seedlings. Pasture management techniques can minimize exposure to PA-containing plants. Overgrazing of contaminated pastures should be avoided. It is essential to remove PA-containing plants before hay or silage is harvested, because drying of plant material reduces the bitter taste but has only a small effect on the PA content. Over the last years *Senecio jacobaea* has been given a lot of media attention in Belgium. Although objective data about the exact distribution of this plant are not available, anecdotal evidence suggests that the plant is spreading and is becoming an increasing threat.

In horses that might have been exposed to *Senecio,* early recognition of the disease, for example by blood analysis, and subsequent exclusion of the plants from the diet may prevent the development of fatal liver failure.

REFERENCES

Amory H., Perron M.F., Sandersen C., Delguste C., Grulke S., Cassart D., Godeau J.M., Detilleux J. (2005). Prognostic value of clinical signs and blood parameters in equids suffering from hepatic disease. *Journal of Equine Veterinary Science 25*, 18-25.

Byars T.D. (2003). Liver disease: contributions to diagnostic and prognostic aids. *Equine Veterinary Journal 35*, 522-523.

Byars T.D. (1983). Chronic liver failure in horses. *Compendium on continuing education for the practicing veterinarian 5*, S423.

Cheeke P. R. (1998). *Natural Toxicants in Feeds, Forages, and Poisonous Plants*, 2nd Edition, Danville, Interstate Publishers, 338-352.

Clarke M. L., Harvey, D. G., Humphreys, D. J. (1981). *Veterinary Toxicology,* 2nd Edition, Bailliere Tindall, London, 203-206.

Craig J. F., Kearney W., Timoney J. F. (1930). Ragwort poisoning in cattle and cirrhosis of the liver in horses. *The Veterinary Record 10*, 159-174.

Curran J.M., Sutherland R.J., Peet R.L. (1996). A screening test for subclinical liver disease in horses affected by pyrrolizidine alkaloid toxicosis. *Australian Veterinary Journal 74*, 236-240.

Divers T.J., Bernard W.V., Reef V.B. (1988). Equine liver disease and liver failure causes, diagnosis and treatment. In: *Proceedings of the 10th Bain -Fallon Memorial Lecture*, Artarmon, Australia. pp, 35-46.

Divers T.J. (1993). Biochemical diagnosis of hepatic disease and dysfunction in the horse. *Equine Practice 15*, 15-17.

Duncan J.R. and Prasse K.W. (1986). *Veterinary Laboratory Medicine 2*. Ames, Iowa State University Press, 105-144.

Durham A.E., Smith K.C., Newton J.R., Hillyer M.H., Hillyer L.L., Smith M.R.W., Marr C.M. (2003a). Development and application of a scoring system for prognostic evaluation of equine liver biopsies. *Equine Veterinary Journal 35*, 534-540.

Durham A.E., Newton J.R., Smith K.C., Hillyer M.H., Hillyer L.L., Smith M.R.W., Marr C.M. (2003 b) Retrospective analysis of historical, clinical, ultrasonographic, serum biochemical and haematological data in prognostic evaluation of equine liver disease. *Equine Veterinary Journal 35*, 542-547.

Durham A.E., Smith K.C., Newton J.R. (2003 c). An evaluation of diagnostic data in comparison to the results of liver biopsies in mature horses. *Equine Veterinary Journal 35*, 554-559.

Ford E.J.H. (1973). Clinical aspects of ragwort poisoning in horses. *The Veterinary Annual 14*, 86-88.

Grabner A. (1990). Enzootische Leberdystrophie und hepatoenzephales Syndrom bei Pferden nach Vergiftung mit Senecio alpinus. *Pferdeheilkunde 6*, 119-124.

Jones T. C., Hunt R. D., King N. W. (1997). *Veterinary Pathology*, 6th Edition. Baltimore, Williams & Wilkins, 712-718.

Mair T.S., Jones R.D. (1995). Acute encephalopathy and hyperammonaemia in a horse without evidence of liver disease. *The Veterinary Record 137*, 642-643.

McGorum B.C., Murphy D., Love S., Milne E.M. (1999). Clinicopathological features of equine primary hepatic disease: a review of 50 cases. *The Veterinary Record 145*, 134-139.

Olsman A.F.S., van Oldruitenborgh-Oosterbaan M.M.S. (2004). Primary liver disease in the horse. *Tijdschrift voor Diergeneeskunde 129*, 510-522.

Pearson E.G., Craig A.M.(1993). Serum bile acids for diagnosis of chronic liver disease in horses. In: *Proceedings of the American college of veterinary internal medicine 4*, 1071-1075.

Rantanen N.W. (1986). Diseases of the liver. *Veterinary clinics of North America-Equine practice 2*, 105-114.

Schmitz D. G. (1998). Toxicological Problems. *In*: Reed SM, Bayly WM (eds.). *Equine Internal Medicine*. Philadelphia, W.B. Saunders Co., 1024-1025.

Talcott P. (2003) Pyrrolizidine Alkaloid Poisoning. *In*: Robinson NE (ed.). *Current Therapy in Equine Medicine,* 5th Edition. Philadelphia, W.B. Saunders Co., 788-790.

Tennant B.C., Hornbuckle W.E.(1980). Diseases of the liver. In: Anderson N. V. (ed.). *Veterinary Gastroenterology.* Philadelphia, Lea and Febiger, 593-620.

West H.J. (1996). Clinical and pathological studies in horses with hepatic disease. *Equine Veterinary Journal 28*, 146-156.

Uit het verleden

KATTENVERBRANDING

'In Parijs was het in de zestiende eeuw een onderdeel van de feestvreugde om op Sint-Jansdag een of twee dozijn katten levend te verbranden. Deze festiviteit was zeer vermaard. Het volk verzamelde zich; er klonk feestelijke muziek. Onder een of andere stellage werd een grote brandstapel opgericht. Vervolgens hing men een zak of korf met katten aan de stelling. De zak of korf begon te smeulen. De katten vielen op de brandstapel en verbrandden terwijl de menigte zich in hun gekrijs en gemiauw verlustigde. Gewoonlijk waren de koning en zijn hofhouding aanwezig. Soms liet men aan de koning of de dauphin de eer de brandstapel aan te steken. Naar verluidt werd er eens op speciaal verzoek van koning Karel IX een vos gevangen en mee verbrand.

Dit schouwspel is strikt genomen zeker niet vreselijker dan de ketterverbrandingen of allerlei folteringen en openbare terechtstellingen. Het lijkt alleen maar erger, omdat ... de lust in het pijnigen van levende wezens zich hier zo naakt, onverhuld, doelloos, want zonder verstandelijk excuus, toont'.

Citaat uit de klassieker "*Het civilisatieproces*" van Norbert Elias (hier in de vertaling van "*Uber den Prozess der Zivilisation. Sociogenetische und psychogenetische Untersuchungen*", Basel, 1939, uitgegeven door Boom, Amsterdam, 2001, p. 292-292).

Het gebeuren wordt door Elias geduid in een hoofdstuk over de veranderingen in de agressiviteit doorheen de eeuwen, binnen de verplaatsing van driftuitingen van het directe handelen naar het toekijken, waarin zich een duidelijke curve van matiging en humanisering van de affecten aftekent.

De naoorlogse heruitgaven van dit boek werden door de auteur (Breslau, 1897 – Amsterdam, 1990) opgedragen aan zijn ouders Hermann, die in 1940 gestorven is te Breslau, en Sophie,vermoedelijk in 1941 gestorven in Auschwitz.

Luc Devriese